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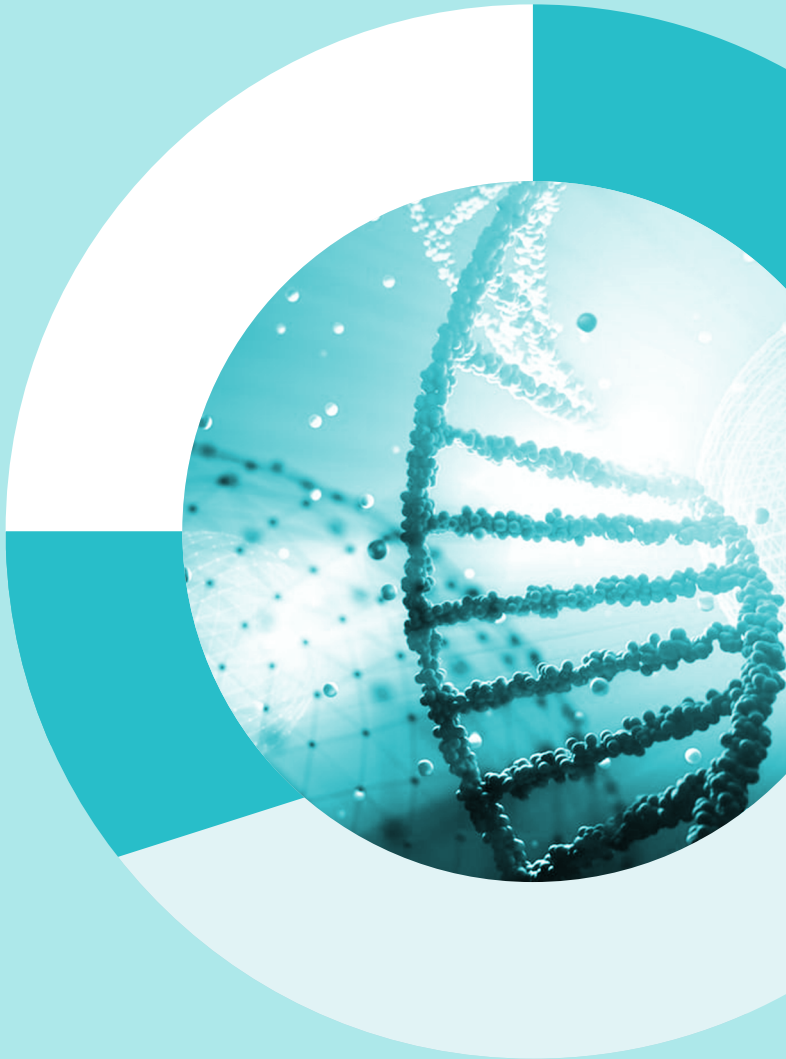
ORIGINAL ARTICLES



Official Journal of Cyprus Turkish Medical Association

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This journal is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles. As of 2022, the journal has become a bimonthly publication, publishing in February, April, June, and August, October and December. The journal's publication language is English. (E-ISSN:2536-507X)

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- For further details, please check ICMJE Clinical Trial Policy at

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As of 1 January 2019, a data sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

Whether individual deidentified participant data will be shared

- What data in particular will be shared
- Whether additional, related documents will be available
- When the data will be available and for how long
- By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

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- Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.
- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
- Data sharing statement should also be stated in the Title Page even the authors do not plan to share it.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be

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provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

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Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The subheadings of the review articles should be planned by the authors. However, each review article should include an "Introduction" and a "Conclusion" section. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion with an unstructured abstract. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000	250 (Structured)	35	6	5 or total of 10 images
Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1200	200	15	No tables	4 or total of 8 images
Letter to the Editor	400	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

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Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIElD/cid.htm.

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A Multidimensional Approach to Chronic Disease Management: The Patient Health Engagement Model

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Abstract

Chronic disease management is a complex process which that requires adaptation to unfamiliar lifestyle changes and long-term treatment, starting from starting from the diagnosis until the end of life. In this case, healthcare professionals should inform the patient about the process, support their self-management skills, and adopt the appropriate approach by taking into account the patient's emotional responses and perceptions about their disease process. The Patient Health Engagement (PHE) Model is the most current person-centered care approach which is based on strengthening the patient's active role in maintaining chronic disease self-management. The model reveals that the patient undergoes sequential phases (blackout, arousal, adhesion, and eudaimonic project) according to the critical situations experienced in this process. By defining these phases, the model enables healthcare professionals to determine the patient's cognitive, emotional, and behavioral needs, plan individualized care, and integrate the patient as an active member of the healthcare team. Therefore, the aim is to describe the patient's experiences in chronic disease management starting from diagnosis, to introduce the PHE Model, and to discuss its use in chronic disease management. It is expected that this review will guide nurses in using this model in chronic disease management and will provide an effective approach to clinical practice.

Keywords: Chronic disease, nursing, self-management, patient engagement

INTRODUCTION

Chronic diseases are irreversible conditions with a long duration, slow progression,[1] and never fully recovered from.[2] The World Health Organization reported that, in 2016, 71% of global deaths were due to chronic diseases,[3] and this number would rise to 22.2 million by 2030.[3] Studies in Turkey have found that 86% of deaths occur due to chronic diseases.[4] Therefore, these results demonstrate that chronic disease management has become a worldwide issue due to its high prevalence and mortality rates.

In addition to being a common problem, chronic diseases typically cause irreversible changes in the long term.[5] The main challenges are reduction/loss of physical function and independence, limitation of daily life activities, matters in family roles, and coping difficulties.[6] These changes have indicated that chronic disease and its complications are not effectively managed. As a challenging process, chronic disease management fundamentally relies on the patient's self-control, which requires individuals to adapt to unfamiliar lifestyle patterns, to comply with medical treatment, and to deal with psychological problems.[7] However, each individual has different perceptions and unique needs in managing their chronic diseases. For this reason, a multidimensional care approach is required to fulfill the patients' demands and to support their active role.

There have been plenty of terms introduced in recent years highlighting the patients' active roles.[8-11] In line with this, the concepts of patient compliance, adherence, involvement, participation, activation, and empowerment support the active role of the patient, but most of these concepts can be used interchangeably and they define

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the patient's different roles in the process.[8,10,11] Lately, the patient engagement concept was introduced as uniting all approaches under one roof, embracing a holistic view by considering individuals' needs at cognitive, emotional, and behavioral levels.[12] Differing from other concepts, patient engagement creates a cooperative atmosphere between individuals and health professionals,[13] strengthening patients by expanding viewpoints to include their experiences and aiming for them to have more "words" in healthcare services delivery.[14] Targeting on developing health knowledge, skills, and the desire of patients to manage their health, it focuses on protecting health and gaining healthy lifestyle habits.[15]

Derived from the patient engagement concept, the Patient Health Engagement (PHE) Model is the most up-to-date approach and is highly recommended in order to maintain chronic disease self-management where the patient takes individual responsibility and an active role during his/her care.[16] Accordingly, this article aimed to discuss the use of the PHE Model addressing cognitive, emotional, and behavioral dimensions in the chronic disease process. This topic is discussed under two main sections of (i) the chronic disease management process and (ii) the use of the PHE Model in chronic disease self-management.

Chronic Disease Management: A Lifelong Development Process

Chronic disease management is a long-term developmental process in which a person adapts to live with a lifelong condition.[17] This process appears with the individual becoming aware of a range of physiologic changes and symptoms in their body. The person initially may not attach importance to these changes and will expect that they will get better; however, when symptoms do not disappear, they try to figure out the cause of these problems and associate with some realities. Symptoms with unknown causes may result in an individual's fear of losing health. To cope with this situation, they may take responsibility for their health in an attempt to resolve their symptoms themselves. For example, they may use nonprescription analgesics to relieve pain, try medications used by other patients, or orient toward alternative medicine. When the person accepts that they cannot manage their symptoms, they utilize the healthcare services.

Until patients seek healthcare services while managing their symptoms, they mainly adopt a passive role during the diagnosis stage because they depend on health professionals to learn and recognize the cause of the changes they cannot manage. Additionally, due to uncertainty, they experience anxiety, have difficulty in perceiving health information and play a dependent role by leaving most decisions to health professionals and their relatives.[18] In this process, the priority for both the patient and the healthcare professionals is to complete diagnostic tests in the shortest time possible and to begin treatment.[19] During the diagnosis period, it was shown that patients experience problems in treatment adherence, they delay doctor's appointments, and are hospitalized repeatedly.[20,21] These outcomes underline the difficulties in chronic disease management when the patient has limited responsibility in this stage.

When encountering new symptoms and dealing with the diagnosis, patients follow a self-management process where they accept the chronic condition and take responsibility for their health. Self-management is defined as an individual undertaking tasks necessary to live well with one or more chronic situations.[22] This inevitable process requires adapting to a new nutritional pattern which most patients are not used to, performing regular physical activity, attending routine check-ups and repeating diagnostic tests, continuing the recommended medication treatment, and adapting self-monitoring behaviors into daily life.[23] It may be difficult for most individuals to adjust to this complicated process,[24] since they need to adopt a new role as a patient. Additionally, they require motivation in order to sustain these behaviors throughout their life.[25] Effective self-management ensures early awareness of newly-occurring symptoms, reduced attendance to emergency services, and lengthened survival durations, which reflect positively in public health in the long term.[26] Ineffective self-management may cause maladaptation to new behavior patterns, more frequent admissions to emergency services due to incompliance with medical treatment, and reduced quality of life.[27]

Previous studies have emphasized that patient education methods focusing on cognitive/behavioral dimensions that require a passive role of the patient are mainly used to used to enhance self-management.[28,29] However, patient education methods remained insufficient to sustain adherence to treatment and lifestyle changes and generally were conducted spontaneously, without planning or determining individual goals.[30] As a result, planned interventions remain limited in ensuring the patients' desires to take responsibility for their health and to continue their self-management skills throughout life.[29] Motivation should be considered for effective self-management because the patient being able to give meaning to their chronic disease in an emotional dimension ensures the development of internal control focus and behavioral changes which can be sustained for life.[31] For this reason, interventions for effective self-management including the cognitive, behavioral, and emotional dimensions will provide the most effective outcomes.[32,33] Thus, concepts targeting giving a more active role to the patient based on cooperation between the patient and health professionals, involving patients in clinical decision-making, supporting self-management, and planning individualized care in three dimensions have gained importance.[34]

Along this path, the patient engagement concept offers a multi-faceted and dynamic nature[12] which encourages individuals to embrace an active role by combining their knowledge, abilities, and willingness to manage their care in order to promote positive health outcomes. With its broader view, patient engagement provides a comprehensive approach in different fields such as chronic care management,[35] patient safety practices,[36] and health information technologies.[37] Additionally, a range of results have shown that patient engagement allowed healthcare professionals to become more easily aware of the patient's needs, improved clinical outcomes, enhanced treatment adherence and compliance to healthy lifestyle habits, increased awareness about risky lifestyle behaviors, all of which reduce complications and contributed to the sustainability of the healthcare system.[9,14,19,38-40] Finally, the "PHE Model" was introduced based on several qualitative studies revealing how individuals become engaged in their own care process.[14]

PHE Model for Chronic Disease Self-Management

The PHE Model aims to assess the patient's attitude to chronic disease management, readiness to manage care, and understanding related to their disease.[9] The model supports the patient at cognitive, emotional,

and behavioral dimensions; not only facilitating obtaining health-related information and self-management skills, but also maintaining the emotional balance of the chronic care continuum.[38] Additionally, the model ensures the collaboration between the patient and the healthcare team, in which the patient mainly makes health decisions and manages their care, and this experience is combined with the knowledge of the healthcare professionals. Therefore, the patient and health professionals form a partnership regarding the decision-making process.[41] From this aspect, the PHE Model can be stated to be more comprehensive than other chronic care approaches.

The PHE Model reveals that individuals pass through phases in sequence according to critical events (e.g., diagnostic testing process, the occurrence of new symptoms, compliance with a new treatment, recurrence of the disease) experienced during the process after receiving a chronic disease diagnosis.[19] Dealing with these unexpected critical events usually causes severe stress and anxiety for the patient. This situation may negatively affect the patient's desire to undertake active self-care and to participate in decisions related to treatment. As a result, healthcare professionals should determine the patient's engagement phase and plan individualized interventions. The phases describing patients' specific experiences are as follows: blackout, arousal, adhesion, and eudaimonic project.[42]

1. Blackout: The blackout phase is where the patient is emotionally fragile due to a newly-occurring critical event (e.g., a new diagnosis, occurence of new symptoms, or recurrence) with the difficulty of facing a new reality.[42,43] The patient initially feels shocked, fearful, anxious, and panicked due to the unexpected situation and they feel unable to manage the health condition which results in a loss of control in his/her health.[45] All these negative emotions cause difficulty in the transformation of this new health information into understanding, interpretation, and behavior; in other words, "cognitive blindness". In the blackout phase, the patient tends to leave decisions related to the chronic disease process to the health professionals with superior professional knowledge and skills and takes a passive role.[44,46] At this point, the most basic expectation of the patient is to receive information about the about the disease and treatment from a trusted healthcare professional and feel understood.

2. Arousal: In the arousal phase, the patient gains initial awareness in emotional terms after their diagnosis. However, they display excessive sensitivity to every clinical symptom in the body and are always tense. As a result, each new symptom qualifies as an "alarm bell".[43] Compared to the blackout, patients have obtained superficial health information; however, this information is still abstract. This is because fear and anxiety continue so the behavior does not reflect their health knowledge and they have difficulty sustaining new lifestyle habits.[35,42] As a result, in this new adjustment process, the patient frequently needs to ask doctors/nurses whether they are correctly doing what they have been told or not.[35] In this phase, although there are positive effects of medication treatment, the most common problem is treatment incompliance.[45] They encounter problems in adjusting the prescribed medication doses, self-administering invasive medications, or taking multiple doses. This may cause a worsening of their disease symptoms, lowering of their quality of life, and a disengagement of daily life activities.[35]

3. Adhesion: In the adhesion phase, the patient has better-developed health literacy levels and chronic disease management skills compared to the blackout and arousal phases and becomes more emotionally stable.[43] The patient accepts the negative feelings caused by the caused by the disease but still lacks full autonomy over self-management. In particular situations with any change in lifestyle habits (e.g., going on holidays, traveling for work), they may experience difficulties sustaining their disease management skills adapted to their routine life[42] because the patient has not fully grasped the rationale for their treatment plan. As a result, the patient may require motivation to sustain their new health behavior in stressful situations or during unexpected changes in lifestyle.[44] In the adhesion phase, the patient begins to recognize the importance of playing an active role in their chronic disease management. This first awareness of the identity role is the starting point of the final eudaimonic project phase.

4. Eudaimonic project: In the eudaimonic project phase, the patient has fully adjusted to the process from the start with skills obtained related to the cognitive, emotional, and behavioral dimensions. Individuals in this phase do not identify themselves as "patients"; in other words, "being a patient" is an experience from their past. The individual succeeds in engaging chronic disease management skills within their daily routine and does not feel stress and anxiety due to the changes experienced; on the contrary, they are hopeful about their health status and the future.[45] The patient has developed an internal control focus to sustain emotional development and aims to reflect this skill in their future life plans.[46] Unlike the adhesion, adhesion, patients in this phase pay attention to changes in their daily routines including what they eat, creating appropriate conditions for taking medications, and continuing to exercise.[43] The patient is specialized in their chronic disease management and becomes an active member of the health team. For example, based on their own experiences, they predict the requirements and expectations of other patients in similar conditions and may offer recommendations to healthcare professionals. Thus, they contribute to developing the quality of healthcare services.

Patient Health Engagement Journey: Transitions from Phases

It is important to determine which engagement phase the patient is in for chronic disease management. Identifying the positions enables nurses to determine which aspects the patient requires support for, setting individualized care goals, identifying factors which may be obstacles to gaining self-management skills, strengthening the patient's autonomy in decision-making, engaging the family in the care management and providing appropriate coping support to the patient.[19] From the blackout to the eudaimonic project phases, patients' experiences and possible approaches of nurses are detailed below.

From Blackout to the Arousal Phase

The basic approach in the shift from blackout to the arousal phase involves supporting health literacy, providing health information, ensuring that patients can manage negative feelings, and establishing a trusting relationship.[43] The trust relationship supports patients in resolving their feelings of shock, fear, and emotional confusion experienced after diagnosis. Due to uncertainty, patients need to frequently ask a trusted healthcare professional about their disease about their disease and treatment process. As a result, it should be

ensured that the patient can communicate with the doctor or nurse whenever required (e.g., telephone, message applications) and receive answers to questions. The patient should be supported in the cognitive aspect considering their readiness, and the basic health information should be given progressively. In this progress, it is recommended to organize informative sessions about the disease, provide written/visual material at the patient's health literacy level, perform individual health-coaching, maintain effective communication with doctors and nurses, and refer patients to psychological counseling.[43]

From the Arousal to the Adhesion Phase

The shift from arousal to adhesion initially requires the patient to have self-confidence in developing self-management skills.[43] In the arousal phase, healthcare professionals are an important reference point for patients,[44] because patients need the knowledge and skills of healthcare professionals to set health goals for their conditions. If effective support is provided, the patient develops self-confidence and becomes able to adapt their skills with enhanced health literacy and emotional strength. To sustain these behaviors and support independence, it is necessary to maintain a patient's motivation to manage this process.[40] Additionally, each new symptom may cause excessive responses so the patient needs to be supported emotionally; for instance, opportunities must be created for patients to express their feelings. It is also recommended that referring patients to accessible scientific health-related information resources, meeting with other patients with the same chronic disease to share experiences, keeping a chronic disease diary recording their knowledge, experiences and feelings related to disease management, reviewing mobile applications to monitor and record information related to the disease (e.g., test results, medication doses and times, appointment dates) and using to-do lists to monitor implementations in their treatment management process.[43]

From Adhesion to the Eudaimonic Project Phase

From adhesion to the eudaimonic project, patients should have adopted and maintained the basic aims of their care and healthy lifestyle for the future.[35] In the adhesion stage, the main focus is still their disease and its treatment; as a result, patients limit daily life activities and social experiences. However, in the eudaimonic project position, the chronic disease should be accepted as a natural part of their life with a full adjustment to the changes and an appropriate environment should be created in all conditions to complete the sustainable self-management skills with the patient's active role.[38] In this development, the patient begins to perceive chronic disease management as a part of their life and describe it as gaining a new identity.[47] As a result, nurses should support the patient in making new plans for the future, even if limited compared to life before the diagnosis of their chronic disease.[48] Furthermore, it is recommended to refer patients to scientific meetings related to their chronic disease, organize home-based services for continuity of care, and encourage patients to utilize web-based applications where they can share their disease experienced (e.g., forums, portals).[38] Figure 1 demonstrates the engagement phases according to the cognitive, behavioral and emotional dimensions of the model.

Multiple studies have investigated the effects of interventions targeting patient engagement and the PHE Model's role in chronic disease management. Menichetti and Graffigna[9] (2017) identified the relationship between patient engagement and the patient's online health-seeking behaviors. Their cross-sectional study conducted with 352 Italian chronic patients showed that when healthcare professionals support patients' autonomy, patients become more engaged in their own healthcare and developed online health information-seeking behaviors. Consequently, chronic patients' emotional elaboration influenced their

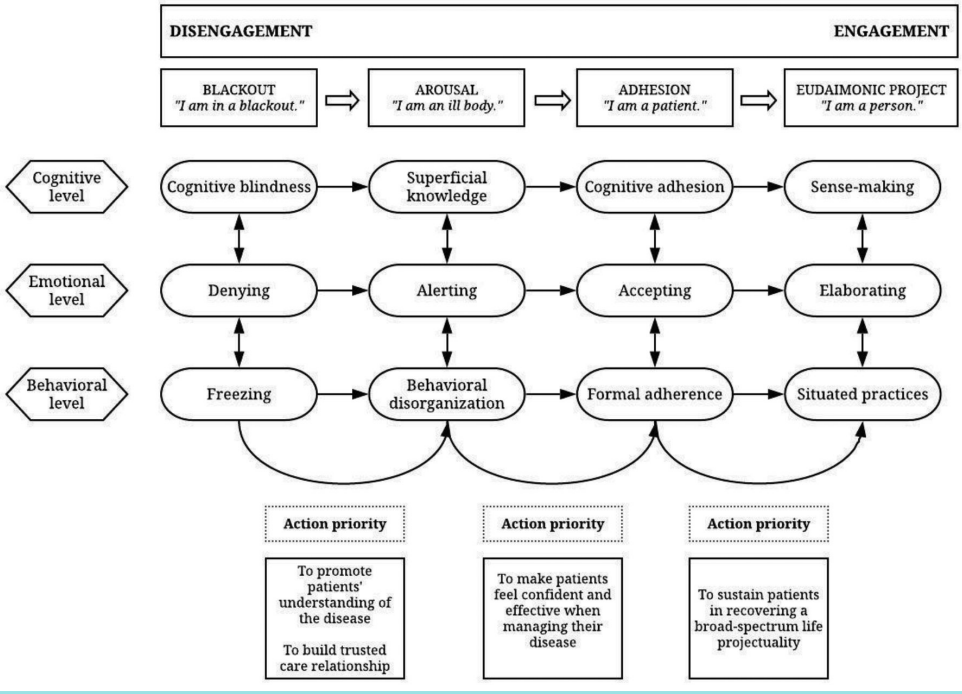

Figure 1. Patient engagement phases based on the Patient Health Engagement Model

ability to participate in care management, and it was recommended to provide reliable online health resources to individuals.[49]

Mazzoni et al.[45] (2018) suggested that patients with systemic lupus erythematosus (SLE) experience a challenging process when living with their disease and self-managing their care. Therefore, they conducted a qualitative study and aimed to determine the SLE patients' engagement process by describing care management experiences. With four focus groups and ten in-depth individual interviews from various European countries, the authors claimed that patients who could reframe their needs in cognitive, emotional, and behavioral dimensions became more engaged in their care. Thus, the PHE Model represented an adequate framework to figure out the SLE patients' engagement process and plan individualized care.[45]

Barello et al.[46] (2015) used a grounded theory approach to reveal the characteristics of the patient-doctor relationship and patient engagement with twenty-two in-depth interviews conducted with thirteen heart heart failure (HF) patients, five physicians, and four caregivers. The results shed light on the HF patients' engagement experiences and strongly underlined the doctors' essential role in fostering the patients' ability to engage in their care. Moreover, the early phases of the engagement process suggested the need for a paternalistic approach because the patients were more prone to delegate clinical decision making to the physicians. It was proposed that HF patients not only need cognitive and behavioral support but also emotional elaboration is crucial for engaging in care.[46]

Graffigna et al.[35] (2014) suggested that patient engagement has become a key factor in improving type-2 diabetes patients' self-care management skills. With twenty-nine uncontrolled type-2 diabetes patients, a narrative qualitative study, in which they kept a one-week diary, was conducted to better understand their experiences of disease management. It was revealed that the greatest difficulty of patients was adapting to new lifestyle habits and that their emotional needs were mostly ignored. Also, the model led to the discovery of numerous unmet needs in different engagement phases and identified possible types of support in the cognitive, emotional, and behavioral dimensions. As a result, the PHE Model provided a strong framework to deeply understand type-2 diabetes patients' self-management experiences.[35]

Additionally, the cognitive, emotional, and behavioral development process can be evaluated with Patient Health Engagement Scale (PHE-s) based on the PHE Model by Graffigna et al.[12] in 2015. The scale has had validity-reliability studies performed in the Chinese[50], Spanish[51], and Turkish[52] languages with ordinal alpha values of 0.89, 0.85, and 0.80, respectively. Comprising five items, the PHE-s has an ordinal structure and can easily be answered by the patient. The scale rapidly determines the patients' engagement position and enables healthcare professionals to plan individualized interventions based on the patient's needs in continuous care.

CONCLUSION

Chronic diseases reduce the quality of life, increase health-related costs, and shorten life expectancy worldwide. After the initial diagnosis, chronic diseases should be managed by the patient throughout their life; thus, strengthening the patient is the key factor to ensure the sustainability of this care process.

Chronic disease self-management requires patients to adjust to complicated treatments and new and unfamiliar lifestyle habits. Additionally, each individual has different attitudes towards their disease and subjective disease experiences; as a result, the patient should be dealt with using a multidimensional approach from cognitive, emotional, and behavioral aspects. At this point, the PHE Model strongly highlights patients' subjective experiences (knowledge about their health, feelings related to the process, and their ability to self-care). The four sequential phases define the causes behind the patient's thoughts, attitudes, and behaviors by revealing the specific features of the engagement process. With these elaborations, the patient's management skills can be strengthened, easing their ability to play an effective role in the healthcare services. Thus, patients with difficulties in difficulties in developing self-management skills can be identified before entering the high-risk group, and cooperation can be established with the patient. Although different care needs may be required for each condition, the self-management approaches of chronic diseases are similar. Therefore, it is thought that the PHE Model may ensure effective self-management for all chronic diseases.

Future research based on the utilization of the PHE Model is highly recommended. For instance, designing web-based applications with interventions specific to the engagement phases, developing post-discharge patient follow-up protocols, and defining the interventions for different integrated contexts (i.e. other chronic conditions, acute situations, or supporting health-protective behaviors). In addition, nurses have a coordinating role in providing chronic care in the healthcare team. Accordingly, arrangements in the clinical practice aimed at increasing nurses' awareness of using this evidence-based model and reorganizing the outpatient chronic care follow-ups by adopting a patient engagement approach are also recommended.

MAIN POINTS

- Chronic disease management requires life-long adherence to complex changes, therefore, the patients' attitudes and subjective experiences should be taken into account in order to provide continuous care.
- After being diagnosed with a chronic disease, each patient goes through engagement phases with specific characteristics of cognitive, emotional, and behavioral aspects.
- Determining the engagement phases enables healthcare professionals to define the patient's unique needs, provide individualized care, and integrate the patient as an active member of the healthcare team.

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REFERENCES

1. WHO. Noncommunicable diseases. World Health Organization; 2016.
2. Bilir N. Changing patterns of health and role of public health professionals: chronic diseases and problems of the elderly. Toplum Hekimliği Bülteni. 2006; 25(3): 1-6.
3. WHO. Global health estimates 2016: Disease burden by cause, age, sex, by country and by region, 2000-2016. Geneva: World Health Organization; 2018.
4. WHO. Türkiye hane halkı sağlık araştırması: Bulaşıcı olmayan hastalıkların risk faktörleri prevalansı. World Health Organization; 2017.
5. Funk SG. Key aspects of preventing and managing chronic illness: Springer Publishing Company; 2001.
6. Lubkin IM, Larsen PD. Chronic illness: Impact and interventions: Jones & Bartlett Learning; 2006.
7. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Aff. 2001; 20(6): 64-78.
8. Anderson RM, Funnell MM, Butler PM, Arnold MS, Fitzgerald JT, Feste CC. Patient empowerment: results of a randomized controlled trial. Diabetes Care. 1995; 18(7): 943-9.
9. Menichetti J, Graffigna G. "PHE in action": Development and modeling of an intervention to improve patient engagement among older adults. Front Psychol. 2016; 7: 1405.
10. Tinetti ME, Naik AD, Dodson JA. Moving from disease-centered to patient goals–directed care for patients with multiple chronic conditions: patient value-based care. JAMA Cardiol. 2016; 1(1): 9-10.
11. Entwistle VA, Watt IS. Patient involvement in treatment decision-making: the case for a broader conceptual framework. Patient Educ Couns. 2006; 63(3): 268-78.
12. Graffigna G, Barello S, Bonanomi A, Lozza E. Measuring patient engagement: development and psychometric properties of the Patient Health Engagement (PHE) scale. Front Psychol. 2015; 6: 274.
13. Ocloo J, Matthews R. From tokenism to empowerment: progressing patient and public involvement in healthcare improvement. BMJ Qual Saf. 2016; 25(8): 626-32.
14. Menichetti J, Libreri C, Lozza E, Graffigna G. Giving patients a starring role in their own care: a bibliometric analysis of the on-going literature debate. Health Expect. 2016; 19(3): 516-26.
15. James J. Patient engagement. Health Aff Health Policy Brief. 2013;14.
16. Pulvirenti M, McMillan J, Lawn S. Empowerment, patient centred care and self-management. Health Expect. 2014; 17(3): 303-10.
17. Hörnsten A, Sandström H, Lundman B. Personal understandings of illness among people with type 2 diabetes. J Adv Nurs. 2004; 47(2): 174-82.
18. Turner J, Kelly B. Emotional dimensions of chronic disease. West J Med. 2000; 172(2): 124-8.
19. Barello S, Graffigna G. Patient engagement in healthcare: pathways for effective medical decision making. Neuropsychol Trends. 2015; 17: 53-65.
20. Tel H, Doğan S, Özkan B, Çoban S. Compliance to treatment among chronic psychiatric disorder patients according to their relatives. Journal of Psychiatric Nurses. 2010; 1(1): 7-12.
21. Üçok A. Şizofreni tedavisinde karşılaşılan güçlükler. Kronik Ruhsal Hastalıklarda Tedavi İşbirliği. 2011; 1: 7-8.
22. Adams K, Greiner AC, Corrigan JM. Patient Self-Management Support. The 1st Annual Crossing the Quality Chasm Summit: A Focus on Communities: National Academies Press (US); 2004.
23. Barlow J, Wright C, Sheasby J, Turner A, Hainsworth J. Self-management approaches for people with chronic conditions: a review. Patient Educ Couns. 2002; 48(2): 177-87.
24. Bratzke LC, Muehrer RJ, Kehl KA, Lee KS, Ward EC, Kwekkeboom KL. Self-management priority setting and decision-making in adults with multimorbidity: a narrative review of literature. Int J Nurs Stud. 2015; 52(3): 744-55.
25. Packer TL, Fracini A, Audulv Å, Alizadeh N, van Gaal BG, Warner G, et al. What we know about the purpose, theoretical foundation, scope and dimensionality of existing self-management measurement tools: a scoping review. Patient Educ Couns. 2018; 101(4): 579-95.
26. Haskett T. Chronic illness management: Changing the system. Home Health Care Management & Practice. 2006; 18(6): 492-4.
27. Carman KL, Dardess P, Maurer M, Sofaer S, Adams K, Bechtel C, et al. Patient and family engagement: A framework for understanding the elements and developing interventions and policies. Health Aff. 2013; 32(2): 223-31.
28. Groller KD. Systematic review of patient education practices in weight loss surgery. Surg Obes Relat Dis. 2017; 13(6): 1072-85.
29. Menichetti J, Graffigna G, Steinsbekk A. What are the contents of patient engagement interventions for older adults? A systematic review of randomized controlled trials. Patient Educ Couns. 2018; 101(6): 995-1005.
30. Ni Z, Dardas L, Wu B, Shaw R. Cardioprotective medication adherence among patients with coronary heart disease in China: a systematic review. Heart Asia. 2019; 11(2): e011173.
31. Teixeira PJ, Carraça EV, Marques MM, Rutter H, Oppert J-M, De Bourdeaudhuij I, et al. Successful behavior change in obesity interventions in adults: a systematic review of self-regulation mediators. BMC Med. 2015; 13: 84.
32. Low JK, Williams A, Manias E, Crawford K. Interventions to improve medication adherence in adult kidney transplant recipients: a systematic review. Nephrol Dial Transplant. 2014; 30(5): 752-61.
33. van Dulmen S, Sluijs E, Van Dijk L, de Ridder D, Heerdink R, Bensing J. Patient adherence to medical treatment: a review of reviews. BMC Health Serv Res. 2007; 7(1): 55.
34. Epstein RM, Fiscella K, Lesser CS, Stange KC. Why the nation needs a policy push on patient-centered health care. Health Aff. 2010; 29(8): 1489-95.
35. Graffigna G, Barello S, Libreri C, Bosio CA. How to engage type-2 diabetic patients in their own health management: implications for clinical practice. BMC Public Health. 2014; 14(1): 648.
36. Scobie AC, Persaud D. Patient engagement in patient safety: Barriers and facilitators. Patient Safety and Quality Healthcare. 2010; 7(2): 42-7.
37. Palmer NR, Avis NE, Fino NF, Tooze JA, Weaver KE. Rural Cancer Survivors' Health Information Needs Post-Treatment. Patient Educ Couns. 2020; 103(8): 1606-14.
38. Graffigna G, Barello S, Riva G, Bosio AC. Patient engagement: the key to redesign the exchange between the demand and supply for healthcare in the era of active ageing. Stud Health Technol Inform. 2014; 203: 85-95.
39. Quinn CC, Butler EC, Swasey KK, Shardell MD, Terrin MD, Barr EA, et al. Mobile diabetes intervention study of patient engagement and impact on blood glucose: Mixed methods analysis. JMIR Mhealth Uhealth. 2018; 6(2): e31.

40. Graffigna G, Barello S, Bonanomi A, Menichetti J. The motivating function of healthcare professional in eHealth and mHealth interventions for type 2 diabetes patients and the mediating role of patient engagement. J Diabetes Res. 2016; 2016: 2974521.

41. Pomey MP, Ghadiri DP, Karazivan P, Fernandez N, Clavel N. Patients as partners: a qualitative study of patients' engagement in their health care. PloS One. 2015;10(4): e0122499.

42. Graffigna G, Barello S. The value of measuring patient engagement in healthcare: new frontiers for healthcare quality. Healthcare Ethics and Training: Concepts, Methodologies, Tools, and Applications: IGI Global; 2017. p. 1268-90.

43. Graffigna G, Barello S. Modelling patient engagement in healthcare: insight for research and practice. Patient Engagement: Sciendo Migration; 2015. p. 27-43.

44. Graffigna G, Barello S. Spotlight on the Patient Health Engagement model (PHE model): a psychosocial theory to understand people's meaningful engagement in their own health care. Patient Prefer Adherence. 2018; 12: 1261.

45. Mazzoni D, Cornet A, van Leeuw B, Myllys K, Cicognani E. Living with systemic lupus erythematosus: A patient engagement perspective. Musculoskelet Care. 2018; 16(1): 67-73.

46. Barello S, Graffigna G, Vegni E, Savarese M, Lombardi F, Bosio AC. 'Engage me in taking care of my heart': a grounded theory study on patient-cardiologist relationship in the hospital management of heart failure. BMJ Open. 2015; 5(3): e005582.

47. Bosio AC. Patient engagement: the key to redesign the exchange between the demand and supply for healthcare in the era of active ageing. Active Ageing and Healthy Living: A Human Centered Approach in Research and Innovation as Source of Quality of Life. 2014; 203: 85-95.

48. Graffigna G, Barello S, Triberti S. Patient engagement: A consumer-centered model to innovate healthcare: Walter de Gruyter GmbH & Co KG; 2016.

49. Graffigna G, Barello S, Bonanomi A, Riva G. Factors affecting patients' online health information-seeking behaviours: The role of the Patient Health Engagement (PHE) Model. Patient Educ Couns. 2017; 100(10): 1918-27.

50. Zhang Y, Graffigna G, Bonanomi A, Choi K-c, Barello S, Mao P, et al. Adaptation and validation of a Chinese version of Patient Health Engagement Scale for patients with chronic disease. Front Psychol. 2017; 8: 104.

51. Magallares A, Graffigna G, Barello S, Bonanomi A, Lozza E. Spanish adaptation of the Patient Health Engagement scale (S.PHE-s)in patients with chronic diseases. Psicothema. 2017; 29(3): 408-13.

52. Usta D, Korkmaz F, Akyar I, Bonanomi A. Patient Health Engagement Scale (PHE-s): Validity and reliability for Turkish patients with chronic diseases. Cukurova Med J. 2019; 44(3): 1055-63.

REVIEW

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Oral Biofilm and Prosthetic Materials

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Abstract

Oral microbiota is altered with the constituents of prosthetic biomaterials and dental restorations which are used for rehabilitation. As a result, such composition may have negative effects on the health of cavum oris and prosthetic biomaterials. The said oral condition is a common dental disorder formed by bacterial biofilms due to uncertain reasons. Problems caused by these biofilms have a close relationship with the kind of restoration carried out or material used. In relation to biomaterials, factors such as surface roughness, surface energy, and chemical structure affect microbiologic composition and biofilm accumulation. Recently, the use of restorative materials which inhibit the accumulation of dental plaque have become common. In consideration of the many problems related to biofilm accumulation on dental materials, the aim is to improve the prosthetic materials used to replace tissues while ameliorating oral health.

Keywords: Dental plaque, biofilm, denture, *Candida albicans, Streptococcus mutans*

INTRODUCTION

The oral cavity is the home to the hundreds of bacteria, fungi and viruses. These microorganisms are cross-linked with each other and form biofilms on the various surfaces of the oral cavity.[1] The microorganisms which form dental biofilm usually have harmless relationship with the host, although they have regular exposure to environment perturbations and host defense factors.[2] Although the biomaterials for the restorative appliances are accustomed to biofilm formation in the oral cavity, they are a major cause of periodontal diseases, tooth decay, and gingivitis.[3]

How does the biofilm formation occur in the oral cavity? What factors can effect this formation? How does the biofilm attach to the restorative materials and what is the treatment choice? This review briefly discusses recent articles to the answer these questions.

Biofilm

The opinion of that microorganisms are live together and can do the biofilms is first characterized by Antonie van Leeuwenhoek, who first reported "microbial aggregation" on the surface of teeth, and Louis Pasteur.[4] Biofilm is a structured league attached to a living or inert surface assemble with microorganism adhering to each other and produced extracellular polymeric elemets.[5] The matrix saturate the biofilm with a range of attributes such as antibiotic resistance, storage of extracellular enzymes, nutrient capture, gradient formation. So that, the matrix is extremely responsible for the structure of biofilm.[6] Biofilm could be formed in two way; (i) formed by single bacteria species called as monofilms or (ii) formed by more than one bacteria species called as multifilms.[7]

Dental plaque is an important example of the polymicrobial biofilm that form on the surfaces of teeth and, can lead to dental caries, periodontitis or other oral diseases.[8]

Oral Biofilm

Estimated more than 700 different bacterial species have been reported in the oral cavity of human saliva (10^8 to 10^9 CFU/mL), and a few of

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bacteria adhere to the teeth and cause the dental biofilm.[9] The oral biofilm includes many bacteria and cell-free organelles entrenched in an extracellular matrix. The extracellular matrix support the microenvironment for the immobilized bacteria.[10] Dental plaque is characterized by its huge diversity (>700 species) and high cell density, which assist the progress of organisms to cross-talk each other.[1,11] Cross-talked between bacteria is important for initial colonization to start forming the biofilm. If the bacteria do not be successful to retain on the tooth surface, the bacteria are cleaned by the mouth fluid. If the bacteria get success to adhere to surfaces, they start to organize other multispecies to form a dental plague (Figure 1). Cell-cell interaction between genetically specific cells can also take place in suspension called as co-aggreation. Oral bacteria have many co-aggreation partner (Table 1). The studies indicated that initial colonizers are *Streptococci* spp. and *Actimomyces* spp.[12] Studies indicated that many types of adhesion are related with the process of dental biofilm such as surface tension and chemical interactions. Also, studies reported that the most dominant group of the adhesion for supragingival bacteria is sucrose-dependent adhesion.[13]

The dental biofilms also has another comminication system called as quarum sensing. This system was based on quarum signal molecules like autoinducer-1 and autoinducer-2 which have an important role into both structure and virulence of the biofilm.[14]

Mechanisms of Biofilm Formation

Biofilm development takes place by five steps: (1) adhesion to tissues; (2) growth; (3) maturation distinguished by metabolic and genetic microbial trades, growth regulated by quorum-sensing molecules and antimicrobial peptides; (4) tissue invasion/destruction; and 5) surface detachment.[15] According to these stages, three-dimensional structure which is formed by microorganisms are seperated by water channels that allow the entry of nutrients, oxygen and discharge the waste products.[16] In the first step, bacterial cells consume the van der Waals forces to join the surface.[17] In step one, cell attachment is still reversible, but in second step; the cells attach themselves more strongly to produce the exopolymeric material. In step three, micro-colonies are produced, and the biofilm become to mature. In step four, included more maturation, and the biofilm evolve into a three dimensional structure. In step five the biofilm distribute the cells.[18]

Table 1. The list of the oral bacterial colonizer on the tooth

Streptococcus oralis and *Streptococcus sanguinis*
Streptococcus mitis
Streptococcus gordonii
Capnocytophaga ochraccea
Propionibacterium acnes
Haemophilus parainfluenzae
Prevotella loescheii
Veillonella spp.
Actinomyces oris and *Actinomyces naeslundii*
Eikenella corrodens
Actinomyces israelii
Capnocytophaga gingivalis
Capnocytophaga sputigena
Fusobacterium nucleatum
Prevotella denticola
Aggregatibacter actinomycetemcomitans
Eubacterium spp.
Treponema denticola
Tannerella forsythia
Porphyromonas gingivalis
Prevotella intermedia
Selenomonas flueggei

The attachment step could be classified into two process: initial reversible attachment and irreversible attachment.[19] The irreversible attached biofilm can allow physical or chemical forces.[20] In the initial attachment, flagella and type IV pili-mediated motilities are important. Flagellas are imporant between cells and surface interactions. Also, type IV pilimediated twitching motilities are important for the attached cells to aggregate and form microcolonies.[21] Different researches evaluated the effect of biofilm accumulation related to surface characteristics like surface free energy, roughness, topography and chemical structure of the dental biomaterials. Surface characteristics and chemical composition was found effectiveon the topography and surface energy as well as the type of restoration.[22]

Impacts of Physical and Chemical Properties of Different Prosthetic Restorations and Biomaterials on Dental Biofilms

Surface Energy

It is noted that polished surfaces have lower surface energy. Dental materials, except ceramics, mostly have a higher surface energy compared to enamel which cause higher risk of biofilm accumulation. It is a known fact that changes in surface roughness (SR) generally influenced the surface energy.[22]

Surface Roughness

It has been shown that nonpolished surfaces tend to have more oral biofilm accumulation than polished one. Although, the surfaces which have roughness higher than the threshold value which is 0.2 µm, may cause a concurrent increase in biofilm development, however there was no decrease in adhesion of bacteria below the threshold.[23] Also, the deeper and larger fossas and grooves may increase the area in contact and become more suitable places for bacterial colonies and biofilm accumulation. Following the accumulation, bacteria will defend against shear forces (washing and brushing) during first reversible bonding which will cause irreversible and powerful bond. Thus, it is hard to remove colonies on the irregular surfaces and this will followed by the development of matured biofilm.[24] Whereas, enhancing implant osseointegration, the SR is indicated as the basic requirement for induction of biofilm growth. Increased SR value may be the reason for growing in bacterial cells exponentially and enable biofilm accumulation regarding the components of the biofilm. On the other hand, a study approved that implants having irregular surfaces are not prone to fail, and the results indicated that similar microbiologic composition for titanium with various SR.[23]

Chemical Composition

The chemical structure of the biomaterial may have an effect on the accumulation of bacteria due to chemical attachment of proteins and microorganisms which can attach chemically or attract to constituents in the material, via bonds or interactions. So, the chemically formed

interaction between biomaterial and microorganisms can alter the surface characteristics.[22]

Antibacterial Properties of Restorative Material

It was found that restorative materials like amalgam, gold alloys which flow ions or glass ionomer cement which flow flouride, inhibite formation or maturation of bacteria.[25]

Dental Restorations

Prosthetic materials and different types of restorations can influence biofilm formation in different ways.

Crowns and Bridges

The joining line for the tooth and restoration may cause problems, since it is not possible to construct fixed prosthesis with ideal adaptation. Irregular, short or improper margins are formed at gingival margin, and this makes mechanic elimination of biofilms harder and change chemical equilibrium for biofilm in this area.[26] In addition, the fossas or edges will increase ormation of plaque and make the mechanical elimination of plaque harder.[22] Fixed partial dentures are generally fabricated by ceramics, metals or combinations. So, assesment of different types of materials used in fabrication of fixed restorations is essential.

Ceramics

Ceramic has smooth and polished surface which can be easily cleaned. Biofilm accumulates on irregular surfaces more than regular surfaces. It is reported that biofilms on ceramics are thin and highly viable. That is why, relative to other materials used in dentistry, ceramics are shown to promote to decrease adhesion of bacteri and biofilm accumulation.[26] Also it is noted margins of ceramic restorations with few tiny defects caused by machining procedures will lead retaining of more deposition and bacteria than a smooth finish line.[22]

Various kinds of ceramics may cause bacterial adhesion with different rates. Hahnel et al.[27] investigated surface properties of dental ceramics belonging to various ceramic groups, and correlated the outcomes to the first adherence of oral streptococcal strains. The lithium disilicate glass ceramic had the highest SR (Ra); the lowest values were found for the glass ceramic, the partially sintered zirconia and the hipped zirconia ceramic. It is concluded that dental ceramics have difference in terms of Ra, free energy and initial streptococcal adhesion; although, correlation between surface characteristics and adherence of streptococcus were poor.

Finishing and polishing methods may cause difference on biofilm formation. In a study[28] the effect of several surface finishing and polishing techniques on SR and *Streptococcus mutans (S. mutans)* adherence to resins and ceramic (VITABLOCS Mark II), was examined. As result,[28] SR were found significantly different according to the prosthetic material and surface treatments. On the other hand, no significance for interaction was noted between restorative materials and surface treatments. The highest SR values were found for indirect composite and it is followed by ceramic group. The lowest vital *S. mutans* adherence was observed in ceramic samples. So it can be said there is a positive correlation between SR and the vital *S. mutans* adhesion. Significant difference between bacterial adhesion of tested materials indicates that chemical composition of surface of the restorative material has important impact on bacterial adhesion. In contrast, porcelain restorations with glazing is indicated as the ideal. It is reported that surface with glazing may not be the smoothest all the time, and polished surface would be required for forming a smoother surface. Kawai et al.[29] approved glazed surface was always not the smoothest, according to Ra values which more plaque was accumulated on surfaces with glazing, in comparison to surfaces with polish (120 or 600 grit abrasive paper). This indicates that surface with glazing would not be clinically favourable biologically. Glaze may create an wavy and nonuniform surface that generally has irregularities, leading more bacterial adherence. Whereas polished surfaces were shown having voids and cracks on subsurface of ceramic, these defects have no effect on Ra or the quantity of plaque accumulation. As a result, samples polished with diamond pastes were found useful in forming a smoother surface which can avoid plaque accumulation. Other researchers[30] evaulated the effect of polishing on ceramic on initial oral biofilm accumulation for zirconium by using a scanning electron microscope after 20 minutes and 1 hour. Deposition of granular aggregations were found on all the samples for the two consecutive analyzes. Granular aggregates adhere stronger on nonuniform regions, and increase in thickness is observed after 1 hour. Bacterial morphology in any time of the research was not significantly different. Irregularities on surface of samples with glazing was found more than polished sample and presented larger tendency to dental biofilm accumulation.

Metal Alloys

Various alloys used in dental practice are basicly gold, nickel chrome and titanium. Prosthetic appliances are fabricated with inert alloys with polished surfaces to avoid the accumulation and attraction of micro-organism not to cause biofilm,[26] however some alloys' tendency is high to bacteria compared to others. It shows that some bacteria are attracted to electrical charges in some alloys. Alloys which contain and release copper and silver were noted to have higher antimicrobial activity than some base metal alloys. Eluates of the metals may have an effect on microorganisms. The mercury leaching in very small amounts have a bacteriostatic effect.[22,26] The relationship regarding adhesion of *Streptococcus mitis (S. mitis), S. mutans, Streptococcus oralis (S. oralis)* and *Streptococcus sanguinis (S. sanguinis)* on precious and non-precious alloys used in dentistry was examined by Grivet et al.[31] and bacterial adherence was found highest for the high gold-contaning alloy, and lowest for the non-precious alloy.

Cements

Gap between the teeth and the restoration is filled with dental cement. There may be few milimeters gap which is in interaction with oral liquids. This space may create ideal enviroment for bacterial adhesion and colonization. It is obvious, the existence of biofilm is only one of the features which can induce surface deterioration, other impacts are acidic fluid intake, temperature changes, or existence of liquid medium. It is noted that roughness of resins having larger filler molecules became lesser noticeably after biofilm maturation.[32]

In addition, effect of false, improper mixing ratios of various luting systems on adherence of *S. mutans* were evaulated.[33] Various tested luting cements displayed significantly different potentially in *S. mutans* adherence. Variations from recommended luting agent ratios cause significant alterations for quantity of adhered *Streptococci*.

Dentures

Polymers used in denture construction, such as acrylic resins, have more porous structure and defects on surface compared to metallic and ceramics restorative materials. Pores will be fulfilled by humidness which cause ideal incubation environment for some microorganisms. Biofilm on polymeric substances grows faster and is harder to elimiate completely. Acidic remnants caused by bacteria will make the surface irregular, that will led complications in elimination of biofilm.[22]

Acrylic Resin (Denture Base)

New areas for biofilm accumulation is formed by removable dentures, thus these areas cause increase in quantity of biofilm appreciably. An increased amount of of microorganisms changes the ecology of the cavum oris that may alter equilibrium between harmful and useful microorganisms in oral cavity. The mucosa which is directly in contact with the dentures are the most influenced sites, however the other soft tissues in the oral cavity are involved, too.[22] In addition, yeasts especially candida species are associated with denture base resins. Different candida species with some bacteria are indicated that are working synergistically for attaching to denture base resin or to each other.[26] Fungal species, like *Candida albicans (C. albicans)*, can grow with chemical or physical changes. Proliferations of *Candida* results in response by inflammation on the mucosa beneath the biofilm which is called "denture stomatitis".[22] Biofilm consisting yeasts are shown to be hard to eliminate associated with high adhesion capacity, because this ability has a close relationship with micro-porous structure of resin.[26]

The hard acrylic prosthesis may cause injuries and ulcerations on mucosa if dentures are not well-fitted. These ulcerated regions are habits for fungis and bacteria leading inflammatory response and pain. In addition, rests are attractive places for microorganism colonization.[22] Thus, all rules related denture should be obeyed in every single step of construction for creating dentures with gold standard.

Denture Liners

The liner biomaterials are made of self curing acrylic, polyvinyl siloxane, or acrylic including plasticizers. These prosthetic materials have porous structure than conventional acrylic and have more complications with inflammation caused by fungis. Dentist should be suspectible for *C. albicans* adhesion while using soft liners. Some soft denture liners, like polyamides have possibly lesser tendency for biofilm accumulation in comparison to acrylic resins related to lesser porosities.[22,26] In an study[34] SR were measured and adherence of *C. albicans* were studied before and after aging procedure of dentures relined with 3 different denture liners. The stimulated saliva was used for assesing effect of aging process on adherence. Non-aged and uncoated samples had not been found significantly different, but aged and uncoated soft liners were noted to have higher degree of *C. albicans* adhesion. Also, non-aged and coated liner samples had not been indicated as significantly different, on the other hand aged and coated biomaterials had higher affinity to *C. albicans* adhesion. It can be concluded that the usage of soft liners with uniform surface decrease the risk of *C. albicans* adhesion.

Dental Implants

There will always be gaps and crevices between small components of implant that are fixed together by small screw, forming a "greenhouse" for bacterias. Pathogenic bacteria in these areas may lead inflammatory response in the bone or affects osseointegration negatively. Also it is noted that rough titanium surface is adequate nish for fast bacterial growth and adhesion that titanium abutment usage is common in implant rehabilitation. It was concluded that surface energy and SR is directly proportional with the bacterial adhesion. So it can be said that plaque accumulation is more on titanium abutments compared to natural teeth that is why titanium have high surface energy. This disadvantage of titanium can be eliminated by good oral hygiene.[35]

Other alternative to titanium is zirconia abutments. Difference between adhesion tendencies of bacteria and several materials were reported. Researchers had compared the rates of bacteria on titanium and zirconium oxide samples. The test samples coated with bacteria on zirconia specimens were found significantly lesser in comparison to titanium samples. The results demonstrated that zirconium oxide is a good biomaterial for fabrication of implant abutments having lower colonization potential.[36] In a study,[37] polished partially stabilized zirconia (PZ), titanium blasted with zirconia (TBZ), TBZ then etched (TBZA), and polished titanium (PT- control) were analyzed by help of scanning electron microscope and profilometry. The zirconia and TBZ surface (TBZ surface) was found effective on titanium superiorly by decreasing the adherence of bacteria following pellicle coverage. Also, modified titanium with zirconia had been found to have same surface characteristics of pure zirconia in decreasing adherence of bacteria.

Chemical and Biological Methods to Control Oral Biofilms

Choosing proper mechanical and biological treatment options or usage of antimicrobial agents may be useful for avoiding biofilm formation and accumulation.

Acrylic Resins

Polishing and finishing techniques should be used and repeated regularly for achieving a SR under the threshold on polymers used in dentistry.[22] Also, modifying resins in alternative form of polyethylene, titanium dioxide coating and using denture cleansers were approved to be discouraging on the biofilm accumulation.[26] Inhibiting *C. albicans* on resins have significant role for prevention of denture stomatitis. The biological acceptance of a newly produced dental biomaterial having antifungal properties was examined by researchers.[38] The results demonsrated which PMMA-silver nanoparticles have significant reducing effect on *C. albicans* adhesion and have no effect on metabolism or proliferation. Even though the solutions containing silver nanoparticles had antifungal activity, Øilo and Bakken[22] noted no impact on *C. albicans* adhesion and biofilm accumulation following the addition of particles into resin. But, long term effecs of surface coatings or slow releasing molecules are uncertain. Coatings may be abrased, their roughness may increased and mechanical characteristics may decrease with time. So, further investigation is needed. Also, cleansing agents like Klorhex and Fittydent have been proposed as effective in prevention of Candida colonization rate on denture surfaces.[39]

Resin Composites

Decreased polymerization shrinkage of resins is thought to have lower rate of microleakage and thus the risk of secondary caries is reduced.[22] So, polymerization procedure should be performed ideally. On the other hand, several techniques for eliminating biofilm on biomaterials used in dentistry can be listed as addition of zinc oxide nanoparticles blend and/or chlorhexidine gluconate in some restorative biomaterials for enhancing the antibacterial activation and reducing growth of bacteria responsible from biofilm formation.[40]

CONCLUSION

Dental biofilm is a complex, organized bacterial community. So, elimination of microorganism from oral soft and hard tissues are a struggle either for patients or dentists. Although biofilm formed on dentures seems harmless, it may cause complex problems. Thus, dentist should be take in consideration the possibility of biofilm formation and should be careful in selection of restorative material and surface treatments for minimizing bacterial adhesion. Also patient should be informed about biofilm formation and routine oral hygiene methods to avoid plaque accumulation. Although the dental biofilm can not be removed it can be decreased with mechanical and chemotherapeutic oral hygiene methods. Further *in situ* studies are much needed to clarify, the role and mechanism of each surface parameter on oral biofilm formation and also especially antimicrobial strategies should be disscussed in upcoming researches.

MAIN POINTS

• Dental plaque is organized and this organized mass forms oral biofilm. Microorganisms that formed dental biofilm generally have harmless relation with host. But this oral condition may be changed negatively by environmental pertubations and restorative materials used for dental rehabilitation.

• Physical and chemical properties of prosthetic restorations, biomaterials and also interactions between them have strong impact on the formation of dental biofilm. So, the dentist should take in account either the composition of dental material or type of restoration while assesing treatment plan.

• There are several chemical and biological techniques which are used in controlling oral biofilm accumulation. Antibacterial agents usage, modification of polymers or titanium dioxide coating are some of the alternative methods used for minimizing plaque formation and thus oral biofilm growth. However, there is no enough data indicating ideal prosthetic material and technique which is effective for inhibition of bacterial adhesion.

Therefore, there is need for further researches based on development of antibacterial agents, techniques and prosthetic materials with ideal physical, microbiologic and chemical properties.

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REFERENCES

1. Kuramitsu HK, He X, Lux R, Anderson MH, Shi W. Interspecies interactions within oral microbiol communities. Microbiol Mol Biol Rev. 2007; 71(4): 653-70.
2. Coyte KZ, Schluter J, Roster KR. The ecology of the microbiome: networks, competition and stability. Science. 2015; 350(6261): 663-6.
3. Maddi M, Scannapieco FA. Oral biofilms, oral and periodontal infections, and systemic disease. Am J Dent. 2013; 26(6): 249-54.
4. Hoiby N. A short history of microbiol biofilms and biofilm infections. APMIS. 2017; 125(4): 272-5.
5. Flemming HC, Wingender J, Szewyk U, Stainberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. Nat Rev Microbiol. 2016; 14(9): 563-75.
6. Liaqat I, Liaqat M, Ali S, Al NM, Haneef U, Mirza SA, et al. Biofilm formation, maturation and prevention: A review. J Bacterial Mycol. 2019; 6(1): 1092.
7. Maksimova YuG. Microbiol biofilms in biotechnological process. Appl Biochem Microbiol. 2014; 50: 750-60.
8. Yu OY, Zhaols MG, Mei ML, Lo Ec, Chu CH. Dental biofilm and labarotory microbial culture models for cariology research. Dent J. 2017; 5(2): e21.
9. Larsen T, Fiehn N. Dental biofilm infections-an update. APMIS. 2017; 125(4): 376-84.
10. Steinberg D. Handbook of Bacterial Adhesion: Principles, Methods and Applications (Eds: Y.H. An, R.J. Friedman). Humana Press, Totawa NJ, 2000, p. 353-70.
11. Overmann PR. Bofilm: a new view of plaque. JCDP. 2000; 18-29.
12. Dige I, Raarup MK, Nyengaard JR, Killian M. Nyvad B. Actinomyces naeslundii in initial dental biofilm formation. Microbiology. 2009; 155 (7); 2116-26.
13. W.F. Lilijemark C, Bloomquist. Crit Rev Oral Biol Med. 1996; 7: 180-98.
14. Bentinez-Paez A, Belda-Ferre P, Simon-Soro A, Mira A. Microbiota diversity and gene expression Dynamics in human oral biofilms. BMC Genomics. 2014; 15: 311-23.
15. Park SJ, Han K_H, Park JY, Choi SJ, Lee KH. Influence of bacterial presence on biofilm formation of Candida albicans. Yonsei Med J. 2014; 55(2): 449-58.
16. AndreLuis Souza dos Santos, Galdını ACM, de Mello TP, Ramos LS, Branquinha MH, Bolognese M. What are the advantages of living in a commnity? A microbial perspective. Mem Inst Oswaldo Cruz. 2018; 113(9): e18021.
17. MSU, Manotana State University 2016. A biofilm primer: how biofilms form. Biofilms online.Available at http://www.biofilmsonline.com/cgi-bin/Biofilmsonline/edhowprimer.htmı.
18. Hall-Stooodley L and Stoodley P.Biofilm formation and the transmission of uman pathogens. Trends Microbiol. 2005; 13(1): 3-10.
19. Renner LD, Weibel DB. Physicochemical regulations of bioflim formaiton MRS Bull. 2011; 36(5): 347-55.
20. Sutherland I. Biofilm exopolysaccharides: a strong and sticky framework. Microbiology. 2001; 147(1): 3-9.
21. O'Toole GA, Kolter R. Flageller and twiching motility are necessary for Pseudoonas aeruginosa biofilm evelopment. Mol Microbiol. 1998; 20(21): 295-304.
22. Øilo M, Bakken V. Biofilm and Dental Biomaterials. Materials. 2015; 8: 2887-900.
23. Hao Y, Huang İ, Zhou X, Li M, Ren B, Peng, et al. Influence of Dental Prosthesis and Restorative Materials Interface on Oral Biofilms International Journal of Molecular Sciences Int J Mol Sci. 2018; 19: 3157.

24. Cazzaniga G, Ottobelli M, Ionescu A. Surface properties of resin-based composite materials and biofilm formation A review of the current literature. Am J Dent. 2015; 28: 313-20.

25. Bani M, Öztaş N. Cam iyonomer içerikli farklı restoratif materyallerin yüzey pürüzlülüklerinin değerlendirilmesi. Acta Odontologica Turcica. 2013; 30(1): 13-7.

26. Al Moaleem MM, Dorout IA, Elamin EF, Mattoo KA, Ghazali NAL. Biofilm Formation on Dental Materials in the Presence of Khat: Review. JSM Dent. 2017; 5(2): 1087.

27. Hahnel S, Rosentritt M, Handel G, Bürgers R. Surface characterization of dental ceramics and initial streptococcal adhesion in vitro. Dent Mater. 2009; 25: 969-75.

28. Aykent F, Yondem I, Ozyesil AG, Gunal SK, Avunduk MC, Ozkan S. Effect of different finishing techniques for restorative materials on surface roughness and bacterial adhesion. J Prosthet Dent. 2010; 103(4): 221-7.

29. Kawai K, Urano M, Ebisu S. Effect of surface roughness of porcelain on adhesion of bacteria and their synthesizing glucans. J Prosthet Dent. 2000; 83: 664-7.

30. Scotti R, Zanini Kantorski K, Scotti N, Monaco C, Valandro LF, Bottino MA. Early biofilm colonization on polished- and glazed-zirconium ceramic surface. Preliminary results. Minerva Stomatol. 2006; 55: 493-502.

31. Grivet M, Morrier JJ, Benay G, Barsotti O. Effect of hydrophobicity on in vitro streptococcal adhesion to dental alloys. J Mater Sci Mater Med. 2000; 11: 637-42.

32. Hannig C, Hannig M. The oral cavity--a key system to understand substratum-dependent bioadhesion on solid surfaces in man. Clin Oral Investig. 2009; 13(2): 123-39.

33. Buergers R, Hahnel S, Reischl U, Mueller R, Rosentritt M, Handel G, et al. Streptococcal adhesion to various luting systems and the role of mixing errors. Acta Odontol Scand 2009; 67(3): 139-45.

34. Bal BT, Yavuzyilmaz H, Yücel M. A pilot study to evaluate the adhesion of oral microorganisms to temporary soft lining materials. J Oral Sci. 2008; 50(1): 1-8.

35. Schmalz G, Garhammer P. Biological interactions of dental cast alloys with oral tissues. Dent Mater. 2002; 18(5): 396-406.

36. Scarano A, Piattelli M, Caputi S, Favero GA, Piattelli A. Bacterial adhesion on commercially püre titanium and zirconium oxide disks: an in vivo human study. J Periodontol. 2004; 75(2): 292-6.

37. Al-Radha AS, Dymock D, Younes C, O'Sullivan D. Surface properties of titanium and zirconia dental implant materials and their effect on bacterial adhesion. J Dent. 2012; 40(2): 146-53.

38. Acosta-Torres LS, Mendieta I, Nuñez-Anita RE, Cajero-Juárez M, Castaño VM. Cytocompatible antifungal acrylic resin containing silver nanoparticles for dentures. Int J Nanomedicine. 2012; 7: 4777-86.

39. Bidar M, Naderinasab M, Talati A, Ghazvini K, As-gary S, Hadizadeh B, et al. The Effect of Different Concentrations of Chlor-hexidine Gluconate on the Antimicrobial Properties of Mineral Trioxide Aggregate and Calcium Enrich Mixture. Dent Rese J. 2012; 9: 466-71.

40. Cheng L, Weir MD, Xu HH, Kraigsley AM, Lin NJ, Lin-Gibson S, et al. Antibacterial and physical properties of calcium-phosphate and calcium-fluoride nanocomposites with chlorhexidine. Dent Mater. 2012; 28(5): 573-83.

REVIEW

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Ligneous Periodontitis Associated with Plasminogen Deficiency: A Review of the Literature with Two Additional Cases

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Abstract

BACKGROUND/AIMS: Ligneous lesions are rare diseases characterized by fibrin deposition due to plasminogen deficiency and they may affect the mucosal areas as conjunctivae and gingiva. The course of this disease is progressive and typically results in early tooth loss. In this study, we aimed to evaluate the demographic, clinical, and histopathological features and treatment approaches for ligneous periodontitis lesions in the literature with additional cases of our own.

MATERIALS AND METHODS: Two patients, siblings, were referred to our clinic with nodular and fragile gingival overgrowth on both jaws. Brown-yellow gingival growths which were prone to bleeding and covered the teeth were observed. While one of the siblings received pharmaceutical treatment, the other received surgical treatment. A literature search was performed to congregate articles using the PubMed database based on the following terms: [(ligneous periodontitis) OR (ligneous)] OR [(ligneous periodontal disease)] AND [English (Language)]. Lesions which were not located on the gingiva were the exclusion criterion.

RESULTS: The literature review revealed 72 cases of ligneous gingival lesions during the years 1973-2020. All lesions found were classified in tables according to their characteristics, treatment approaches, recurrence rates, and follow-up periods. Ligneous lesions are rare diseases characterized by fibrin deposition due to plasminogen deficiency and they may affect the mucosal areas.

CONCLUSION: It has been reported that there is still no consensus on treatment for these lesions. More studies are needed in the future in order to provide effective periodontal treatment for cases of ligneous periodontitis.

Keywords: Ligneous periodontitis, ligneous gingivitis, plasminogen deficiency, treatment

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INTRODUCTION

Plasminogen is a proenzyme which is converted into active plasmin by plasminogen activators on the fibrin surface. Plasminogen plays an important role in many events, such as cell migration, angiogenesis, and fibrinolysis. It passes into the bloodstream in proenzyme form after being synthesized in the liver and turns into plasmin, the active enzyme format. During the healing of a wound surface, it activates the "tissue plasminogen activator" and thus leads to the destruction of the fibrin.[1] Mucosal areas acquire a coarse appearance due to the accumulation of fibrin in the absence of complete or partial plasminogen. For this reason, the term "ligneous", which means "woody" in Latin, is used.[2] The term "ligneous periodontitis" was first defined by Günhan et al.[3] as a periodontal disease characterized by membranous gingival overgrowth and severe bone loss due to the accumulation of amyloid-like material.

Plasminogen deficiency, which can be congenital or acquired, is characterized by the development of fibrin-rich pseudo-membranes on mucosal surfaces such as the mouth, eyes, nasopharynx, trachea, and genital mucosa as a result of impaired fibrin organization and delayed wound healing.[4]

Ligneous mucosal diseases are very rare (0.3-0.4%) autosomal recessive conditions characterized by fibrin deposition in the tissue due to plasminogen deficiency.[5] Generally, children are affected, but this disease can occur at any age.[6] Ligneous mucosal diseases may show involvement in several tissues. However, gingival and conjunctival involvements are often observed in childhood.[7]

Among these rare involvements, gingival tissue is a remarkable early sign which is characterized by asymptomatic gingival enlargement and severe periodontal tissue damage.[8] Local factors, such as poor oral hygiene, infections, irritations, and surgical procedures are predisposing factors in the formation of ligneous periodontal lesions.[9] The course of this disease is progressive and typically results in early tooth loss. In the hypoplasminogenemic condition, the rare periodontal disease, characterized by ulcerated gingival tissue and rapid tooth loss is defined as "destructive membranous periodontal disease" or "ligneous periodontitis".[10]

In this case report, we share the cases of two siblings with ligneous periodontitis and their long-term therapeutic results in order to (1) bring attention to and foster greater familiarity with the clinical and histopathologic features of this condition among dentists, which is essential for its timely diagnosis and management, and (2) review the literature for features and treatment options about this rare disease.

MATERIALS AND METHODS

Cases

The patients (18- and 21-year-old females) were referred to our clinic with nodular, fragile, and painless gingival overgrowth at the maxilla and mandible. Prior to their dental examination, they were also referred to the department of ophthalmology for various eyelid lesions and they were diagnosed with ligneous conjunctivitis. The conjunctival lesions were detected at 6 months in the younger sibling, and at 10 years in the older sibling.

Their medical examinations revealed hydrocephalus and respiratory distress for the younger sibling and vision loss in the left eye and bilateral hearing loss (30%) for the older sibling.

Both siblings were very similar in a clinical perspective in respect to the appearance and the extension of their ligneous lesions. The brown-yellow gingival overgrowths were prone to bleeding and covered the teeth (Figure 1). Radiographic examination showed severe bone destruction and floating teeth in both siblings (Figure 2). Since the older sibling could not get approval for general anesthesia due to hydrocephalus, she was treated using only pharmaceutical methods.[11] This treatment included 2% corticosteroid eye drops applied every 2 hours for 4 weeks for ligneous conjunctivitis and chlorhexidine mouthwash combined with systemic doxycycline for ligneous periodontitis. The younger sibling was operated on under general anesthesia with the support of the replacement of plasminogen. All overgrowth gingival tissue was

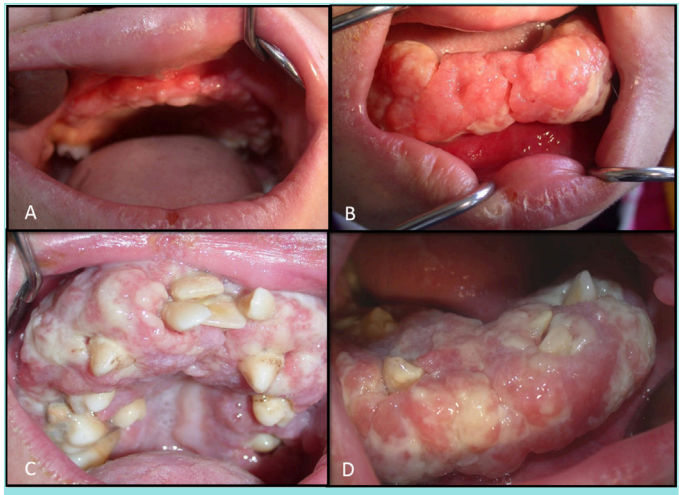

Figure 1. (A) Intraoral view of the older sibling's maxilla. (B) Intraoral view of the older sibling's mandible, (C) Intraoral view of the younger sibling's maxilla, (D) Intraoral view of the younger sibling's mandible.

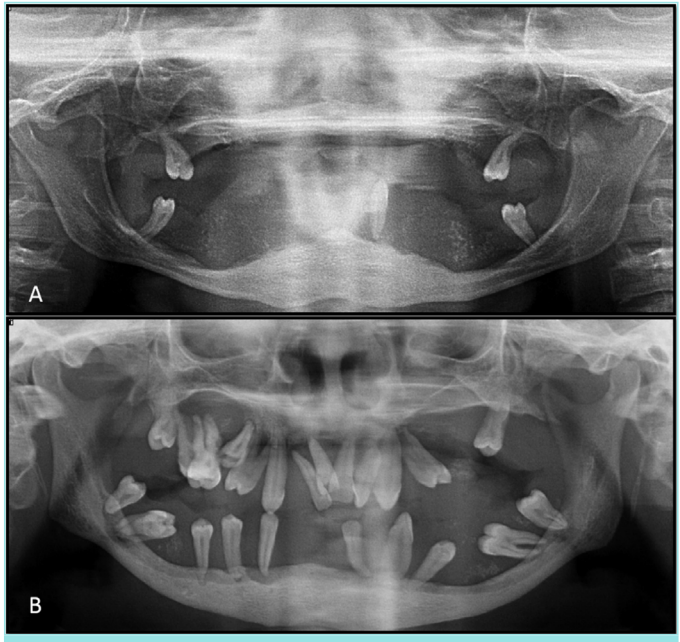

Figure 2. (A) The orthopantomograph of the older sibling. (B) The orthopantomograph of the younger sibling.

removed along with the teeth. After clinical healing was established, a total prosthesis was fabricated in order to restore/regain/maintain oral function and esthetics (Figure 3). Recurrence was observed at a 1-year follow-up. One of the siblings was treated with a combination of surgical and pharmaceutical treatment, and the other was given only pharmaceutical treatment because general anesthesia was contraindicated, yet recurrence was found in both.

The histological findings of our cases revealed acanthotic squamous epithelium showing hyperplasia on the surfaces, accumulation homogeneous eosinophilic fibrinous material deposition and inflammatory reactions around the underlying epithelium. These histological findings revealed ligneous periodontitis.

Literature Review

A literature search was performed to gather articles published in English using the PubMed database. The literature review was based on the following terms and words: (ligneous periodontitis) OR (ligneous periodontal disease) OR (ligneous gingivitis) OR (ligneous) AND [English (Language)]. We evaluated the features of ligneous lesions, including age, age at onset, gender, nationality, presence of consanguineous marriage, medical condition, oral findings, histopathological findings, affected organs other than the mouth, treatment, recurrence, and follow-up (Table 1, 2). Lesions which were not located in the gingiva were excluded.

RESULTS

Our PubMed search identified 31 articles and 72 cases with ligneous gingival lesions dating from 1973 to 2020. The demographic features of all reported cases are given in Table 1 and the characteristic features of all reported cases are given in Table 2. The treatment approaches with different success rates are listed in Table 3. In the literature, different treatment results were reported with varying success and recurrence rates. The recurrence and follow-up results are very important and these are summarized in Table 4.

DISCUSSION

Since ligneous periodontitis is a rare disease, it is usually presented as case reports in the literature. There are also reviews which focus on the genetic sequences and plasminogen levels of ligneous diseases.[4,12] Biopsy is the gold standard in the diagnosis of ligneous diseases. Fibrin deposition is diagnosed by hematoxylin, eosin staining, and a negative response to Congo Red. The patient is investigated systemically for plasminogen deficiency and ligneous disease is diagnosed after a biopsy.[9] Since there is no comprehensive review of the clinical features and treatment of cases, a literature review was needed regarding the clinical evaluations of this disease.

Figure 3. 1-year of post-operative follow-up of the younger sibling. (A) Clinical appearance, (B) Recurrence in the maxilla, (C) Intraoral image of the mandible.

Features of Population

As stated before, this condition may be congenital or acquired. The patients in the literature are reported with a wide age range (1 to 66 years old).

Plasminogen deficiency is an autosomal recessive disease caused by homozygous or compound heterozygous mutations of the plasminogen gene (PLG).[12] Plasminogen deficiency is a rare condition with autosomal recessive inheritance OMIM (Online Mendelian Inheritance in Man): 217090 and its incidence increases with the consanguineous marriage of parents. There are few articles focusing on this condition.[1,10,12-17] Our review is the first comprehensive review in which consanguineous marriage was questioned. Unfortunately, there was no data regarding consanguineous marriage in 44 out 74 cases. Furthermore, among 30 cases reporting on the presence of consanguineous marriage, only 19 cases were positive (1.7:1).

The Turkish population constitutes the majority of cases involving ligneous lesions in the literature.[1-3,10,13,16,18-22] In our review, focusing on gingival involvement, a total of 74 cases were included, and nearly half of them (30/74) were reported as being of Turkish origin (40.5%). It is estimated that the reason why many cases are seen in the Turkish population is due to the prevalence of consanguineous marriages, especially in rural areas.

In a genetic disorder with an autosomal recessive inheritance pattern, a female-to-male ratio of 1:1 is expected. However, according to the literature, the female/male ratio in ligneous lesions ranges from 1.4:1 to 2:1.[23] In a 2012 review in which only oral ligneous lesions were evaluated, the female/male ratio was reported to be 3.4:1 (77%).[24] Similarly, the female (n=55)/male (n=19) ratio was 2.89:1 (74.3%) in our review.

Clinical Features of Lesions

The characteristic clinical features of ligneous gingival lesions are solid, painless, nodular, fragile erythematous, hyperplastic, white-yellow fibrinous pseudomembrane-covered gingival enlargements involving the marginal and attached gingiva, generalized severe periodontal tissue destruction, and ulceration with generalized gross plaque accumulation.[3,10,12,25,26]

The intraoral clinical examination of our cases had characteristic clinical features as described above. The extension of the gingival overgrowth along with the severe periodontal tissue and alveolar bone destruction both in the maxilla and mandible had the tendency to bleed. A floating teeth appearance within the overgrowth tissue was observed.

Histological Features of Lesions

Early studies in the literature suggested that this disease was caused by a substance which accumulated in the eyes. This amyloid-like eosinophilic material was found to be fibrin. Subepithelial and perivascular fibrin deposition became the characteristic finding of this disease in later studies.[24]

Characteristic histological features in ligneous lesions are areas of ulceration and hyperkeratosis, acanthosis, granulation tissue formation, an amorphous, fibrin-rich, amyloid-like substance deposition due to insufficient fibrin degradation, subepithelial, and perivascular mixed inflammatory cell infiltrate as neutrophils, lymphocytes, and plasma cells.[12,13,19,27]

Other Involvements

Ligneous lesions can occur in all organs covered by mucous membranes. Initial studies of ligneous mucosal diseases focused on ligneous conjunctivitis, where the disease is more serious and disruptive. Severe hypoplasminogenemia often presents with ligneous conjunctivitis. The most frequently affected organs in the literature were reported as conjunctiva (81%) and gingiva (30%), respectively.[12,23,24] In more than 12% of the patients, hydrocephalus was also present.[28]

In parallel with the literature, the most frequently affected organs in our review were conjunctiva (60.8%), genital tract (17.5%), respiratory tract (14.8%), ear (10.8%), skin (4%), hydrocephalus (4%), vocal cords (2.7%), and peritoneum (1.3%).

Treatment Approaches

There is no clear-cut treatment regimen for the management of ligneous lesions.[4] Various pharmacuetical, surgical, or combined treatment approaches have been tried for these lesions, and most have been found to be successful. The clinician may prefer a more precise and effective treatment method by surgically removing the lesion, as in one of our cases, or consider a pharmaceutical approach in early lesions. In the surgical method, although the patient has postoperative pain, recurrence is expected to occur later as the lesion is eliminated.[1,12,19,29] The total number of cases which provided information about treatment was 55 out of all 74 cases. Surgical methods were preferred in 36.3% (n=20) of the reported cases with a 29.4% (n=5) success rate (no recurrence), whereas pharmaceutical methods were preferred in 43.6% (n=24) of the cases with a 64.2% (n=9) success rate; there are also combined (surgical + pharmaceutical) method reports found in 20% (n=11) of all cases with a 83.3% (n=5) success rate (Table 3).

Systemic or topical corticosteroids, systemic warfarin, low-dose doxycycline, chlorhexidine rinsing, cyclosporine A, PLG eye drops, PLG oral preparations, fresh frozen plasma eye drops, oral contraceptives, topical heparin, topical plasminogen, and azathioprine are some agents of these treatments.[3,4,14,17,19,26,27] The most popular agents preferred were antibiotics (doxycycline or tetracycline) with chlorhexidine rinsing.[3,12,19,21,27,30] However, it must be emphasized that evaluation of success is generally dependent on the initial response to any kind of treatment, including surgery.

Glu-plasminogen,[31] a new treatment method at the approval stage, achieved clinical efficacy and improved disease management by increasing patients' plasminogen levels. Glu-plasminogen is defined as the naturally circulating form of the plasminogen molecule. Plasmin is activated much more efficiently when bound to cells than in solution. This plasmin binds to plasminogen receptors and produces plasminogen. Thus, Glu-plasminogen therapy promises to increase patients' plasminogen levels. This promising treatment, whose effect on ligneous periodontitis lesions and its recurrence rate are not yet known, requires more studies and clinical trials.[32]

Table 1. Review of all reported cases of gingival ligneous lesions

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
1	Frimodt-Moller[33]	1973	4	14 months	F	ND	ND	Diffuse, hard thickening and redness of the eyelid	Recurrent mandibular mucosa swelling
2	Hidayat and Riddle[34]	1987	7	ND	F	ND	ND	ND	Membranous gingival swelling
3	Nüssgens and Roggenkämper[18]	1993	12	10	F	Turkish	ND	ND	Gingival hyperplasia
4	Günhan et al.[13]	1994	20	15	M	Turkish	Yes	Healthy	Diffuse and yellowish-pink gingival enlargement
5			20	ND	F	Italian	ND	No relevant past medical history and no other dermatologic disorder	Diffuse with pinkish, waxy, painless gingival overgrowth with no tendency to bleed
6			18	ND	M	Turkish	ND	No relevant past medical history, the family history was negative	Pinkish and pale, waxy, nodular gingival enlargement with no tendency to bleed
7	Gokbuget et al.[19]	1997	24	6 months for conjunctivitis	F	Turkish	ND	Mild hypochromasia	Generalized gingival swelling, ulcerated and friable
8			15	ND	M	Turkish	ND	ND	Generalized ulcerated gingival swelling and pain
9			10	ND	F	Turkish	ND	ND	Gross gingival swelling with ulcerated surface
10			4	ND	F	Turkish	ND	Iron deficiency anaemia due to poor dietary iron intake	Ulcerated gingival swelling around deciduous molars
11			10	ND	F	Turkish	ND	ND	Generalized gingival swelling
12	Schuster et al.[2]	1999	16	14	F	Turkish	ND	ND	Gingival hyperplasia

Table 1. continued

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
13	Günhan et al.[3]	1999	19	17	M	Turkish	ND	ND	Painless, nodular, fragile gingival enlargements, covered by white-yellow membranes
14			18	16	F	Turkish	ND	ND	
15			14	1 year for ligneous conjunctivitis	F	Turkish	ND	ND	Nodular, membranous, pale yellow to pink, fleshy gingival overgrowth
16	Scully et al.[35]	2001	35	10	F	United States	ND	ND	Ulcerated gingival swelling
17			8	5	F	United Kingdom	ND	ND	
18			31	12	M	Spain	ND	ND	
19			19	13	F	Turkish	ND	ND	
20			11	9	F	Turkish	ND	ND	
21			13	6	F	United States	ND	ND	
22	Watts et al.[14]	2002	5	2 years for ligneous conjunctivitis	F	Caucasian	No	ND	Gingival hyperplasia
23			18 months	1 month for ligneous conjunctivitis	M	Libyan	No	ND	Severe form of the disease with gingival involvement
24	Suresh et al.[8]	2003	59	53	F	ND	ND	Hypertension, miral valve prolapse, allergy to meperidine hydrocloride	Recurrent gingival hyperplasia with ulceration
25	Pantanowitz et al.[15]	2004	46	ND	F	Italian	No	Enlarged ovaries with multiple ovarian cysts	Gingival hyperplasia and multiple friable, white plaques; significant bone loss and loss of teeth
26	Baykul and Bozkurt[21]	2004	32	ND	F	Turkish	ND	Nodules, vaginal discharge, menstrual disorder and chronic conjunctivitis with acute attacks	Gingival membranous enlargement and periodontal tissue destruction
27	Silva et al.[30]	2006	9	8	M	ND	ND	ND	Painless nodular gingival enlargement with ulceration covered by yellowish pseudomembrane
28	Pierro et al.[26]	2006	12	ND	M	Italian	ND	Low functional plasminogen level, hyperextensibility, hypermobility of the limb joints, atrophic scars on knees, spontaneous ecchymoses, diagnosed as Ehlers-Danlos syndrome type VIII	Generalized gross plaque accumulation and a painless, massive, nodular fragile gingival enlargement with white-yellowish membranes, with a tendency to bleed
29	Tefs et al.[1]	2006	ND	10 years	F	U.S.	No	ND	ND
30		2006	ND	Childhood	F	Turkish	Yes	ND	ND
31		2006	ND	3 months	F	Turkish	Yes	ND	ND
32		2006	ND	Childhood	M	Turkish	Yes	ND	ND
33		2006	ND	Adolescence	M	Turkish	No	ND	ND
34		2006	ND	18 years	F	Turkish	Yes	ND	ND
35		2006	ND	24 years	F	Turkish	No	ND	ND
36		2006	ND	3 months	F	Brazil	ND	ND	ND
37		2006	ND	6 months	F	US	ND	ND	ND
38		2006	ND	Early childhood	F	US	No	ND	ND
39		2006	ND	Early childhood	F	US	No	ND	ND
40		2006	ND	3 days	M	Turkish	Yes	ND	ND
41		2006	ND	ND	M	Brazil	ND	ND	ND
42		2006	ND	20 days	F	Turkish	Yes	ND	ND
43		2006	ND	2 months	F	Turkish	Yes	ND	ND

Table 1. continued

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
44	Naudi et al.[36]	2006	46	Several years before	F	ND	ND	Systemically healthy, no known allergies, non-smoker	A granular, ulcerated, erythematous area on the alveolar ridge in the lower left molar region, 36-37 numbered teeth had been extracted several years previously
45	Karaer et al.[16]	2007	21	1 month for ligneous conjunctivitis	F	Turkish	Yes	Polipoidal growth on the vaginal wall and chronic conjunctivitis and had a malodorous vaginal discharge + dyspareunia	Gingival hyperplasia and ulceration
46	Kurtulus et al.[10]	2007	18	9	F	Turkish	No	Medical history was clear	Painless, massive, membranous, nodular and fragile gingival enlargement with bone loss
47	Baltacioğlu et al.[29]	2007	13	ND	F	ND	ND	Bilateral vesicoureteral reflux, phenytoin usage and suffered from delayed puberty and some hearing loss	Painless fragile nodular gingival enlargement covered with a yellow-white membrane
48		2007	15	10	F	ND	ND	90% visual loss in the right eye and 50% in the left eye owing to a condition	
49	Chi et al.[25]	2009	33	26	F	ND	ND	Chronic rhinosinusitis	Gingival inflammation due to poor oral hygiene, ulceration, whitish yellow pseudomembrane
50	El-Darouti et al.[9]	2009	12	9	F	ND	ND	No medical history of disease	Painless gingival swelling, massive alveolar bone loss, lips swelling
51	Fine et al.[27]	2009	52	13	F	ND	ND	History of infertility, and was diagnosed with ligneous cervicitis	Multiple, tender firm ulcerated nodular growths, gingival pain, loss of several teeth.
52	Cha et al.[37]	2011	66	ND	F	ND	ND	Hypertension, peripheral neuropathy, mild arthritis and glaucoma in her left eye	Ulcerated interdental papilla between the right first and second lower molars with significant gingival enlargement and inflammation, exhibited loss of stippling and an uneven hypertrophic surface right above the right upper central incisor with bleeding on palpation
53	Neering et al.[22]	2015	17	9	F	Turkish	ND	Type I PLG deficiency, severe pneumonia and hematocolpos	Generalized increased pocket, tooth mobility, gingival hyperplasia
54	Kızılocak et al.[17]	2017	11	6 months	F	ND	Yes	Cervicovaginitis, hydrocephaly	Ligneous gingivitis, tooth loss
55			12	2 months	F	ND	Yes	Hydrocephaly, mental retardation, deafness, cervicovaginitis	Ligneous gingivitis
56			3	10 days	F	ND	Yes	ND	Ligneous gingivitis
57			3	3	M	ND	No	Deafness, hydrocephaly	Ligneous gingivitis
58			7	2	M	ND	No	ND	Ligneous gingivitis
59			8	3	F	ND	Yes	Severe pulmonary disease	Ligneous gingivitis
60			4	3	M	ND	Yes	ND	Ligneous gingivitis, tooth loss
61			1	4 months	F	ND	Yes	ND	Ligneous gingivitis
62			7 months	10 days	F	ND	Yes	ND	Ligneous gingivitis
63			24	4	M	ND	Yes	ND	Ligneous gingivitis
64	Ertas et al.[38]	2017	6	4	F	ND	ND	White membrane surrounding in the lower and upper eyelids mucosa	Nodular symptomatic gingival hypertrophy and ulceration around the molar site

Table 1. continued

No	Authors	Publication year	Age	Age at onset	Gender	Patient's origin	Consanguineous marriage	Medical condition	Oral findings
65	Shapiro et al.[31]	2018	24	ND	F	ND	ND	ND	Gingival lesions
66			37	ND	F	ND	ND	ND	Gingival lesions
67			33	ND	M	ND	ND	ND	Gingival lesions
68			42	ND	F	ND	ND	ND	Gingival lesions
69	Sartori et al.[4]	2019	43	Childhood	F	ND	ND	Ligneous conjunctivitis, pseudomembranes on vocal cords, ligneous pseudomembranes on uterine cervix	Ligneous mucositis, multiple nodular gingival lesions
70	Malthiery et al.[39]	2019	35	25	F	Turkish	ND	Cervical lymphadenopathy in the right side, bilateral early stage of ligneous conjunctivitis with no pseudomembranes	Gingival granulomatous masses and whitish neck proliferations
No	**Authors**	**Publication year**	**Age**	**Age at onset**	**Gender**	**Patient's origin**	**Consanguineous marriage**	**Medical condition**	**Oral findings**
71	Sadasivan et al.[12]	2020	26	15	M	ND	Yes	Ulticystic hydrocephalus which was drained by ventriculoperitoneal shunt, profuse granulomatous growth in conjunctiva in both eyes, plasminogen activity <5%	Solid, nodular, fragile erythematous and hyperplastic gingival enlargements involving the marginal and attached gingiva and severe periodontitis, white-yellow fibrinous pseudomembranes
72	MacPherson et al.[40]	2020	14	ND	M	ND	ND	Systemically healthy, no history of any medical conditions	Multiple, exophytic, ulcerated masses of soft tissue resembling granulation tissue of the posterior mandibular aspects of the gingiva
73	Kayhan et al.	2001	18	3 months	F	Turkish	Yes	Low functional plasminogen level, hydrocephalus	Generalized nodular, fragile, painless, gingival overgrowth covered by brown-yellow pseudomembranes with severe periodontal tissue destruction on both the maxilla and mandible with a tendency to bleed
74		2001	21	ND	F	Turkish	Yes	Low functional plasminogen level, visual loss in the left eye and bilateral hear loss (30%)	

Recurrence Rates According to the Treatment Approaches

The total number of patients for whom information about recurrence was available was 37. The reported recurrence rate was 50%, and there was no information about recurrence in 37 of them. Recurrence was observed in 48.6% (n=18) of all 37 cases. No information was reported about recurrence in 3 out of 20 cases who were treated surgically, while recurrence was observed in 70.5% (n=12) of the remaining 17 patients, and recurrence was not observed in 29.4% (n=5) of them. No information about recurrence was reported in 10 out of 24 patients who were treated with pharmaceuticals, recurrence was observed in 35.7% (n=5) of 14 patients, and recurrence was not observed in 64.2% (n=9) of them. There is a gap regarding recurrence among 5 out of 11 patients who were treated with the combined method, and recurrence was observed in 16.6% (n=1) out of 6 (Table 3). The rate of recurrence seems to be higher in those cases treated only surgically when the follow-up period is not considered.

Follow-up Periods According to the Treatment Approaches

The follow-up periods were classified into three groups in order to estimate the long-term success of treatment modalities given in the literature. The categories were determined as: up to one-year, 1-3 years, and more than 3 years. Considering the follow-up periods according to treatment approaches, no information was reported about the follow-up periods in 11 out of 20 cases who were treated with surgery, and follow-up rates were 22.2% (n=2) for up to one year, 66.6% (n=6) for 1-3 years, and 11.1% (n=1) for more than 3 years in 9 cases. The recurrence rate in surgically treated patients with follow-up information was 66.6% (n=6).

No information was provided in 21 out of 24 cases who were treated pharmaceutically, and follow-up data was only given for 33.3% of 3 cases (n=1) up to 1 year, and 66.6% of them (n=2) for more than 3 years. The recurrence rate of pharmaceutically treated (antibiotics) cases with follow-up information was 100% (n=3).

The follow-up period was not reported for 7 out of all 11 patients who were treated with the combined method. There was no case followed up to 1-year, the follow-up rate in 1-3 years was 75% (n=3), and more than 3 years was 25% (n=1) out of the 4 patients. No recurrence was reported among those patients with follow-up information for the combined method, and the success rate was 100% (n=3) (Table 4).

Table 2. Features of all reported cases of gingival ligneous lesions

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
1	Frimodt-Moller[33]	ND	Conjunctivae	Surgical excision, extraction and antibiotic therapy	Disease disappeared after dental extraction	3 years
2	Hidayat and Riddle[34]	Subepithelial, eosinophilic, amorphous material; hyperpermeable blood vessels	Conjunctiva, vocal cords, larynx, trachea, vagina, cervix	Multiple surgical excisions	ND	ND
3	Nüssgens and Roggenkämper[18]	ND	Conjunctivae; occlusive hydrocephalus	Excision of gingival lesions	ND	ND
4	Günhan et al.[13]	Areas of ulceration, granulation tissue, subepithelial inflammatory infiltration and amorphous nodular deposits of a homogeneous, eosinophilic substance beneath the gingival squamous epithelium.	ND	Unsuccessful periodontal treatment, lost all teeth	No recurrence was found in two years follow-up	2 years
5			ND	ND	ND	ND
6			Conjunctivae	ND	ND	ND
7	Gokbuget et al.[19]	Hyperplastic epithelium; focal areas of ulceration. Moderate chronic inflammatory cell infiltrates and deposits of hyalinized eosinophilic fibrin in the connective tissue.	Conjunctivae	A detailed professional oral hygiene care + long-term systemic tetracycline + chlorhexidine + gingivectomy	ND	ND
8					ND	ND
9			ND		ND	ND
10			ND		ND	ND
11			Conjunctivae		ND	ND
12	Schuster et al.[2]	ND	Conjunctivae; occlusive hydrocephalus	ND	ND	ND
13	Günhan et al.[3]	Subepithelial, homogeneous, eosiniphilic, sometimes mineralized, amyloid-like material.	Conjunctivae; ear; kidney	Subgingival curettage, gingivectomy, chlorhexidine rinsing, antibiotics	Rapid regrowth after excision	1 year
14			Conjunctivae; delayed puberty			1 year
15			Conjunctivae	Gingivectomy	Recurrence 3 months after excision	3 months
16	Scully et al.[35]	Ulcerated surface epithelium and subepithelial eosiniphilic infiltrates containing fibrin	Larynx; genital tract; eye	ND	ND	5 years
17			ND	ND	ND	5 years
18			ND	ND	ND	5 years
19			ND	ND	ND	5 years
20			ND	ND	ND	5 years
21			ND	ND	ND	5 years
22	Watts et al.[14]	Focally atrophic thickened epithelium with subepithelial focal necrosis, fibrinous eosinophilic exudates, amorphous eosinophilic debris, and acute and chronic inflammatory cells fibrin and fibrovascular tissue infiltrated with lymphocytes, plasma cells, neutrophils, and eosinophils.	Conjunctivae; respiratory tract	ND	ND	ND
23			Conjunctivae; occlusive hydrocephalus	Corticosteroid drops and surgical debridement + cyclosporin A	No recurrence	1 year
24	Suresh et al.[8]	Surface ulceration; large subepithelial deposits of eosinophilic material	ND	Surgical excision	Recurrence of asymptomatic lesions several times.	ND
25	Pantanowitz et al.[15]	Reactive squamous epithelium with subepithelial eosiniphilic fibrin deposition, acanthosis and focal inflammation	Genital tract; infertility; middle ear	ND	ND	ND
26	Baykul and Bozkurt[21]	ND	Conjunctivae; genital tract	Subgingival curettage, gingivectomy, chlorhexidine rinsing and antibiotics in the past. Extraction of all mobile teeth	Conservative treatments were unsuccessful; regression after teeth extraction	3 years
27	Silva et al.[30]	Hyperplastic epithelium, large subepithelial eosinophilic deposits of fibrin-like material	Eye; conjunctivae; skin; polydactylia	Gingivectomy followed by chlorhexidine and dexamethasone elixir; topical and systemic heparin; topical and systemic corticosteroids	No efficacy of chlorhexidine and heparin protocols. Complete remission after corticosteroid therapy	3 years

Table 2. continued

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
28	Pierro et al.[26]	Areas of ulceration, granulation tissue, subepithelial inflammatory infiltration, amorphous nodular deposits of a homogeneous, eosinophilic substance beneath the gingival squamous epithelium	Conjunctivae	Topical plasminogen, together with periodontal therapy	ND	ND
29	Tefs et al.[1]	ND	Gingiva; larynx; vagina	Surgical removals every 6 to 12 weeks; heparin shots after surgeries; warfarin, sodium daily; Fluticasone propionate and salmeterol twice daily	Fluticasone propionate and salmeterol successful almost 3 years since any surgery on vocal cords, voice improved.	ND
30		ND	Gingiva	ND	ND	ND
31		ND	Conjunctiva; gingiva; colloid millium	ND	ND	ND
32		ND	Gingiva, eyelid lesions	ND	ND	ND
33		ND	Gingiva	ND	ND	ND
34		ND	Gingiva	Gingivectomy	Without any success; lost all of her teeth	ND
35		ND	Conjunctiva; gingiva	Gingivectomy	Without any success; lost all of her teeth	ND
36		ND	Conjunctiva; gingiva	ND	ND	ND
37		ND	Gingiva; ears	Warfarine sodium heparin mouthwash - no longer using	ND	ND
38		ND	Gingiva	Oral steroids	ND	ND
39		ND	Gingiva	Oral steroids	ND	ND
40		ND	Conjunctiva; gingiva	Topical cyclosporin; chemotrypsin; eye drop with antibiotic	ND	ND
41		ND	Gingiva; Ehlers-Danlos syndrome	ND	ND	ND
42		ND	Conjunctiva; gingiva	Excision of the membranes in the eyes many times + gingivectomy of the mouth lesions	Recurrences occurred	ND
43		ND	Conjunctiva; gingiva	Excision of the membranes in the eyes many times + gingivectomy of the mouth lesions	Recurrences occurred	ND
44	Naudi et al.[36]	Lightly keratinized epithelium, which was atrophic in parts and acanthotic in others, non-specific chronic ulceration area, a scattered chronic inflammatory cell infiltrated within the areas of hyalinization of upper lamina propria	Gingiva	Incisional biopsy	The lesion remained unchanged	3 months
45	Karaer et al.[16]	Massive deposition of amorphous eosinophilic material	Conjunctivae; genital tract	Ethinil estradiol and gestoden combination	ND	ND
46	Kurtulus et al.[10]	Subepithelial homogeneous eosinophilic deposits, inflammatory infiltration	ND	SRP, gingivectomy, chlorhexidine, topical heparin and corticosteroids	Recurrence	ND
47	Baltacioğlu et al.[29]	Intense acute inflammation, subepithelial fibrin accumulation	Conjunctivae; ear	Gingivectomy every 3 months	Recurrence	ND
48			Conjunctivae	Cyclosporine for ligneous conjunctivitis; gingivectomy every 2 months, dental extractions	Partial regrowth even after dental extraction	ND
49	Chi et al.[25]	Subepithelial and perivascular deposits of eosinophilic material, ulceration, chronic inflammation	Genital tract, peritoneum, paranasal sinuses	ND	ND	ND
50	El-Darouti et al.[9]	Epithelial hyperplasia, subepithelial and perivascular fibrin deposition	Conjunctivae	ND	ND	ND
51	Fine et al.[27]	Hyperkeratosis, epithelial eosinophilic deposition, focal inflammation, acanthosis	Genital tract	Surgical excision, chlorhexidine mouth rinses, low-dose doxycycline and warfarin daily	No recurrence, no increased tooth mobility	3.5 years

Table 2. continued

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
52	Cha et al.[37]	Inflamed multiple fragments of fibrous tissue surfaced in orthokeratinized-stratified squamous epithelium, which exhibited significant thickening of the spinous cell layer, the majority of fibrous connective tissue by the deposition of an amorphous, amyloid-like material	Gingiva	Improvement of oral hygiene, scaling, root planing, gingival curettage and dexamethasone elixir rinse two to three times daily	Partial improvement of soreness, inflammation, and discontinuation of gingival bleeding within 1 year	1 year
53	Neering et al.[22]	A reactive squamous epithelial hyperplasia with localized fibrin precipitation and massive ulcerations	Conjunctivitae, middle ear, respiratory tract, vagina	Periodontal treatment, full mouth disinfection, antibiotics	Supra- and subgingival debridement in every three months	3.5 years
54	Kızılocak et al.[17]	ND	Conjunctivitae, vagina	Eye surgery, FFP IV, cyclosporin	ND	ND
55		ND	Conjunctivitae, vagina, ear	Eye surgery, FFP IV, cyclosporin, FFP eye drops	No response	ND
56		ND	Conjunctivitae	Eye surgery 3 times, FFP IV, cyclosporin, betadin, dexamethason	Clinical benefits	ND
57		ND	Conjunctivitae, ear	FFP eye drops	No response	ND
58		ND	Gingiva	Mouth hygiene theraphy	Clinical benefits	ND
59		ND	Conjunctivitae, respiratory tract	FFP IV + bronchial FFP	Response to FFP	ND
60		ND	Gingiva	Mouth hygiene theraphy	ND	ND
61		ND	Conjunctivitae, gingiva	Eye surgery 8 times, FFP IV, cyclosporin, FFP eye drops	Response to FFP	ND
62		ND	Conjunctivitae, gingiva	Eye surgery 6 times, FFP IV, cyclosporin, FFP eye drops	Response to FFP	ND
63		ND	Conjunctivitae, gingiva	Eye surgery 5 times, FFP IV, cyclosporin, FFP eye drops	ND	ND
64	Ertas et al.[38]	Hyperplastic changes in the epithelium, extensive intraepithelial neutrophilic infiltration and eosinophilic fibrinoid accumulation between the basal membranes	Conjunctivitae, gingiva	Extraction of the tooth, gingivectomy	ND	ND
65	Shapiro et al.[31]	ND	Gingiva, bronchus	Plasminogen replacement therapy	Resolution	ND
66		ND	Conjunctivitae, gingiva, bronchus, nares		Resolution	ND
67		ND	Conjunctivitae, gingiva, skin, palmar and plantar wounds		Improvement	ND
68		ND	Conjunctivitae, gingiva, tumors, palmar warts		Improvement	ND
69	Sartori et al.[4]	Granulation tissue formation due to insufficient fibrin degradation, resulting in the formation of an amorphous, fibrin-rich, amyloid-like substance accumulated in the lamina propria	Conjunctivitae, vocal cords, uterine cervix	Tooth extraction+ a second-stage surgery using diode laser without raising a flap	Nodular gingival lesions due to plasminogen deficiency and the progression of marginal gingivitis to periodontal irreversible lesions	1 year
70	Malthiery et al.[39]	Deposition of amorphous eosinophilic Congo red negative material	Conjunctivitae, gingiva	Rivaroxaban treatment	ND	ND
71	Sadasivan et al.[12]	Parakeratinised stratified squamous surface epithelium with anastomosing rete ridges in association with a fibrovascular connective tissue. The connective tissue showed subepithelial deposits of homogenous eosinophilic material that resembled amyloid. The deeper parts of the connective tissue showed a diffuse mixed inflammatory cell infiltrate comprised predominantly of neutrophils, lymphocytes, and plasma cells.	Conjunctivitae, progressive blindness of the left eye	Supra and subgingival debridement + Oral hygiene instructions + CHX + Surgical excision	Recurrence of the lesion was seen after 3 months	ND

Table 2. continued

No	Authors	Histopathological findings	Affected organs	Treatment	Recurrence	Follow-up
72	MacPherson et al.[40]	Prominent spongiosis and acanthosis of the surface epithelium, granulation tissue, surface erosion, and pools of eosinophilic material located subepithelially	ND	Chlorhexidine mouthwash	Generally stable and fluctuation in the severity of the lesions	Every 6 months
73	Kayhan et al.	The patient was inoperable due to severe hydrocephalus	Conjunctivae, respirotary tract	Medical treatment	Recurrence reported	10 years
74		Acanthotic squamous epithelium showing hyperplasia in the surfaces, accumulation homogeneous eosinophilic fibrinous material deposition and inflammatory reactions around the underlying epithelium	Conjunctivae, ears	Gingivectomy	Recurrence at 1-year follow-up	10 years

Table 3. Distribution of patients according to treatment approaches and presence of recurrence

Treatment approach	(n)	Recurrence (+)	Recurrence (-)	ND
ND (E/A)	19 (10/9)	-	-	-
Surgical (E/A)	20 (8/12)	12 (3/9)	5 (3/2)	3 (2/1)
Medical (E/A)	24 (8/16)	5 (1/4)	9 (6/3)	10 (1/9)
Combined (surgical + medical) (E/A)	11 (5/6)	1 (0/1)	5 (4/1)	5 (1/4)

ND: no data, E: early lesions, A: advanced lesions.

Table 4. Distribution of patients according to treatment and follow-up periods

Follow-up period	Recurrence	Surgical treatment	Medical treatment	Combined treatment	ND
Up to 1 year	1	2	1	-	-
1-3 years	3	6	-	3	-
>3 years	2	1	2	1	6
ND	11	11	21	7	13
Total	17	20	24	11	19

ND: no data.

As stated in the literature, the follow-up period for most cases is between 1-3 years, and in many cases, the follow-up period was not reported. Since the recurrence rate is high regardless of the treatment, the follow-up of these cases is one of the most important stages of the treatment process.

Recurrence rates for advanced lesions were higher than early lesions in all treatment approaches. The advance of the lesion may be a factor which increases the recurrence rate. Clinicians may prefer the pharmaceutical method for early-stage ligneous periodontitis and the combined method which includes both pharmaceutical and surgical treatment for advanced ligneous periodontitis.

Based on the literature and the cases followed, the plasminogen values of individuals should be followed, especially if there is consanguineous marriage in their history. Patients should be followed up by an ophthalmologist and dentist regularly, and treatment should be started as soon as any eye or gingival lesion occurs. If oral ligneous lesions occur, the clinician should keep the patient's oral hygiene at a maximum level in order to keep the patient's teeth functioning longer and slow bone loss, and also clean any lesions as much as possible at each appointment in order to create cleanable surfaces for the patient.

The primary goal of clinicians in treating oral ligneous lesions is to keep teeth in the mouth or to improve the patient's quality of life with a prosthesis which can facilitate the chewing function.

As a treatment approach in oral ligneous lesions, pharmaceutical methods can be used in early lesions and surgical methods in advanced cases. However, it can be said that there is no consensus on the treatment of oral ligneous lesions with a low recurrence rate based on the cases in which different treatments and recurrence rates have been reported in the literature. The possibility of recurrence should be considered for all treatment options.

CONCLUSION

Ligneous lesions are rare diseases characterized by fibrin deposition due to plasminogen deficiency and may affect the mucosal areas. Regular follow-up and maximum oral hygiene are essential for the maintenance of these lesions. The main purpose of this study was to inform clinicians about the features and treatment options for these lesions, although this was not fully achieved due to a lack of long-term follow-up and recurrence reports in the literature. Future studies on ligneous periodontitis lesions which investigate the host response with long-term clinical follow-up can be performed.

MAIN POINTS

- Ligneous lesions are rare and hard-to-manage lesions with high recurrence rates. Therefore, we aimed to present our two cases with a literature review including the features and treatment options of ligneous gingival lesions in this study.
- Ligneous lesions are autosomal recessive conditions characterized by impaired fibrin organization due to plasminogen deficiency. These lesions affect organs covered by mucous membranes such as the conjunctiva, gingiva and genital tract.

• Although there is no consensus about the treatment of ligneous lesions, both pharmceutical and surgical approaches may regress them, however, their recurrence rate is very high.

• Ligneous gingival lesions affect the quality of life and clinicians may not have a good command of their management. Although there is no definitive treatment, the pharmaceutical approach may be preferred in early lesions and radical surgery may be preferred in advanced cases. Regardless of the treatment approach, regular follow-up and maintenance of oral hygiene are essential.

ETHICS

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.B.K., B.B., Design: K.B.K., R.B.K.Ü., Supervision: K.B.K., T.Ç., Materials: K.B.K., B.B., T.Ç., Data Collection and/or Processing: K.B.K., B.B., T.Ç., Analysis and/or Interpretation: R.B.K.Ü., Literature Search: R.B.K.Ü., Writing: K.B.K., R.B.K.Ü., Critical Review: T.Ç.

DISCLOSURES

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REFERENCES

1. Tefs K, Gueorguieva M, Klammt J, Allen CM, Aktas D, Anlar FY, et al. Molecular and clinical spectrum of type I plasminogen deficiency: A series of 50 patients. Blood. 2006; 108(9): 3021-6.
2. Schuster V, Seidenspinner S, Zeitler P, Escher C, Pleyer U, Bernauer W, et al. Compound-heterozygous mutations in the plasminogen gene predispose to the development of ligneous conjunctivitis. Blood. 1999; 93(10): 3457-66.
3. Günhan O, Günhan M, Berker E, Gurgan CA, Yildirim H. Destructive membranous periodontal disease (Ligneous periodontitis). J Periodontol. 1999; 70(8): 919-25.
4. Sartori MT, Sivolella S, Di Pasquale I, Saggiorato G, Perini A, Boscaro F, et al. Prophylactic protocol for dental care in ligneous gingivitis due to severe plasminogen deficiency: Case report and review of literature. Haemophilia. 2019; 25(4): 693-8.
5. Tefs K, Georgieva M, Seregard S, Tait CR, Luchtman-Jones L, Ziegler M, et al. Characterization of plasminogen variants in healthy subjects and plasminogen mutants in patients with inherited plasminogen deficiency by isoelectric focusing gel electrophoresis. Thromb Haemost. 2004; 92(2): 352-7.
6. De Cock R, Ficker LA, Dart JG, Garner A, Wright P. Topical heparin in the treatment of ligneous conjunctivitis. Ophthalmology. 1995; 102(11): 1654-9.
7. Toker H, Toker MI, Goze F, Turgut M, Yilmaz A. A ligneous periodontitis and conjunctival lesions in a patient with plasminogen deficiency. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007; 103(6): e35-8.
8. Suresh L, Aguirre A, Kumar V, Solomon LW, Sielski EA, Neiders ME. Recurrent recalcitrant gingival hyperplasia and plasminogen deficiency: a case report. J Periodontol. 2003; 74(10): 1508-13.
9. El-Darouti M, Zayed AA, El-Kamah GY, Mostafa MI. Ligneous conjunctivitis with oral mucous membrane involvement and decreased plasminogen level. Pediatr Dermatol. 2009; 26(4): 448-51.
10. Kurtulus I, Gokbuget A, Efeoglu A, Cintan S, Tefs K, Schuster V, et al. Hypoplasminogenemia with ligneous periodontitis: a failed local therapeutic approach. J Periodontol. 2007; 78(6): 1164-75.
11. Weinzierl MR, Collmann H, Korinth MC, Gilsbach JM, Rohde V. Management of hydrocephalus in children with plasminogen deficiency. Eur J Pediatr Surg. 2007; 17(2): 124-8.
12. Sadasivan A, Ramesh R, Mathew DG. Ligneous Periodontitis in a Patient with Type 1 Plasminogen Deficiency: A Case Report and Review of the Literature. Case Rep Dent. 2020; 2020: 5680535.
13. Günhan O, Celasun B, Perrini F, Covani U, Perrini N, Ozdemir A, et al. Generalized gingival enlargement due to accumulation of amyloid-like material. J Oral Pathol Med. 1994; 23(9): 423-8.
14. Watts P, Suresh P, Mezer E, Ells A, Albisetti M, Bajzar L, et al. Effective treatment of ligneous conjunctivitis with topical plasminogen. Am J Ophthalmol. 2002; 133(4): 451-5.
15. Pantanowitz L, Bauer K, Tefs K, Schuster V, Balogh K, Pilch BZ, et al. Ligneous (pseudomembranous) inflammation involving the female genital tract associated with type-1 plasminogen deficiency. Int J Gynecol Pathol. 2004; 23(3): 292-5.
16. Karaer A, Mert I, Akinsu F, Tug M, Tefs K, Schuster V, et al. Ligneous inflammation involving the female genital tract. J Obstet Gynaecol Res. 2007; 33(4): 581-4.
17. Kızılocak H, Ozdemir N, Dikme G, Koç B, Atabek AA, Çokuğraş H, et al. Treatment of plasminogen deficiency patients with fresh frozen plasma. Pediatr Blood Cancer. 2018; 65(2). doi: 10.1002/pbc.26779.
18. Nüssgens Z, Roggenkämper P. Ligneous conjunctivitis. Ten years follow-up. Ophthalmic Paediatr Genet. 1993; 14(3): 137-40.
19. Gokbuget AY, Mutlu S, Scully C, Efeoglu A, Porter SR, Speight P, et al. Amyloidaceous ulcerated gingival hyperplasia: a newly described entity related to ligneous conjunctivitis. J Oral Pathol Med. 1997; 26(2): 100-4.
20. Scully C, Gokbuget A, Kurtulus I. Hypoplasminogenaemia, gingival swelling and ulceration. Oral Dis. 2007; 13(6): 515-8.
21. Baykul T, Bozkurt Y. Destructive membranous periodontal disease (ligneous periodontitis): a case report and 3 years follow-up. Br Dent J. 2004; 197(8): 467-8.
22. Neering SH, Adyani-Fard S, Klocke A, Ruttermann S, Flemmig TF, Beikler T. Periodontitis associated with plasminogen deficiency: a case report. BMC Oral Health. 2015; 15: 59.
23. Schuster V, Seregard S. Ligneous conjunctivitis. Surv Ophthalmol. 2003; 48(4): 369-88.
24. Sivolella S, De Biagi M, Sartori MT, Berengo M, Bressan E. Destructive membranous periodontal disease (ligneous gingivitis): a literature review. J Periodontol. 2012; 83(4): 465-76.
25. Chi AC, Prichard E, Richardson MS, Rasenberger KP, Weathers DR, Neville BW. Pseudomembranous disease (ligneous inflammation) of the female genital tract, peritoneum, gingiva, and paranasal sinuses associated with plasminogen deficiency. Ann Diagn Pathol. 2009; 13(2): 132-9.
26. Pierro VS, Vazquez-Sullca R, Vieira AS, Takiya CM, Carakushansky G, Feres-Filho EJ. Ligneous periodontitis and Ehlers-Danlos syndrome. J Periodontol. 2006; 77(1): 123-8.
27. Fine G, Bauer K, Al-Mohaya M, Woo SB. Successful treatment of ligneous gingivitis with warfarin. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 107(1): 77-80.
28. Schuster V, Hügle B, Tefs K. Plasminogen deficiency. J Thromb Haemost. 2007; 5(12): 2315-22.

29. Baltacioğlu E, Akalin FA, Topaloğlu E, Süküroğlu E, Cobanoğlu U. Ligneous periodontitis and gingival antioxidant status: report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007; 104(6): 803-8.

30. Silva GB, Bariani C, Mendonca EF, Batista AC. Clinical manifestations due to severe plasminogen deficiency: a case report. J Dent Child (Chic). 2006; 73(3): 179-82.

31. Shapiro AD, Nakar C, Parker JM, Albert GR, Moran JE, Thibaudeau K, et al. Plasminogen replacement therapy for the treatment of children and adults with congenital plasminogen deficiency. Blood. 2018; 131(12): 1301-10.

32. Celkan T. Ligneous gingivitis: Hard to diagnose and treat. Haemophilia. 2020; 26(2): e49-50.

33. Frimodt-Moller J. Conjunctivitis ligneosa combined with a dental affection. Report of a case. Acta Ophthalmol (Copenh). 1973; 51(1): 34-8.

34. Hidayat AA, Riddle PJ. Ligneous conjunctivitis. A clinicopathologic study of 17 cases. Ophthalmology. 1987; 94(8): 949-59.

35. Scully C, Gokbuget AY, Allen C, Bagan JV, Efeoglu A, Erseven G, et al. Oral lesions indicative of plasminogen deficiency (hypoplasminogenemia). Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2001; 91(3): 334-7.

36. Naudi KB, Hunter KD, MacDonald DG, Felix DH. Ligneous alveolar gingivitis in the absence of plasminogen deficiency. J Oral Pathol Med. 2006; 35(10): 636-8.

37. Cha S, Cohen D, Bhattacharyya I, Katz J. Ligneous gingivitis associated with plasminogen deficiency: a challenge in diagnosis. J Investig Clin Dent. 2011; 2: 207-11.

38. Ertas U, Saruhan N, Gunhan O. Ligneous periodontitis in a child with plasminogen deficiency. Niger J Clin Pract. 2017; 20(12): 1656-8.

39. Malthiery E, Torres JH, Costes-Martineau V, Fauroux MA. Diagnosis of a case of ligneous gingivitis in a patient with moderate plasminogen deficiency. J Stomatol Oral Maxillofac Surg. 2019; 120(3): 270-2.

40. MacPherson M, Pho M, Cox J, Armstrong J, Darling MR, McCord C. Ligneous gingivitis secondary to plasminogen deficiency: a multidisciplinary diagnostic challenge. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020; 130(3): e87-95.

RESEARCH ARTICLE

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Examination of the Relationship Between Breastfeeding Self-Efficacy and Perceived Breastfeeding Sufficiency of Mothers

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Abstract

BACKGROUND/AIMS: This study aimed to investigate the relationship between breastfeeding self-efficacy and perceived breastfeeding sufficiency of mothers with healthy infants aged 0-6 months who applied to the pediatric outpatient clinic of a public hospital and a university hospital in the Turkish Republic of North Cyprus.

MATERIAL and METHODS: This was a descriptive and correlational study. The universe of this study consisted of mothers who had 0-6 months old infants who applied to the pediatric outpatient clinic of a public hospital and the gynecology service of a university hospital. The data of this study were collected by using a questionnaire form containing the mothers' descriptive information, the Breastfeeding Self-efficacy Scale and the Perceived Insufficient Milk Questionnaire.

RESULTS: When the mothers' mean scores on the Breastfeeding Self-Efficacy Scale and the Perceived Insufficient Milk Questionnaire were evaluated, it was found that the mean score on the Breastfeeding Self-Efficacy Scale was X:60.16 ± standard deviation (SD) =9.00 and the mean score on the Perceived Insufficient Milk Questionnaire was X:42.06 ± SD =8.26. A statistically significant positive correlation was found between the scores on these two scales (r=0.66, p=0.00). Those mothers who were 25 years old or younger and those mothers who were 36 years old or older were found to have 19 higher perceptions of breastfeeding self-efficacy than the mothers in the other age groups ($p<0.05$).

CONCLUSION: In this study, the mothers' status of giving complementary foods affected their perceived milk insufficiency. This study found that breastfeeding self-efficacy increased when the perception of milk adequacy increased.

Keywords: Breast milk, breastfeeding, self-efficacy, perceived milk insufficiency

INTRODUCTION

It has been identified that the infant mortality rate decreases by 13% and, annually, 1.4 million deaths in children under the age of five are prevented as a result of feeding babies only with breast milk.[1] The World Health Organization, the United Nations Children's Fund and the American Academy of Pediatrics recommend that babies only consume breast milk in their first six months after birth, and they only start to consume liquid and solid complementary foods, respectively, from the sixth month of their life. It is recommended that babies continue to be fed with breast milk in addition to these complementary foods until at least two years of age.[2,3] In this context, breastfeeding in the first six months after birth includes feeding only with breast milk without any complementary food, including water, except for vitamins, minerals and drugs.[4,5]

It is stated that mothers who started breastfeeding early in the postpartum period breastfeed their babies for a longer period. According to data from the Turkey Demographic and Health Survey

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2018, 71% of babies began to suck in the postpartum first hour. It has been shown that 98% of all infants are fed with breast milk for a while.[6] Although breastfeeding is a widespread practice in the first hour after birth due to the support of health personnel, mothers do not continue breastfeeding at home after discharge.[7] In one study, it was found that the ratio of feeding with breast milk alone was 37.9% in one-month old babies and 26.5% in those infants aged 6 months.[8] In a systematic review, it was reported that 16% of breastfeeding problems reported by mothers were due to milk insufficiency/thinking that the baby was not satiated, and/or insufficient weight gain of the baby.[9]

One of the most important factors affecting breastfeeding is the maternal perception of breastfeeding self-efficacy. According to Bandura, self-efficacy is the perceived difficulty in behavior in order to perform a task.[10] The presence of a sense of self-efficacy in a person indicates sufficient motivation to fulfill his/her wishes. The perception of breastfeeding self-efficacy is the adequacy about breastfeeding felt by the mother. Maternal self-efficacy related to breastfeeding may be due to previous breastfeeding difficulties.[11]

According to Dennis and Faux[12], maternal perceptions of breastfeeding self-efficacy show whether mothers breastfeed or not, how much effort they will make for breastfeeding, their thoughts about breastfeeding and their ability to cope with the difficulties in the breastfeeding process. Therefore, maternal willingness to breastfeed is an important factor in increasing the success of breastfeeding. It has been thought that breastfeeding success and breastfeeding self-efficacy perception have a positive correlation.[13]

The most common concern that mothers experience during the breastfeeding period is the idea that their breast milk is not enough. The thought of having an inadequate amount of breast milk leads to mothers giving complementary foods and it also negatively affects both the breast milk production of the mothers and the milk intake of their babies. Problems such as beginning to use complementary products early or terminating breastfeeding can be prevented by informing mothers about the symptoms which show concretely whether their babies are getting enough breast milk or not.[14] In one study, it was determined that the frequent crying of babies caused anxiety in mothers about the adequacy of the milk intake of their babies and this affected the beginning of complementary product usage in addition to breast milk.[15] In that study, Dennis[16] found that the low maternal perception of breastfeeding self-efficacy was associated with the perception of inadequacy of breast milk. The maternal thoughts regarding insufficiency of breast milk is due to the mother's lack of self-confidence in her breastfeeding skills and coping with difficulties which may arise during breastfeeding. In one study examining the relationship between breastfeeding self-efficacy perceptions and perceived milk inadequacy, it was found that the perception of milk adequacy increased as maternal self-efficacy perception increased.[17]

There have been four studies on breastfeeding in the Turkish Republic of North Cyprus (TRNC) to date. Duran[18] found that mothers did not receive sufficient information about the importance of breastfeeding and breast milk, and the ratios of feeding babies with only breast milk and also breastfeeding within the first 30 minutes of the postpartum period were low. Özlüses[19], determined that the rate of feeding babies with breast milk in working mothers during the first 6 months of the postnatal period was 22.4%. Örsdemir[20] found that maternal knowledge levels and behaviors related to breastfeeding in a public hospital were not at the desired level. Sökücü Yorgancı and Aslan[21] determined that the positive employment status of mothers decreased the frequency and duration of breastfeeding and increased the rate of feeding with complementary foods.

Nurses play an important role in initiating and maintaining successful breastfeeding. Although there have been studies about breastfeeding self-efficacy and the perception of insufficient milk in the world and Turkey, no study on the relationship between the perception of insufficiency of breast milk and breastfeeding self-efficacy level in the TRNC was found. Therefore, this study was carried out to investigate the relationship between the breastfeeding self-efficacy and the perception of breast milk sufficiency of those mothers who had healthy babies aged 0-6 months. This study was carried out at the children's polyclinics of a university hospital and a state hospital in the TRNC.

Research Questions

1) What is the breastfeeding self-efficacy of those mothers who are breastfeeding with infants aged 0-6 months?

2) What is the perception of breastfeeding mothers with babies aged 0-6 months about the adequacy of their breast milk?

3) What is the relationship between the mean scores on the Breastfeeding Self-efficacy Scale and the Perceived Insufficiency of Milk Questionnaire for mothers with babies aged 0-6 months?

4) What are the factors associated with the socio-demographic characteristics, delivery, and breastfeeding history which affect the mean scores on the Breastfeeding Self-efficacy Scale and the Perceived Insufficiency of Milk Questionnaire?

MATERIAL AND METHODS

Type of the Study

This was a descriptive and correlational study.

Universe and Sample of the Study

The universe of this study consisted of mothers with babies aged 0-6 months who applied to a public hospital's polyclinic between April, 24th and September, 29th, 2017, and to the gynecology and obstetrics department and pediatric polyclinic of a university hospital between April, 24th, 2018 and August, 3rd, 2018. Using non-probability sampling, 95 women from the public hospital and 21 women from the university hospital who met the sampling criteria and volunteered to participate in this study constituted the sample.

Data Collection

The data were collected using face-to-face interviews with the mothers and data resources (documents/publications). The data of this study were collected by a questionnaire containing introductory information, the Breastfeeding Self-Efficacy Scale and the Perceived Insufficient Milk Questionnaire. The questionnaire containing introductory information consists of 15 questions. The postpartum Breastfeeding Self-Efficacy Scale consists of 14 statements, and the Perceived Insufficient Milk Questionnaire consists of 6 statements.

Breastfeeding Self-Efficacy Scale: This is a 33-item scale developed by Dennis[11] in 1999. The scale was first applied on 130 English-speaking

Canadian women and the Cronbach's alpha value of the scale was found to be 0.96. The Short Form of the Breastfeeding Self-Efficacy Scale (BSES-SF) was developed in 2003 by reducing the number of items to 14 items in 2003. The total correlation of the short form of the scale was found to be below 0.60 and the Cronbach alpha value was found to be 0.94. Aluş Tokat[14] conducted the Turkish reliability and validity study of the Breastfeeding Self-Efficacy Scale-Short Form and found the Cronbach's alpha value to be 0.86. The Breastfeeding Self-Efficacy Scale-Short Form is a 5-point Likert Type scale. The items of the scale are answered from 1= "*not at all confident*" to 5= *"always confident"*. The minimum score on the scale is 14, and the maximum score is 70. It is thought that breastfeeding self-efficacy increases as the score increases.

The perceived insufficient milk questionnaire: It was developed in 2001 by McCarter-Spaulding to determine the perception of breast milk insufficiency. The Perceived Insufficient Milk Questionnaire consists of 6 questions. The first question of the scale is about whether the mother perceives her breast milk as sufficient or not. Mothers who answer the scale answer this question as *"yes"* or *"no"*. Other questions of the scale are intended to measure the perception of milk inadequacy. Mothers are asked to score these questions between 0-10. When the score obtained from the scale is "0", the breast milk level is perceived as completely insufficient; when the score is "10", the milk level is perceived as sufficient. The lowest score on the scale is 0 and the highest score is 50. Higher total scores on the scale indicate that there is a sufficiency perception of breast milk. The Cronbach's alpha value was determined to be 0.81 for the original version of the scale. The Turkish validity and reliability study of the scale was conducted by Küçükoğlu and Gökçeoğlu[29] in Turkey in 2014. The Cronbach's alpha value of the Turkish version of the Perceived Insufficient Milk Questionnaire was found to be 0.82.

Statistical Analysis

The Statistical Package for Social Sciences for Windows (SPSS) 22.0 statistical package program was used for data coding and statistical analysis. In the evaluation of the data, Pearson correlation analysis was used to determine the relationship between the two scales while percentages and means were used for data analysis. The Mann-Whitney U test, Kruskal-Wallis test and variance analysis were used to compare the characteristics of these two scales related to socio-demographic features, delivery and breastfeeding history.

Inclusion Criteria

For mothers;

- Being 18 years old or older,
- Having a baby aged 0-6 months,
- Being able to speak Turkish,
- Having no health problem preventing breastfeeding,
- Having no visual and/or hearing impairment,
- Being open to communication and cooperation,
- Volunteering to participate in this study.

For infants;

- Being born in the 37th week or in the following weeks of the pregnancy,
- Being born with a weight of 2,500-4,000 grams,
- Having no congenital abnormalities preventing breastfeeding (cleft lip and palate, etc.).

Ethical Statement

Informed consent was obtained from the mothers who participated in this study. In order to use the scales, the necessary permission was obtained from those who conducted the validity and reliability studies. In order to use the data collection forms, the required written permission was obtained from the chief physicians of the university hospital and the state hospital where this study was conducted. Ethics committee approval was obtained from the Near East University Ethics Committee (approval number: 2018/56-541).

RESULTS

The socio-demographic characteristics of the mothers in this study are shown in Table 1. 37.9% of the mothers were aged 26-30 years and their mean age was 28.05 years (SD: ±5.3). It was determined that 37.9% of the mothers were primary school graduates or had a lower education level, 21.6% of them were university graduates or had a higher level of

Table 1. The distribution of the descriptive characteristics of the mothers (n=116)

Characteristics	Number (n)	Percentage (%)
Age		
≤25	34	29.3
26-30	44	37.9
31-35	28	24.2
≥36	10	8.6
Educational level		
Primary school or below	44	37.9
Middle school	20	17.2
High school	27	23.3
University or above	55	21.6
Perceived income level		
Income < expenses	26	22.4
Income = expenses	87	75.0
Income > expenses	3	2.6
Employment status		
Employed	84	72.4
Unemployed	32	27.6
The status of health insurance		
No	7	6.0
TR* social health insurance	22	19.0
TRNC health insurance	87	75.0
Profession		
Housewife	79	68.1
Self-employed	29	25.0
Civil servant	3	2.6
Academician	3	2.6
Health staff	2	1.7

*Turkish Republic.

education and only 27.6% of them were employed. It was determined that 68.1% of the mothers had no health insurance, 68.1% of them were housewives and 75% of them perceived their income as being equal to their expenses. When the characteristics of the mothers related to their delivery and breastfeeding history were evaluated, it was determined that 98.3% of them went for a prenatal checkup but only 9.5% of them were informed about breastfeeding (Table 2). It was determined that 52.6% of the mothers gave birth by cesarean section and 26.8% of them had three or more children. 96% of the mothers with more than one delivery were found to have breastfed their previous baby. The breastfeeding period of more than half of the mothers who had breastfed their previous baby was found to be 12.9 months (minimum: 0 months, maximum: 28 months).

The mean score of the mothers on the Breastfeeding Self-efficacy Scale was X: 60.16± SD: 9.00 and their mean score on the Perceived Insufficient Milk Questionnaire was X: 42.06± SD: 8.26 (Table 3).

The relationship between breastfeeding self-efficacy and perceived milk insufficiency levels is shown in Table 4. The relationship between the mothers' breastfeeding self-efficacy and their perceived milk insufficiency was evaluated by Pearson correlation analysis. A positive statistically significant correlation (r=0.661, p=0.00) was detected between these two scales.

Table 5 shows the comparison of the mothers' socio-demographic characteristics with their delivery and breastfeeding history. According to the comparison of the sociodemographic characteristics of the mothers and their scores on the breastfeeding self-efficacy scale, a statistically significant difference was found between the age, education level and the scores on the breastfeeding self-efficacy perception scale ($p<0.05$). The mean Breastfeeding self-efficacy scale scores of those mothers aged 25 or younger and those mothers aged 36 or older were higher than those of the mothers in the other age groups ($p<0.05$). The mothers' breastfeeding self-efficacy decreased as their education level increased ($p<0.05$). There was no statistically significant relationship between the mothers' mean score on the Breastfeeding Self-efficacy Scale and their perceived income level or employment status ($p>0.05$) (Table 5).

The distribution of the birth and breastfeeding histories related characteristics of the mothers according to their mean scores on the scales was analyzed. Statistically significant differences were found between the mothers' mean scores on the Breastfeeding Self-efficacy Scale according to their status of receiving prenatal care, their delivery mode and their status of being informed about breastfeeding ($p<0.05$). The mean breastfeeding self-efficacy score of those mothers who had received information about breastfeeding was 59.36±5.51 while that of the mothers who had received no information about breastfeeding was 60.24±9.31 ($p<0.05$). Statistically significant differences were found between the mothers' mean scores on the Breastfeeding Self-efficacy Scale according to their number of deliveries, their status of breastfeeding for their previous babies and their status of giving supplementary foods ($p<0.05$). It was found that breastfeeding self-efficacy increased as the number of deliveries increased ($p<0.05$). The mean breastfeeding self-efficacy score of the mothers who had breastfed their previous baby was 61.46±8.67, while it was 58.11±9.23 for those mothers who had not breastfed their previous baby ($p<0.05$). It was found that those mothers who fed their babies with supplementary foods had a lower mean breastfeeding self-efficacy score than those who did not fed their babies with these foods ($p<0.05$).

There was no statistically significant difference between the mothers' mean perceived milk insufficiency scores according to their status of receiving prenatal care, their type of delivery, their number of

Table 2. The distribution of the delivery and breastfeeding history related characteristics of the mothers (n=116)

Characteristics	Number (n)	Percentage (%)
The status of having received prenatal care		
Yes	114	98.3
No	2	1.7
The method of delivery		
Vaginal	55	47.4
Cesarean section	61	52.6
Number of deliveries		
1	42	36.2
2	43	37.0
≥3	31	26.8
The status of having received information about breastfeeding		
Yes	11	9.5
No	105	90.5
Information received (n=11)		
The importance of breastfeeding	7	63.6
The duration of breastfeeding	4	36.4
The status of having breastfed previous babies (n=74)		
Yes	71	96.0
No	3	4.0
The age of the youngest baby		
In the first month	42	36.2
In the second month	20	17.2
In the third month	14	12.1
In the fourth month	9	7.8
In the fifth month	13	11.2
In the sixth month	18	15.5
The status of giving formulas/complementary foods		
Yes	62	53.4
Noa	24	46.6

Table 3. The mean scores of the mothers on the BSES and PIMQ

	n	Mean ± standard deviation	X ± SD X_{min}-X_{max}
Mean BSES* score	116	60.16±9.00	21-70
Mean PIMQ** score	116	42.06±8.26	12-51

BSES*: Breastfeeding Self-Efficacy Scale. PIMQ**: Perceived Insufficient Milk Questionnaire. min: minimum, max: maximum.

Table 4. The correlation between the mothers' postpartum BSES and PIMQ scores

	PIMQ	
	r*	p*
BSES	0.661	0.001

r: Pearson correlation coefficient. BSES: Breastfeeding Self-efficacy Scale. PIMQ: Perceived Insufficient Milk Questionnaire. SD: standard deviation.

deliveries, their status of breastfeeding previous babies, or their status of receiving information about breastfeeding (p>0.05). The perceived milk insufficiency score of the mothers who gave complementary foods to their babies was 38.54±9.14, while it was 46.09±4.57 for those who did not. The perceived milk sufficiency of those mothers who did not give complementary foods was found to be high (p<0.05) (Table 5).

Table 5. The comparison of the mothers' sociodemographic characteristics, characteristics related to delivery and breastfeeding according to their score on the BSES and the PIMQ (n=116)

Characteristics	BSES	PIMQ	Significance test
	X ± SD	X ± SD	
Age			
≤25	63.23±5.72	44.02±7.16	KW*=8.23, **p=0.04** KW**=5.18, p=0.15
26-30	58.38±9.51	40.63±8.09	
31-35	58.57±10.4	41.03±9.94	
≥36	62.00±9.68	44.50±6.31	
Educational level			
Primary school or below	63.20±6.23	44.65±5.32	KW*=11.32, **p=0.01** KW**=7.34, p=0.06
Middle school	61.15±6.15	38.70±9.31	
High school	57.70±11.4	41.81±9.75	
University or above	56.68±10.5	40.44±5.72	
Perceived income level			
Income < expenses	58.11±11.3	41.50±7.61	KW*=2.19, p=0.33 KW**=0.78, p=0.67
Income = expenses	60.85±8.26	42.25±8.52	
Income > expenses	58.00±5.29	41.33±8.50	
Employment status			
Employed	61.10±8.49	40.75±9.64	z*=-1.93, p=0.05 z**=-0.96, p=0.33
Unemployed	57.68±9.96	42.55±7.67	
The status of having received prenatal care			
Yes	60.08±9.05	41.98±8.30	z*=-0.66, p=0.50 z**=-0.81, p=0.41
No	64.50±4.94	46.50±4.94	
The method of delivery			
Vaginal	61.98±7.12	43.07±7.46	z*=-1.80, p=0.07
Cesarean section	58.52±10.2	41.14±8.88	z**=-1.05, p=0.29
Number of deliveries			
1	58.00±9.37	40.57±8.40	KW*=8.83, **p=0.01** KW**=3.56, p=0.16
2	60.23±9.35	42.23±8.53	
≥3	63.00±7.31	43.83±7.52	
The status of having received information about breastfeeding			
No	59.36±5.51	42.18±7.33	z*=-1.17, p=0.24 z**=-0.30, p=0.76
Yes	60.24±9.31	42.04±8.38	
The status of having breastfed previous infants (n=74)			
Yes	61.46±8.67	43.02±7.96	z*=-2.52, **p=0.01**
No	58.11±9.23	40.53±8.57	z**=-1.87, p=0.06
The status of giving formulas/complementary foods			
Yes	59.36±5.51	38.54±9.14	z*=-5.15, **p=0.01**
No	60.24±9.31	46.09±4.57	z**=-5.13, **p=0.01**

*This is the analysis result which was compared with the BSES mean score. **This is the analysis result which was compared with the PIMQ mean score. KW: Kruskal-Wallis test, z: Mann-Whitney U test. BSES: Breastfeeding Self-efficacy Scale. PIMQ: Perceived Insufficient Milk Questionnaire. SD: standard deviation.

DISCUSSION

Prenatal education, which is thought to play an important role in the initiation and maintenance of breastfeeding, was not given to most of the mothers in this study. Although almost all of the mothers received prenatal care, only a few of them stated that they had received prenatal breastfeeding training (Table 2). Only 7 out of 11 women who received breastfeeding training received information about the importance of breastfeeding, and only 4 of them were informed about the correct duration of breastfeeding (Table 2). However, other studies found that prenatal breastfeeding training and motivation programs for breastfeeding increased the mothers' breastfeeding self-efficacy scores.[22,23] Therefore, it can be said that it is important to train and support mothers about breastfeeding during the prenatal period.

A significant proportion of the mothers fed their babies with formulas or supplementary foods in the first 6 months (Table 2). According to many studies on the causes of breastfeeding problems and the early transition to supplementary foods, the most important problem was that the mothers thought that their breast milk was insufficient.[24,25] Gatti[26] reviewed studies in which insufficient milk perception was measured and determined that the most common problem experienced in the early termination of breastfeeding was perceived milk insufficiency. In a study covering 423 mothers and their babies aged 0-6 months in northwestern Ethiopia, it was reported that additional nutrients were started in the early period, as 18% of mothers thought that their breast milk was insufficient and that it was not enough for their baby.[27]

A statistically significant relationship was found between the mean scores on the Breastfeeding Self-efficacy Scale and the mean scores on the Perceived Insufficient Milk Questionnaire (Table 4). It was found that mothers perceived their breast milk levels more adequately as their breastfeeding self-efficacy levels increased. In a study by Akkoyun and Taş Arslan,[28] the breastfeeding self-efficacy of the mothers was found to be moderate. In the study of Akkoyun and Taş Arslan[28], age, educational level and employment status, number of pregnancies and deliveries, number of living children and the age of the baby (week) affected breastfeeding self-efficacy. In the studies of Küçükoğlu and Gökçeoğlu[29], many factors related to the mother, the baby, the pregnancy and the environment affected the perception of breastfeeding self-efficacy and milk inadequacy. It was found that as the level of breastfeeding self-efficacy increased, perceived milk sufficiency increased.[29] Otsuka et al.[30] compared the Breastfeeding Self-efficacy Scale and the Perceived Insufficient Milk Questionnaire and similarly found a positive correlation between the two scales. In their study, Yenal et al.[13] compared the mean scores on the Breastfeeding Self-efficacy Scale and LATCH breastfeeding success scores and found that breastfeeding self-efficacy positively affected breastfeeding success. The findings of other studies presented above support the results of our study and showed that there is a positive relationship between breastfeeding self-efficacy and perceived milk sufficiency.

In our study, we found similar results to the literature in that the number of deliveries and having experience of breastfeeding increased the mothers' breastfeeding self-efficacy scores (Table 5). Küçükoğlu and Çelebioğlu[31] examined the breastfeeding self-efficacy and breastfeeding success of mothers and they found that the mean breastfeeding self-efficacy score of those mothers with breastfeeding experience were higher. In the study conducted by Akkoyun and Taş Arslan[28] it was found that the breastfeeding self-efficacy of the mothers increased as

their number of deliveries increased. Having breastfed previous babies increased the experience of the mothers in breastfeeding and had a positive effects on their breastfeeding self-efficacy.

Unlike the literature, the breastfeeding self-efficacy scores of those mothers younger than 25 years were higher in our study (Table 5). It has been suggested that internet usage had a positive effect on the breastfeeding self-efficacy of young mothers by providing access to more information about breastfeeding. Goulet et al.[32] found that the education levels and ages of the mothers were important factors in making decisions about breastfeeding and maintaining breastfeeding. In the study conducted by Akkoyun and Taş Arslan[28] it was found that breastfeeding self-efficacy scale scores increased as the ages of the mothers increased. In our study, unlike the literature, the breastfeeding self-efficacy scores of the mothers decreased as their education levels increased (Table 5). In the study conducted by Akkoyun and Taş Aslan[28] it was observed that the education level of the mothers increased their breastfeeding self-efficacy scores. It is recommended to conduct further studies on this subject.

In our study, a significant difference was found between the mothers' perceived milk insufficiency scores according to their statuses of previous breastfeeding and giving formulas/complementary foods (p=0.00) (Table 5). Similarly, another study found that breastfeeding time was shortened as a result of the perceived inadequacy of breast milk.[26] In the study of Gölbaşı and Koç[33] it was found that the ratio of women who thought that their milk level was insufficient and therefore started to give complementary foods was 41.4%. In a study investigating the causes of using complementary foods in babies aged 0-6 months, 38.8% of the mothers stated that they started to give complementary foods because they thought that the amount of their milk was inadequate.[34]

CONCLUSION

The mothers' perceived breastfeeding self-efficacy was affected by their age, their level of education, their number of deliveries, their status of having breastfed previous babies and their status of giving formulas/complementary foods to their baby. The mothers' perceived breast milk inadequacy affected the use of formulas/complementary foods in infant nutrition. In our study, it was found that when breastfeeding self-efficacy increased, the perceived milk adequacy increased. Mothers should be informed about the sufficiency of their milk with embodiments (weight gain of the baby, not getting sick frequently, etc.) and necessary training and support should be provided on the importance of giving breast milk.

MAIN POINTS

• The mothers' perceived breast milk inadequacy is related with the use of formulas/complementary foods in infant nutrition in the first 6 months.

• One of the most important factors affecting breastfeeding is the maternal perception of their breastfeeding self-efficacy.

• Nurses/midwives can attempt to increase the mothers' self-efficacy in order to increase breastfeeding success.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from the Near East University Ethics Committee (approval number: 2018/56-541).

Informed Consent: In order to use the data collection forms, the required written permission was obtained from the chief physicians of the university hospital and the state hospital where this study was conducted.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.A., D.S.G., Design: Ö.A., D.S.G., G.V., Data Collection and/or Processing: D.S.G., Literature Search: Ö.A., S.T., Writing: G.V.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Cai X, Wardlaw T, Brown DW. Global trends in exclusive breastfeeding. International Breastfeeding Journal. 2012; 7(1): 12.
2. UNICEF, Baby-friendly hospital initiative : revised.,updated and expanded for inte grated care. Section 3, Breastfeeding promotion and support in a baby-friendly hospital: a 20-hour course for maternity staff. 2009, available date: 12.12.2018, avalilable from: http://www.unicef.org/nutrition/files/BFHI_2009_s3.1and2.pdf
3. American Academy of Pediatrics. Policy Statement Breastfeeding and the Use of Human Milk. Pediatrics. 2012; 129(3): 827-41.
4. WHO. Indicators for Assessing Infant and Young Child Feeding Practices: Part I Definitions. 2007, Geneva, Switzerland
5. Thulier D. A Call for Clarity in Infant Breast and Bottle-Feeding Definitions for Research. JOGNN. 2010; 39(6): 627-34.
6. Türkiye Nüfus ve Sağlık Araştırması (2018). Available date: 10.01.2020, Available from: http://www.hips.hacettepe.edu.tr/TNSA2018 sonuclar_sunum_2122014.pdf.
7. Çalık KY, Çetin FÇ, Erkaya R. Breastfeeding Practices of Mothers and Influencing Practices. GÜSBD. 2017; 6(3): 80-91.
8. Güner Ö, Koruk F. Breastfeeding status of 0-6 month old infants and the effective factors in Şanlıurfa. Journal of Harran University Medical Faculty. 2019; 16(1): 111-6.
9. Karaçam Z, Sağlık M. Breastfeeding problems and interventions performed on problems: systematic review based on studies made in Turkey. Türk Pediatri Arşivi. 2018; 53(3): 134-48.
10. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev. 1977; 84(2): 191-215.
11. Dennis CL. Theoretical under pinnings of breast-feeding confidence: a self-efficacy framework. J Hum Lact. 1999; 15: 195-201.
12. Dennis CL, Faux S. Development and psychometric testing of the Breastfeeding Self-Efficacy Scale. Res Nurs Health. 1999; 22: 399-409.
13. Yenal K, Aluş Tokat M, Durgun Ozan Y, Cece O, Bakılan Abalın F. The Relation Between Breastfeeding Self-Efficacy and Breastfeeding Success in Mothers. Hemşirelikte Eğitim ve Araştırma Dergisi. 2013; 10: 14-9.
14. Aluş Tokat M. Antenatal dönemde verilen eğitimin annelerin emzirme öz-yeterlilik algısına ve emzirme başarısına etkisi. Doktora tezi, 2009, Dokuz Eylül Üniversitesi Sağlık Bilimleri Enstitüsü, İzmir.
15. Bolat F, Uslu S, Bolat G, Bülbül A, Arslan S, Çelik M, et al. Factors Affecting Breast Feeding in the First Six Months of Life. Çocuk Dergisi. 2011; 11(1): 5-13.

16. Dennis CL. Breastfeeding initiation and duration: a 1990–2000 literature review. J Obstet Gynecol Neonatal Nurs. 2002; 31: 12-32.

17. Mirghafourvand M, Malakouti J, Mohammad-Alizadeh-Charandabi S, Faridvand F. Predictors of Breastfeeding Self-efficacy in Iranian Women: A Cross-Sectional Study. International Journal of Women's Health and Reproduction Sciences. 2018; 6(3): 380-5.

18. Duran S. Annelerin İlk 6 Ayda Bebeklerini Anne Sütü İle Besleme Durumlarının Saptanması. Yüksek Lisans Tezi, 2018, Yakın Doğu Üniversitesi Sağlık Bilimleri Enstitüsü, Lefkoşa.

19. Özlüses E. Ebeveynlere Verilen Doğal Besleme Öğretiminin, Tek Başına Anne Sütü Verme Süresine, Bebeklerin Büyüme Parametrelerine, Hastalanma Oranlarına ve Ebeveyn-Bebek Bağlanmasına Etkisi. Doktora Tezi, 2014; Yakın Doğu Üniversitesi Sağlık Bilimleri Enstitüsü, Lefkoşa.

20. Örsdemir Ç. Doğum Sonu Dönemde Annelerin Emzirmeye İlişkin Bilgileri Ve Emzirme Davranışlarının Belirlenmesi. Yüksek Lisans Tezi, 2011; Yakın Doğu Üniversitesi Sağlık Bilimleri Enstitüsü, Lefkoşa.

21. Sökücü Yorgancı F, Aslan E. The Effect of Woman's Work Status on Breast-Feeding. İ.Ü.F.N. Hem Derg. 2012; 20(1): 62-8.

22. Tokat Aluş M, Okumuş H. Mothers Breastfeeding Self-Effi cacy and Success: Analysis The Effect of Education Based on Improving Breastfeeding Self-Efficacy. Hemşirelikte Eğitim ve Araştırma Dergisi. 2013; 10(1): 21-9.

23. Cangöl E, Şahin NH. The Effect of a Breastfeeding Motivation Program Maintained During Pregnancy on Supporting Breastfeeding: A Randomized Controlled Trial. Breastfeed Med. 2017; 12(4): 218-26.

24. Zhang K, Tang L,Wang H, Qiu LQ, Binns CW, Lee AH. Why do mothers of young infants choose to formula feed in China? Perceptions of mothers and hospital staff. Int J Environ Res Public Health. 2015; 12(5): 4520-32.

25. Safon C, Keene D, Guevara WJU, Kiani S, Herkert D, Muñoz EE, et al. Determinants of perceived insufficient milk among new mothers in León, Nicaragua. Matern Child Nutr. 2017; 13(3): e12369.

26. Gatti L. Maternal perceptions of insufficient milk supply in breastfeeding. Journal of Nursing Scholarship. 2008; 40(4): 355-63.

27. Mekuria G, Edris M. Exclusive breastfeeding and associated factors among mothers in Debre Markos, Northwest Ethiopia: a cross-sectional study. International Breastfeeding Journal. 2015; 10: 1.

28. Akkoyun S, Taş Arslan F. Breastfeeding Self-Efficacy of Mothers Who Breastfed for First Six Months. J Pediatr Res. 2016; 3(4): 191-5.

29. Küçükoğlu S, Gökçeoğlu E. The relationship between insufficient milk perception and breastfeeding self-efficacy among Turkish mothers. Glob Health Promot. 2015; 24(4): 53-61.

30. Otsuka K, Dennis CD, Tatsuoka H, Jimba M. The Relationship Between Breastfeeding Self – Efficacy and Perceived Insufficient Milk Among Japanese Mothers. J Obstet Gynecol Neonatal Nurs. 2008; 37(5): 546-55.

31. Küçükoğlu S, Çelebioğlu A. Effect of natural-feeding education on successful exclusive breast-feeding and breast-feeding self-efficacy of low-birth-weight infants. Iran J Pediatr. 2014; 24(1): 49-56.

32. Goulet L, D'Amour D, Pineault R. Type and timing of services following postnatal discharge: do they make a difference? Women and Health. 2007; 45: 19-39.

33. Gölbaşı Z, Koç G. Beastfeeding Behaviour of Women During Postpartum First Six Months and Effect of Prenatal Breastfeeding Attitude on Postpartum Breastfeeding. Sağlık Bilimleri Fakültesi Hemşirelik Dergisi. 2008; 16-31.

34. Sivri, BB. The Knowledge And Practices Of Mothers With 6 Month-Old Babies Related With The Transition To Solid Complementary Feeding Food And Breastfeeding. Acıbadem Üniversitesi Sağlık Bilimleri Dergisi. 2014; 5(1): 59-65.

RESEARCH ARTICLE

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Clinical Decision-Making Levels of Nursing Students and Affecting Factors

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Abstract

BACKGROUND/AIMS: Although clinical decision-making is an integral part of nursing practice, there are very few studies which investigate the factors affecting decision-making. This study was conducted to find out nursing students' levels of clinical decision-making and their affecting factors.

MATERIALS AND METHODS: This research was carried out with a cross-sectional and descriptive design. This research was carried out on 362 1st, 2nd, 3rd and 4th grade students studying at a faculty of health sciences department of nursing. The data of this research were collected by using a "Sociodemographic Data Collection Form" and "The Clinical Decision-Making in Nursing Scale (CDMNS)." In the analysis of the data, numbers, percentages, and means were used with Mann-Whitney U test and Kruskal-Wallis test.

RESULTS: The mean age of the students was 20.75±1.91 years, 80.9% of the students were female and 63% were graduates of elite Anatolian or science high schools. The students' total "CDMNS" score mean was 100.81±18.06. It was found that variables such as grade, gender, the high school of graduation, the number of people living in the family, education and employment status of the parents, having chosen the department willingly, and income and employment status did not affect the clinical decision-making status of the students ($p>0.05$).

CONCLUSION: As a result of this study, it was found that the students' status of clinical decision-making is at a medium level. It is recommended to repeat this study on students studying in different curricula in nursing, on a larger sample group and to analyze the students' level of clinical decision-making in terms of variables such as critical thinking, problem solving and their clinical learning environment.

Keywords: Nursing, clinical, decision, practice, education

INTRODUCTION

Decision-making can be defined as selecting the most appropriate possible way to solve a problem. The process of decision-making is a mental process which starts with the perception of a situation as a problem by an individual and includes the selection of an activity related to a behavior from one or more options, in order to achieve a desired goal.[1]

Clinical decision-making is the ability to use the basic and current knowledge of nursing, which includes nonlinear and multi-faceted interactions.[2] According to this approach, clinical decision-making

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allows the nurse to observe the patient's condition, evaluate the observed data, critically question their causes, and identify alternative hypotheses. It includes choosing the most possible hypothesis among them and determining and implementing the most suitable action for the hypothesis chosen.[3,4]

Clinical decision-making is a basic skill which needs to be developed in all health professionals who offer health care, especially nurses.[5] Clinical decision-making, which expresses the ability of nurses to use and combine their theoretical and practical knowledge, requires nurses to access new information through different methods during this process.[2] In order for the nurse to make a correct and effective decision, it is very important to obtain the most accurate information for the solution of the existing problem and to use it in the process of decision-making.[6] Clinical decision-making, which is a complicated process which involves a series of decisions in order to achieve the targeted results in patient care, is also an essential part of the nursing process.[7,8]

Clinical decision-making is one of the skills which should be learnt by students in their nursing education.[9-11] Therefore, there is a need to determine the clinical decision-making perception of nursing students and to improve and evaluate their decision-making skills during the education process, and there are currently only a limited number of studies on the perceptions of nursing students and their understanding of clinical decision-making.[11,12] As decision-making is a complex process and many factors affect this process, it is difficult to study clinical decision-making in nursing students.[9,11] In the study by Garrett[11], it was found that nursing senior students perceive clinical decision-making as a complex conceptual process and at the same time think that clinical decision-making is related to knowledge and experience. In the literature, it has been suggested that there have been changes in critical thinking and intellectual development with undergraduate nursing education, however, these changes will take several years and should be applied in clinical decision-making processes.[11-13] In their qualitative study, Jahanpour et al.[14] reported that an insufficient number of clinical instructors, low self-sufficiency, an unsuitable clinical learning environment and stress negatively affect decision-making in students and that students cannot decide independently. In the study conducted by Ho et al.[15] on senior students at a nursing school in Malaysia, it was reported that the students' "Clinical Decision-Making in Nursing Scale (CDMNS)" mean score were good, and that this result was affected by the fact that nursing was their first preference and they were satisfied with being a nurse. In another study in which the clinical decision-making perception of nursing students were analyzed in our country,[13] it was found that there was a difference between grades in clinical decision-making levels of the students, and as a result of a one-year follow-up, it was found that the clinical decision-making scores of the senior students were lower. In a study conducted by Özden et al.[16] to determine the clinical decision-making levels of nursing students and the factors affecting them, the students' status of clinical decision-making was reported to be affected by variables such as the employment status of the mother, Having entered the department willingly or not, liking nursing as a profession, having a positive opinion about the profession, not having problems in clinical practice and thinking that they use their theoretical knowledge in their clinical practice.

Although there are studies on the clinical decision-making levels of students in the literature, it has been observed that there are only a limited number of studies which reveal the factors which affect the clinical decision-making levels of students. It is thought that the findings obtained through this study can assist instructors in improving clinical decision-making in nursing students and in identifying appropriate educational and clinical strategies. This research was carried out to find out the clinical decision-making levels of nursing students and their effecting factors. This study aimed to answer the question "*What are the factors affecting the clinical decision-making skills of nursing students?*"

MATERIALS AND METHODS

Design and Sample

This research was conducted in Bursa Uludağ University Faculty of Health Sciences, Department of Nursing, between March and April of 2019, in a descriptive and cross-sectional design.

The universe of the research consisted of 771 1st, 2nd, 3rd and 4th grade students who were studying in the nursing department of the university's faculty of health sciences during the 2018-2019 academic year. The sample of this study comprised 362 students who agreed to take part in this study and completed the study forms after the necessary explanations about this study were made. No sampling methods on the students comprising the target population were used.

The dependent variable of this study was the clinical decision-making skills of the students, while the independent variables were their grade, age, gender, number of siblings, number of family members, type of high school graduated from, status of choosing the department willingly or not, income status, accommodation, employment status, the educational background of their parents and the place where they had lived longest. All of these data were collected via the sociodemographic data form.

Data Collection Tools

The data of this study were collected using the "Socio-Demographic Data Collection Form" and "The CDMNS-Tr".

Socio-Demographic Data Collection Form: This form was developed by the researchers. It consists of 9 closed-ended questions which include the grade, age, school of graduation of the students, whether they had chosen the nursing department willingly or not, where they lived, their employment status, and the education and employment status of their parents.

The Clinical Decision-Making in Nursing Scale: Developed by Jenkins[17] on nursing students in the USA, this scale describes the clinical decision-making perception of nursing students based on self-expressions. The Cronbach alpha reliability coefficient of this scale was found to be 0.83.[18] The Cronbach alpha reliability coefficient of the CDMNS which was adapted into Turkish by Edeer and Sarikaya[19] was found to be 0.78. In this study, the Cronbach alpha reliability coefficient was calculated to be 0.81.

The original CDMNS consists of 40 items and four subscales. The sub-scales of the scale are as follows; "*search for alternatives or options", "canvasing of objectives and values*", "*evaluation and reevaluation of consequences*", and "*search for information and unbiased assimilation of new information*". Each sub-scale is composed of 10 items. Twenty-two items (1, 3, 5, 7, 8, 9, 10, 11, 14, 16, 17, 18, 20, 26, 27, 28, 29, 33, 35, 36, 37, 38) are positively assessed and 18 items (2, 4, 6, 12, 13, 15, 19, 21, 22, 23, 24, 25, 30, 31, 32, 34, 39, 40) are negatively assessed. The 18 negatively assessed items of this scale are inversely scored. Each item

of the scale is evaluated as 5: Always, 4: Frequently, 3: Occasionally, 2: Seldom, and 1: Never.

The minimum and maximum points are from 40 to 200 for the whole scale from 10 to 50 for each sub-scale. A high score taken from this scale indicates that the perception in decision-making is high and a low score indicates that the perception in decision-making is low. The scale is evaluated considering each sub-scale and the total score of the scale.[17-19]

Data Collection

These questionnaire forms were applied outside the course and clinical practice periods. Before the questionnaire forms were given, the participants were informed about the objectives of this research. The questionnaire forms, which were distributed on a voluntary basis, were filled out under the supervision of the researcher. It took participants about 20 minutes to complete the questionnaire forms.

For the implementation of this research, written permissions from the Faculty in which the research was conducted and from the Bursa Uludağ University Health Sciences Research and Publication Ethics Committee (approval number: 2019/03) and verbal informed consent from the students were obtained.

Statistical Analysis

The data obtained from this research were analyzed using the SPSS 22.0 (Statistical Package for Social Science) statistical program software. In the analysis of the data; numbers, percentages, means, the Mann-Whitney U test, and the Kruskal-Wallis test were used. A p-value under 0.05 was accepted as statistically significant.

RESULTS

The mean age of the students who participated in this study was 20.75±1.91 and 80.9% of them were female. 25.1% of the students were 1st grade, 27.6% were 2nd grade, 21.5% were 3rd grade, and 25.7% were 4th grade students. 63% of the students were graduates of Anatolian-science high schools, which are both elite schools in Turkey. 71.5% of the students did not enter the nursing department willingly. The mothers of 4.0% of the students and the fathers of 18.0% of the students were university graduates.

The mean score of the Students" CDMNS-Tr was 100.81±18.69. When the sub-dimensions of the CDMNS mean scores were analyzed; "*Search for Alternatives or Options*" was 25.52±5.38, "*Canvasing of Objectives and Values*" was 22.95±5.19, "*Evaluation and Reevaluation of Consequences*" was 26.54±5.61, and "*Search for Information and Unbiased Assimilation of New Information*" was 25.59±5.15 (Table 1).

Table 2 shows the distribution of the students' CDMNS-Tr and its sub-scale mean scores. The CDMNS-Tr mean scores of the 1st, 2nd, 3rd and 4th grade nursing students were; 100.98±18.82, 100.37±20.00, 102.61±14.88, and 99.60±20.11, respectively. It was determined that the total CDMNS-Tr mean scores were similar among all of the students and any differences were not statistically significant (p=0.082). It was found that the students' CDMNS-Tr sub-dimension mean scores did not show a statistically significant difference (p=0.091) (Table 2).

In Table 3, the distribution of The CDMNS mean scores are shown according to some of the characteristics of the nursing students. It was found that male students (110.10) had a higher score mean in CDMNS-Tr, compared to female students (100.97), but this difference is not statistically significant (p>0.05). The students were examined in terms of the variables of the high school they graduated from, whether they had entered the department willingly or not, their employment status, their place of residence and their income status. In terms of these criteria, their CDMNS-Tr mean scores were not found to be statistically significant (p>0.05).

DISCUSSION

Technological developments have helped the development of nursing and strengthened its roles and functions. While problem solving in

Table 1. Results of the Clinical Decision-Making in Nursing Scale and sub-scale analysis (n=362)

	X ± SD	Minimum	Maximum	Range
The total of CDMNS	100.81±18.69	40.00	141.00	101.00
CDMNS and sub-scales				
Search for alternatives or options	25.52±5.38	10.00	43.00	33.00
Canvassing of objectives and value	22.95±5.19	10.00	41.00	31.00
Evaluation and reevaluation of consequences	26.54±5.61	10.00	38.00	28.00
Search for information and unbiased assimilation of new information	25.59±5.15	10.00	40.00	30.00

SD: standard deviation, CDMNS: Clinical Decision-Making in Nursing Scale.

Table 2. Comparison of the scores of students on the Clinical Decision-Making in Nursing Scale according to year (n=362)

CDMNS and subscales	1st year (91)	2nd year (100)	3rd year (78)	4th year (93)
	X ± SD	X ± SD	X ± SD	X ± SD
Search for alternatives or options	25.69±5.48	25.48±5.71	26.24±4.66	25.52±5.38
Canvassing of objectives and value	23.19±5.87	22.71±5.56	22.87±4.27	23.04±4.84
Evaluation and reevaluation of consequences	26.43±5.55	26.39±5.91	27.10±4.63	26.35±6.13
Search for information and unbiased assimilation of new information	25.39±5.06	25.60±5.74	26.20±3.94	25.29±5.50
The total of CDMNS	100.98±18.82	100.37±20.00	102.61±14.88	99.60±20.11

CDMNS: Clinical Decision-Making in Nursing Scale.

nursing was mostly carried out through trial and error, decision-making has gained an information-based infrastructure in light of certain scientific approaches today.[20,21] Clinical decision-making, which expresses the ability of the nurses to use and combine their theoretical and practical knowledge, requires the nurse to access new information through different methods in this process. In order for the nurse to make the correct and effective decision, it is very important to obtain the most accurate information for the solution of the existing problem and use it in their decision-making process.[6,22] In addition to that, the ability of decision-making in nursing is one of the most important skills that nursing students should learn and use in their nursing practice in order to ensure patient safety and provide the most appropriate care service.[15] Based on this approach, in this study, it was aimed to reveal the clinical decision-making levels of the nursing department students, who were the candidates for the nursing profession, and any affecting factors. As a result of this study, the students' CDMNS-Tr mean score was

Table 3. Comparison of the scores of students on the Clinical-Decision-Making in Nursing Scale according to various features (n=362)

CDMNS and subscales	(n)	CDMNS	Statistical evaluation	
			7/Z/t	p
Gender				
Male	69	110.10	Z: -0.068	0.946
Female	293	100.97		
Educational status				
High school	64	103.20	K-W: 2.738	0.066
Vocational high school	70	96.31		
Elite Anatolian-Science high school	228	101.52		
Voluntarily choosing the nursing department				
Yes	266	100.96	Z: 0.261	0.804
No	96	100.38		
Working status				
Working	23	95.52	K-W: 0.983	0.375
Not working	318	101.16		
Part-time working	21	101.23		
Educational status of mothers				
Illiterate	33	103.78	K-W: 0.977	0.420
Elementary school	170	101.12		
Secondary school	67	102.64		
High school	77	97.66		
University	15	98.66		
Educational status of fathers				
Illiterate	8	97.12	K-W: 1.056	0.378
Elementary school	105	101.69		
Secondary school	63	103.74		
High school	119	100.59		
University	67	97.49		
Parental employment status				
Only father works	257	100.42	K-W: 1.435	0.232
Only mother works	25	107.36		
Both parents work	69	99.20		
Income status				
Low	16	102.62	K-W: 1.515	0.221
Medium	290	101.47		
Good	56	96.85		
Currently living status				
At home with family	135	99.48	K-W: 0.945	0.419
At home with friends	64	99.00		
State dormitory	104	102.47		
Private dormitory	59	102.89		

CDMNS: Clinical Decision-Making in Nursing Scale.

found to be 100.81±18.69. Considering that the highest score which can be obtained from this scale is 200, it is possible to say that the students' clinical decision-making levels are medium. When considering other national and international studies on this subject, it was noticed that the clinical decision-making levels of other students were found to be higher than for our students.[13,15,16,22,23] The results of our study were not similar to these other study findings. This difference between studies may have resulted from the fact that the other studies were carried out in schools where different course curricula and educational methods were applied.

Nursing students must be able to maintain the process of fast and accurate clinical decision-making in changing conditions by interpreting different information.[16,24] It was found that the clinical decision-making perception of the nursing students was at medium levels in the sub-dimensions of "*search for alternatives or options", "canvasing of objectives and values*", "*evaluation and reevaluation of consequences*" and "*search for information and unbiased assimilation of new information*". When the literature was reviewed, in the studies of Özen et al.[22], the sub-dimensions of the CDMNS-Tr of the students were observed to be above average, and in the studies of Özden et al.[16], they were observed to be high. In terms of these, our research results were not similar to the literature.

Another study on nurses by Chen et al.[25] emphasized that clinical experience affects clinical decision-making. As a result of our study, it was observed that the grade/year at which the students study did not affect their clinical decision-making levels. Although there was no significant difference between them, the highest CDMNS-Tr mean score was found in 3rd grade students and the lowest mean score was found in 4th grade students. In the literature, it was reported that the clinical decision-making skills of students increased with their clinical experience at all stages of their education.[13,26] However, in our study, the clinical decision-making levels of the senior students were observed to be lower than those students studying in the lower grades. When the literature was reviewed, it was observed that simulations of practices had a positive effect on the clinical decision-making levels of nursing students.[27,28] The fact that the clinical skills of the students who participated in this research were supported by simulation only in their first grade and the lack of simulation-based practices in the higher grades may have caused the fourth-year students to have the lowest clinical decision-making skills. On the other hand, in the fourth-grade internship practice, students take on a responsibility almost identical to a nurse and therefore, they have a lot of new information to learn. In addition to this, nurses started working with the clinical "*Computer Based Decision Support Systems*". [29] Within the education curriculum, these systems are mentioned only theoretically and the students do not practice on these systems. This may have caused them to feel insufficient in the clinical decision-making process. Moreover, similar to our study topic, as a result of the study conducted to reveal the clinical decision-making levels of nursing students and the variables which affect them by Özden et al.[16], it was found that the variable of grade/year did not affect the clinical decision-making levels of the students. Aktaş and Karabulut[30] and Özen et al.[22] found similar results in their studies. The result of our study supports the findings of these two studies.

In this research, it was concluded that the gender factor of the students did not affect their clinical decision-making levels. Similar results were also found in the study conducted by Özden et al.[16]. Unlike this study, some studies stated that gender was directly related to the decision-making process.[3,31] Our study result did not support those others study results. This made us think that this difference may be due to the fact that the majority of the students who participated in our study were female, and that a balanced ratio could not be established in our study sample group. Furthermore, as a result of this study, it was found that the high school type and income status of the students did not affect their clinical decision-making levels. However, the results of other studies which analyzed the effects of these two variables on the clinical decision-making levels of the students could not be found. Therefore, based on our results alone, it is possible to conclude that the high school type and income status of the students do not have a significant effect on their clinical decision-making levels.

It is thought that providing a democratic environment in the family, which is the closest environment where individuals grow, can change the factors which may affect students' decision-making skills, such as their self-expression and their capacity to take responsibility.[32] For this reason, when the education levels of their parents and the students' status of having chosen the nursing department willingly or not were questioned, no significant difference was found between these variables and the CDMNS-Tr mean score. Özden et al.[16] found in their research that individual differences, such as the employment status of the mothers of the students and whether they had entered the nursing department willingly, affected their clinical decision-making levels. The difference with the literature may have resulted from the fact that very few of the students in the sample group had working mothers, and therefore, a homogeneous distribution could not be provided in this regard.

CONCLUSION

Clinical decision-making, which involves a series of decisions in order to carry out the patient care process effectively, is a complicated process, but it is a critical skill which should be developed during the education process of nursing students. As a result of this study, it was revealed that the nursing students' status of clinical decision-making is at a medium level. It was found that variables such as grade, gender, type of high school, number of members living in the family, education status of parents, having entered the department willingly, income and employment status did not affect the clinical decision-making status of students.

Nurse educators and administrators have a great responsibility in the improvement of nursing students' skills in decision-making. In this context, we suggest the following recommendations;

- Repeating the study on a larger sample group, and on students studying in different curricula in nursing.

- Investigating the clinical decision-making levels of students in terms of other variables, such as critical thinking, problem solving, the clinical learning environment, while also considering their individual differences and communication skills.

- Improving the current conditions of "realistic patient simulation" training, which will contribute to the clinical decision-making processes of the students in the first grades and also adding them to the curricula of the second, third and fourth grade students.

- In addition to the theoretical knowledge about computer-based decision support systems, implementing training methods which are

based on practice and also providing computer skills to the student nurses in a more professional manner during their nursing education.

MAIN POINTS

• Although clinical decision-making is an integral part of nursing practice, the nursing students' status of clinical decision-making is at a medium level.

• It was found that variables such as grade, gender, high school of graduation, number of members living in the family, the education status of the parents, having entered the nursing department willingly, or income and employment status do not affect the clinical decision-making status of the students.

ETHICS

Ethics Committee Approval: For the implementation of this research, written permissions from the faculty in which the research was conducted and from the Bursa Uludağ University Health Sciences Research and Publication Ethics Committee (approval number: 2019/03).

Informed Consent: Verbal informed consent from the students were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.A., D.Y., H.G.Ç., R.U., Design: B.A., D.Y., H.G.Ç., Supervision: B.A., Fundings: B.A., D.Y., Materials: B.A., D.Y., H.G.Ç., Data Collection and/or Processing: B.A., D.Y., R.U., Analysis and/or Interpretation: B.A., D.Y., H.G.Ç., Literature Search: B.A., D.Y., H.G.Ç., R.U., Writing: B.A., D.Y., H.G.Ç., R.U., Critical Review: B.A., H.G.Ç.,

DISCLOSURES

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REFERENCES

1. Sucu G, Dicle A, Saka O. Decision making in clinical nursing: decision-making models and affecting factors. Hemşirelikte Eğitim ve Araştırma Dergisi. 2012; 9(1): 52-60.
2. Thompson C. A conceptual treadmill: The need for 'middle ground' in clinical decision making theory in nursing. J Adv Nurs. 1999; 30(5): 1222-9.
3. Lauri S, Salanterä S, Chalmers K, Ekman SL, Kim HS, Käppeli S, et al. An exploratory study of clinical decision-making in five countries. Jf Nurs Scholarsh. 2001; 33(1): 83-90.
4. Inangil D, Uzen Cura S. Nursing Students' Perceptions of Nursing Diagnoses and Clinical Decision-Making. Clin Exp Health Sci. 2020; 10: 131-6.
5. Tanner CA. Thinking like a nurse: a research-based model of clinical judgment in nursing. J Nurs Educ. 2006; 45(6): 204-11.
6. Junnola T, Eriksson E, Salanterä S, Lauri S. Nurses' decision-making in collecting information for the assessment of patients' nursing problems. J Clin Nurs. 2002; 11(2): 186-96.
7. ONeill ES, Dluhy NM, Chin E. Modelling novice clinical reasoning fora computerized decision support system. J Adv Nurs. 2005; 49(1): 68-77.
8. Günerigök F, Yılmaz Kurt F, Küçükoğlu S. Determination of Nursing Student's Self-Confidence and Anxiety Levels in The Process of Clinical Decision Making: Example of Two Different Programs. Journal of Anatolia Nursing and Health Sciences. 2020; 23(1): 77-94.
9. Canova C, Brogiato G, Roveron G, Zanotti R. Changes in decision-making among Italian nurses and nursing students over the last 15 years. J Clin Nurs. 2016; 25(5-6): 811-8.
10. Durmaz A. Hemşirelik öğrencilerinin ameliyat öncesi ve sonrası hasta bakım yönetimini öğrenmesinde bilgisayar destekli simülasyon tekniğinin etkisi. Hemşirelik Programı Yayınlanmamış Doktora Tezi, Dokuz Eylül Üniversitesi Sağlık Bilimleri Enstitüsü. İzmir; 2012.
11. Garrett B. Student nurses' perceptions of clinical decision-making in the final year of adult nursing studies. Nurse Educ Pract. 2005; 5(1): 30-9.
12. Botti M, Reeve R. Role of knowledge and ability in student nurses' clinical decision-making. Nurs Health Sci. 2003; 5(1): 39-49.
13. Dicle A, Durmaz Edeer A. Examination of clinical decision making perceptions of nursing students. The New Educational Review. 2013; 33(3): 134-44.
14. Jahanpour F, Sharif F, Salsali M, Kaveh MH, Williams LM. Clinical decision-making in senior nursing students in Iran. Int J Nurs Pract. 2010; 16: 595-602.
15. Ho SE, Koo YL, Ismail S, Hing HL, Widad O, Chung HT et al. Clinical decision making ability of nursing students in a tertiary hospital. Medicine & Health. 2013; 8(2): 73-80.
16. Özden D, Özveren H, Gülnar E. Nurse Students' Clinical Decision-Making Abilities Level and The Factors That Affect Abilities. DEUHFED. 2018; 11(1): 41-7.
17. Jenkins HM. Cinical decision making in nursing scale. In: Waltz CF, Jenkins LS, (Eds), Measurement of Nursing Outcomes volume:1 measuring nursing performance in practice, education and research. USA: Springer Publishing Company; 2001; p. 33-7.
18. Jenkins H. Perceptions of decision making among baccalaureate nursing students as measured by the clinical decision making in nursing scale, doctors theses. University of Maryland; 1983.
19. Edeer DA, Sarıkaya A. Adaptation of Clinical Decision Making in Nursing Scale to Undergraduate Students of Nursing: The Study of Reliability and Validity. International Journal of Psychology and Educational Studies. 2015; 2(3): 1-9.
20. Azak A, Taşcı S. Clinical decision making and nursing: review. Türkiye Klinikleri J Med Ethics. 2009; 17(3): 176-83.
21. Taşçı S. The Problem Solving Process in Nursing. Journal of Health Sciences. 2005; 14(Suppl): 73-8.
22. Özen N, Yazıcıoğlu İ, Çınar Fİ. Analyzing the Correlation between the Attitudes of Nursing Students towards Using Computers in Health Care and Clinical Decision Making Skills. Hemşirelikte Eğitim ve Araştırma Dergisi. 2017; 14(2): 112-8.
23. Krumwiede AK. An examination of accelerated and basic baccalaureate nursing students' perceptions of clinical decision making. Capella University, Doctor of Philosophy, 2010, UMI Number: 3409185. (Accessed on; 13 April 2020). Available from: https://eric.ed.gov/?id=ED518161
24. Johansen ML, O'Brien JL. Decision making in nursing practice: a concept analysis. Nurs Forum. 2016; 51(1): 40-8.
25. Chen SL, Hsu HY, Chang CF, Lin ECL. An exploration of the correlates of nurse practitioners' clinical decision-making abilities. J Clin Nurs. 2016; 25(7-8): 1016-24.
26. Atasoy I, Sütütemiz N. A group of final year students views on nursing education. Florence Nightingale Hemşirelik Dergisi. 2014; 22(2): 94-104.

27. Bonnetain E, Boucheix JM, Hamet M, Freysz M. Benefits of computer screen-based simulation in learning cardiac arrest procedures. Med Educ. 2010; 44(7): 716-22.

28. Salyers VL. Teaching psychomotor skills to beginning nursing students using a web- enhanced approach: A quasi-experimental study. Int J Nurs Educ Scholarsh. 2007; 4(1): Article11.

29. Randell R, Mitchell N, Dowding D et al. Effects of computerized decision support systems on nursing performance and patient outcomes: A systematic review. J Health Serv Res Policy. 2007; 12(4): 242-9.

30. Aktaş YY, Karabulut N. A Survey on Turkish nursing students' perception of clinical learning environment and its association with academic motivation and clinical decision making. Nurse Educ Today. 2016; 36: 124-8.

31. Bjørk IT, Hamilton GA. Clinical decision making of nurses working in hospital settings. Nurs Res Pract. 2011; 2011: 524918.

32. Eldeleklioğlu J. The relationship between Parental attitudes and decision making strategies. Türk Psikolojik Danışma ve Rehberlik Dergisi II. 1997; 11: 7-13.

RESEARCH ARTICLE

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Investigating the Relationship Between Emotional Well-Being and Academic Performance in Nursing Students In Turkey

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Abstract

BACKGROUND/AIMS: Emotional intelligence (EI) and codependency (CD) are concepts which affect nurses' personal well-being and the care provided by them. This study aimed to investigate the relationship between emotional well-being and academic performance in nursing students in Turkey

MATERIALS and METHODS: This study was of a longitudinal, descriptive design on nursing students in Turkey. The participants were a cohort of 138 student nurses who had commenced their training in the Faculty of Health Sciences at Ankara University.

RESULTS: It was found that average EI scores decreased over the 4-year study program and average CD scores increased throughout the nursing education. It was also observed that there was a relationship between EI and CD; and also there was a relationship between EI and academic grades. These findings revealed areas for improvement in the current nursing education in order for the student nurses to become more healthy and effective nurses.

CONCLUSION: Nursing education programs should be reviewed and new strategies should be planned for the well-being of the students. For beneficial patient outcomes, the EI and the CD of the students should be determined and improved and outcomes of nursing education should be measured.

Keywords: Education, emotional intelligence, codependency, nursing students, academic performance, nursing education, Turkish

INTRODUCTION

Anticipating patients' needs and providing personalized holistic care are core expectations of the nurse's role and deeper levels of intimacy and empathy are increasingly recognized as essential components of a positive nurse/patient relationship. Emotional intelligence (EI)[1-4] and codependency (CD)[5-7] are concepts which require understanding, using and managing emotions for effective relationships in a healthy way and these affect the nurses' personal well-being and the care provided by them. However, managing one's own emotions and the emotions of patients is a complex and demanding activity which carries risks of over-involvement and ultimately harm to the emotional well-being of the nurse. While EI is a positive concept, CD is a negative concept which affects nurses individually and professionally. If we could encourage and select nursing applicants who have an apparent ability in this

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regard, perhaps we could enhance the profession and create a positive impact on patient care. If it was possible to identify these inter and intra personal qualities in prospective students, we would expect such students to fit into the profession, with all its emotional demands, more readily than those student who struggle to understand and utilize emotions in a proactive way. If we cannot select suitable nursing applicants, theses necessary skills must be gained through nursing education programs.

In this study, the following questions were asked:

1. Is there any difference between the levels of EI and CD of the nursing students throughout their four-year education program?

2. What is the relationship between EI and CD in nursing students?

3. What is the relationship between EI and CD and the academic performance of the nurse students?

Background

EI was originally described by Mayer et al.[1] as a set of skills which includes the ability to perceive emotion, involving the capacity to recognize emotions through non-verbal behavior; use emotion to facilitate thought; understand emotions by analysis and prediction and manage emotions in the context of other personality characteristics. Augusta Landa and López-Zafra[8] investigated the impact of EI on nursing and highlighted that, "…. emotions play an important role in a profession that requires not only technical expertise but also psychologically oriented care, knowledge about the self and emotions in nursing would be crucial to further development and growth of the profession." EI plays an important part in the ability to form successful interpersonal relationships in nursing.[9,10] EI is identified as central to clinical practice as nurses are managing their own emotions as well as providing emotional support to their patients.[11,12] All nursing interventions are affected by EI and EI enables emotional awareness in relation to oneself and others, professional efficiency and emotional management.[13]

EI is a major focus in nursing education but it has not been considered as essential for personal and professional competency.[3,9,11] In the study by Rankin[14], a predictive relationship was found between EI and program outcomes, such as practice performance, academic performance and retention in students. According to the results of a systematic review which covered articles published between 2007 and 2021, EI has an impact on students' clinical and academic performance, physical and mental health and social relationships.[11] Similarly, it was found that EI is an important variable in nurses' own health and so providing education or training on EI may help prevent occupational stress, burnout and associated impacts on health in nurses and nursing students.[8,13] The EI of nursing students was associated with perceived stress, problem focused coping, subjective well-being, perceived nursing competency and academic performance[2], personal well-being, stress management, higher academic performance, stronger nursing leadership, practice performance, and greater patient safety.[4] Many studies have highlighted the potential value of facilitating the EI of nursing students. In a review of studies covering 1996-2016, Lewis et al.[15] suggested that EI should be developed in order to improve academic and clinical performance and to reduce the risk of emotional distress during clinical placement experiences. Therefore, EI needs to be explicitly promoted within nursing education to facilitate learning, to improve academic grades, to transform theory to clinical application, and to enhance the well-being of the students coping with stress.[8,11,12,15,16]

CD is a behavioral pattern and way of thinking which includes an inability to identify, express, and manage feelings; the tendency to adopt a caretaking role; to experience low self-worth and the desire to control the self, people or events.[6] External focus, self-sacrifice and dysfunctional coping behaviors are identified as the main elements of CD in a systematic review of the concept by Dear et al.[17] A review of the literature reveals a wide variety of symptoms associated with CD including compulsive caretaking; perfectionism; a distortion of boundaries; an inability to tolerate separation; using maladaptive strategies to cope with stressful life events; hiding the self, feeling responsible for others; and seeking others' approval.[18,19] CD was examined especially between 1980-2000 and described as a learned behavior in the family;[20] a personality disorder;[21] as an addiction which includes being addicted to the confirmation of others to gain self-security, self-confidence and self-identity and an unhealthy and self-defeating approach to human relationships.[22] CD is especially common in nurses, which may lead to burnout, unsatisfactory performance, and flight from the profession.[18] By increasing awareness of CD, effective strategies can be applied to enhance the well-being of the nursing students.

There is evidence regarding the importance of EI and CD in nursing. Although studies on EI continue to increase in the literature, it must be emphasized that little research has been carried out on nursing students to date and many studies have only been developed recently.[2,4,11] On the other hand, studies on CD have decreased since 2000. Although EI and CD are important concepts in terms of nursing education, student nurses' and nursing professionals' well-being, we have found no studies which examine EI and CD together in relation to academic achievement over the course of a program of nursing education. In the literature EI and CD were examined together in just one study by Belyea[7] on graduate students in a counselor education program and it was determined that there was a direct link between EI and CD. This current study located significant gaps in knowledge related to EI and CD in nursing education. In addition to these, there have been a few longitudinal studies across a two year nursing program on EI in nursing students[4] but no longitudinal study on CD. This four-year longitudinal study aimed to be useful in highlighting the potential value of facilitating EI and reducing CD in nursing students. We hope that the results from this study will firstly inform the growing debate about the importance of EI and well-being in nursing students and discussions about the role of EI in the recruitment and development of nursing students. Secondly, we hope that our results will shed light on the importance of EI and CD and lead to them being taken into account in future nursing curricula as a core component for the quality of care and well-being of students and nursing professionals.

MATERIALS AND METHODS

Study Design

This study utilized a longitudinal, descriptive design.

Sample

The participants were a cohort of 138 student nurses who commenced their training in October, 2012 and graduated in 2016 from the nursing department of the faculty of health sciences at a university. Nursing department which provides a general nursing degree-level program over 4 years. Totally, 158 students who enrolled in the nursing program

were invited to participate in this study, 138 students were accepted but 9 students left, 2 did not complete this study and so a total of 127 (92%) completed the questionnaires.

Data Collection

Data were collected using two relatively short questionnaires, the EI Scale (AES) and the Co-dependency Assessment Tool (CODAT), with additional questions to identify important socio-demographic information from the nursing students such as their age, gender and marital status. Overall end of year scores for academic performance were obtained from the students' records at the end of each academic year. The questionnaire data were collected at three time points: at the start of the first year fall period, at the end of the second year spring period; and at the end of the final year spring period. Academic performance scores were collated at the end of each year until July, 2016. The students were asked to complete the questionnaires in a classroom reserved for this study and this took about 30 minutes each time.

Assessing Emotions Scale (AES)

Schutte et al.[23] developed AES, a self-report measure of EI, based on the model of EI developed by Salovey and Mayer[1] in 1990. Schutte et al.[23] reported a Cronbach alpha of 0.90 for the internal consistency for adults. The AES was revalidated for the Turkish population by Ançel et al.[24] The revalidated AES form, which has 28 items with a five-point Likert-type scale (1= *strongly disagree*, 5= *strongly agree*), was used in this study and the total scores can range from 28 to 140. Higher total scores indicate higher EI. The measure has three sub-scales: (a) *awareness of their own emotions* (to identify one's own emotions and be aware of them, their triggers and their impact); (b) *managing emotions* (using managing strategies in a healthy way in relationships); and (c) *awareness of others' emotions* (to recognize and understand what might be behind their emotions). In the current study, the Cronbach alpha value was 0.83 for the total and for the sub-dimensions, it was 0.72, 0.78 and 0.84, respectively.

The Codependency Assessment Tool (CODAT)

CODAT was developed by Hughes-Hammer et al.[20] to assess CD. CODAT is a 25-item 5-point Likert type scale. Participants are asked to record how often they feel in the way indicated by the item on a scale ranging from 1= "*rarely or never*" to 5= "*most of the time*". The scale has five factors: a) *other focus/self-neglect*, b) *low self-worth*, c) *hiding oneself*, d) *medical problems*, and e) *family origin issues*. Higher scores indicate higher levels of CD. CODAT has good internal consistency and criterion group validity and the Cronbach's alpha reliability is 0.91. Criterion validity was determined by known group techniques. The psychometric qualities of the Turkish version of CODAT were evaluated by Ançel and Kabakçi[25] and research results support the internal consistency and validity of the Turkish version of CODAT.

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) program Version 17.0 for Windows (IBM, Armonk, New York, USA). Coded, anonymous questionnaire data were entered, then checked and cleaned by a second researcher prior to statistical analysis. In the summary of the data, the median (minimum-maximum) identifier was used as the measure. The Friedman test was used to examine time-dependent changes of subscale scores. Post-hoc tests were used to determine the group(s) which produced the differences when any were found. The Spearman correlation coefficient was calculated in evaluating correlations between scale scores and between scale scores and grade averages. $P<0.05$ was considered statistically significant

Ethical Considerations

Ethical approval for this study was obtained from the Ankara University Ethics Committee (approval number: 129-566). The students were asked to provide written consent to participate in this study and complete the questionnaires and allow access to their academic grade records. The students could decline to take part or withdraw from the study at any time with no impact on their studies or practice. Confidentiality was assured with only the researchers having access to the research data. Students were anonymized using coded identity numbers and no individual could be identified. The participants were also assured that no judgments would be made on their actual performance in the program on the basis of any information taken as part of this study and that no information would be passed to their assessors throughout this study.

RESULTS

With respect to the students' characteristics; 89.0% of the students were female, their average age was 23.31±0.99 years (minimum: 22, maximum: 26), and all were single. Most (71.7%) lived with friends; 10.2% of them lived with family and 3.9% lived alone, 92.2% of the students reported that no family member had mental disorders. The students were asked whether they were receiving any treatment or support for psychological/psychiatric problems; 5.5% said "*yes*" at their first assessment, 5.3% at their second assessment, and 11.2% at their third assessment.

The time comparison of scale points on the AES found that students reported being more able to manage emotions at the beginning of their studies than at the end ($p<0.05$). No significant difference was found between the first and last scores of the sub-scales of *awareness of own emotions* and *awareness of others' emotions* ($p>0.05$) (Table 1). On the CODAT, scores on the sub-scales suggested that over the course of their studies, there were significant differences in the scores of *low self-worth*, *family origin issues* and *medical problems* ($p<0.05$) and no significant differences in the scores of *hiding oneself* and *other focus/self-neglect* ($p>0.05$) (Table 1).

According to the Spearman correlation coefficient, higher AES scores correlated with better grades in the final year, but scores on CODAT did not correlate with grade scores (Table 2). With regards to the AES, higher scores of *awareness of own emotions* ($p<0.05$), *managing emotions* ($p<0.01$), and *awareness of others' emotions* ($p<0.001$) were correlated with higher grade scores. However, with regards to the scores on the sub-scales of CODAT; *low self-worth*, *family origin issues*, *medical problems*, *hiding oneself* and *other focus/self-neglect* did not correlate with grade scores at all.

When exploring correlations between scores on the two scales used, Table 3 shows that poorer scores on the AES sub-scales of *awareness of own emotions* and *managing emotions* were associated with ratings of *low self-worth* ($p<0.001$), *medical problems* ($p<0.01$, $p<0.001$) and *hiding oneself* ($p<0.05$, $p<0.01$) but were not associated with *family origin issues*, and *other focus/self-neglect* on the CODAT. Greater *awareness of others' emotions* as scored on the AES was associated with higher levels of *focus on others/self-neglect* ($p<0.05$, $p<0.01$) on CODAT.

Table 1. Time comparison of Emotional Intelligence Scale (AES) and Codependency Assessment Tool (CODAT) scores

Scales	Sub-dimensions	Time measurements			p
		First scores	Second scores	Third scores	
AES	Awareness of own emotions	4.23 (2.46-5.00)*	4.15 (2.33-5.00)	4.15 (1.38-5.00)	0.157
	Managing emotions	4.56 (2.22-5.00)*	4.33 (1.67-5.00)	4.33 (1.00-5.00)	0.037
	Awareness of others' emotions	3.33 (2.17-4.00)	3.33 (2.17-4.50)	3.5 (2-4.67)	0.689
CODAT	Low self-worth	1.5 (1-3.67)	1.5 (1-4.67)	1.67 (1-4.83)	0.039
	Family origin issues	1.8 (1-4)	2 (1.2-4.6)	2.2 (1.4-4.6)	<0.001
	Medical problems	1.25 (1-4)	1.75 (1-4.25)	1.75 (1-5)	<0.001
	Hiding oneself	2.8 (1.2-4.6)	2.8 (1.2-4.6)	2.6 (1.2-4.8)	0.612
	Other focus/Self-neglect	2.4 (1-4.8)	2.3 (1-4.6)	2.4 (1-4.6)	0.236

*values in the cells correspond to the median (minimum-maximum).

Table 2. Correlation between Emotional Intelligence Scale (AES), Codependency Assessment Tool (CODAT) and grades

Scales	Sub-dimensions	Grade average			
		1st year spring semester	2nd year spring semester	3rd year spring semester	4th year spring semester
AES	Awareness of own emotions	-0.179	-0.101	-0.175	-0.229*
	Managing emotions	-0.091	-0.085	-0.144	-0.295**
	Awareness of others' emotions	-0.019	-0.041	-0.151	-0.195*
CODAT	Low self-worth	0.098	0.130	0.010	0.136
	Family origin issues	0.018	-0.009	0.106	0.034
	Medical problems	-0.049	0.100	0.044	0.144
	Hiding oneself	-0.030	0.028	-0.161	-0.070
	Other focus/Self-neglect	-0.086	0.059	0.165	0.167

The values in the cells correspond to the correlations between the grade average and the subscale score in the related term: *: p<0.05, **: p<0.01, ***: p<0.001.

Table 3. Correlations between Emotional Intelligence Scale (AES) and Codependency Assessment Tool (CODAT)

Low self-worth		*CODAT*				
		Family origin issues	Medical problems	Hiding oneself	Other focus/self-neglect	
AES	Awareness of own emotions	-0.376*** -0.337*** -0.408***	-0.119 -0.069 -0.153	-0.043 -0.243** -0.302**	0.252** 0.234* 0.091	0.136 0.019 -0.016
	Managing emotions	-0.316*** -0.389*** -0.376***	-0.204* -0.065 -0.147	-0.127 -0.260** -0.351***	0.258** 0.183* 0.216*	0.069 -0.139 -0.100
	Awareness of others' emotions	0.063 0.056 0.152	0.087 0.080 0.077	0.088 -0.021 -0.007	0.068 0.183 0.100	0.278** 0.191* 0.243**

The first values in the cells correspond to the correlations of the "first fall period", The second values are correlations of the "second year-spring period" and the third values are the correlations of the "fourth year-spring period". *: p<0.05, **: p<0.01, ***: p<0.001.

DISCUSSION

To the best of our knowledge, this is the first longitudinal study on EI, CD and academic grades in nursing students undertaking a four-year nursing program in the literature in Turkey. EI and CD were examined in nursing students in order to investigate the well-being of the participants. Contrary to our expectations, the students' EI scores did not increase during the 4-year program. In fact, increased scores of the CODAT (Table 1) and increased the rates of mental illness in the fourth year (11.2%) compared to first year (5.5%) were observed, which suggests some deterioration in the well-being of the students during the four years. This was actually an expected finding that the EI score did not increase as there was only a 28-hour interpersonal relations course in the first year in the entire curriculum and the nursing program had neither a goal, educational strategies, nor a course to develop or raise EI. Nurses provide care through relationships with their patients and the nature of nursing obliges nurses to have high EI[9] and higher EI scores are associated with better levels of health.[2,8,11] Therefore, EI should be incorporated in the nursing curriculum of the department where this study was conducted in order to contribute to both the student's own health and their professional performance.

EI and nursing students' mental health has been discussed more in recent years in the literature. According to study by Por et al.[2], increased emotional competence assists nursing students in effective coping strategies which in turn enhances their well-being and also their professional competence. In one study, it was found that there was an association between EI, stress and health[8] and also it was found that EI moderates the relationship between stress and depression, hopelessness and suicidal ideation[26] and that higher EI was associated with a positive mood and higher self-esteem.[27]

Due to the relationship between EI and mental health, EI should be improved in nursing students. There are studies which show EI increased[4] or did not not change[10] throughout nursing education. However, according to authors, EI could be improved by training programs.[8,9,11,28,29] In these programs, different topics, teaching/learning methods and lengths are recommended. Transformatory learning, expressive modalities of teaching such as reflective practice, emotional learning, interventional programs and curriculum contents are recommended in order to develop EI.[9] Self-awareness,[9] social perspective taking,[28] and social and communication skills training[8] for nursing students are suggested to improve EI. Since EI is influenced by students' clinical competence; and could be affected by curriculum,[3,15,30] clinical experiments and curriculum should be involved in EI developer strategies. The emerging trend is for nurse educationalists to embrace the notion of EI as a valid measure of suitability for nursing.[16] The better "*fit*" the student has in a nursing program, the greater her/his chance of successful completion.[14] Unfortunately, there is a general, central entrance examination to nursing in Turkey. Therefore, the EI of students needs to be developed through their nursing education.

In this study, as well as EI, a deterioration in the CD levels of the participants during the four years indicates a risk for the students' mental health and also for their physical health. Evidence of stress related physical problems[31] and mental health problems[5,26] in CD have been shown. CD was associated with decreases in perceived health and the ability to function in daily activities[6] and low self-esteem.[22] The increasing CD in the current study requires questioning the values and structure of the environment in which the students acquire their clinical experience and theoretical education. In the literature, the patriarchal values based caring, the hospital structure as a patriarchal organization which is similar to the structure of a dysfunctional family and the stressful work environment are associated with CD.[18] Increasing CD also may be related to the participants' family background. In a previous Turkish study, Ançel and Kabakçi[25] indicated that nursing students with higher CD scores had more attachment-related anxiety and reported more family problems. Problematic parenting experiences in childhood have been highlighted in CD.[17,22,31,32] Therefore, a supportive learning environment, psycho-educational interventions, health education (i.e., assertiveness training, problem-solving, and skills-building) and group therapy for CD and the related mental health problems of the students should be maintained during nursing education.[32,33] The structure of hospitals, and patriarchal values based nursing education should be identified and strategies for preventing and changing these negative influences should be applied for the well-being of students. However, this is the first longitudinal study and further prospective research would be helpful in order to determine the reasons for the increase in CD in the students.

Another finding of this study was that increased EI was associated with improved grades in the final year (Table 2). The relationship between EI and academic success has been explained in various studies. The annual average grade has been related to EI in nursing students[16] and higher academic and clinical practice performance have also been associated with higher EI.[3,4,12,14] This association between EI and academic success suggests that the incorporation of EI-related skills in the nursing curriculum has significant implications for nursing education to achieve the required competencies.[12] The relationship between higher EI and academic success can also be explained by the emotional state and well-being of the students. EI facilitates learning by enhancing the ability to cope with stress[2] and high EI leads to high self-esteem and this in turns increases academic achievements and work productivity.[11,34] However, the relationship between EI and academic performance is not specific and the mechanism for the correlation between them is still unclear in the literature[3]. In the current study, academic success increased through the four years despite a degeneration in EI and CD. In this case, the relationship between EI and academic success needs to be examined in further studies to determine the mechanism and reasons why EI was associated with improved grades in only the final year of the four years.

A correlation was found between EI and CD. Poorer ratings of both *awareness of own emotions* and *managing emotions* on the AES were associated with higher scores of *low self-worth*, *medical problems* and *hiding oneself* on the CODAT. Another correlation was found between *awareness of others' emotions* on the AES and *other focus/self-neglect* on the CODAT (Table 3). This correlation was expected since the sub-dimensions of both AES and CODAT incorporate emotional issues. Focusing on others, awareness of emotions, perceiving, understanding and managing emotions of one's own and others are the same requirements for both EI and CD. However, using emotions in healthy ways indicates EI[29] while using emotions in unhealthy way indicates CD.[6,19] Emotional sensitivity and awareness of the feelings of others is an important skill and a measure of high EI, while an "*over*" sensitivity or "*controlling*" of others emotions while hiding one's own feelings are signs of CD. According to Belyea[7] who was the only author to examine EI and CD together, there is a clear association between the constructs of CD and EI. Belyea[7] suggests that the definitions of the two concepts overlap and have common concepts such as empathy, nurturance, and

awareness of the emotions of others. In fact, nursing care requires a depth of emotional involvement within relationships which carries risks of hiding oneself, focusing on others' needs and certain related emotional problems. At this point, there is a need to know what the borders and balance are in the relationships with others for nursing students.

Study Limitations

This study is limited to one university in Turkey. As a consequence, generalization from the results is limited. However, this study provides important data about EI, CD and academic success in nursing students in this setting, allowing comparisons to be made with other institutions and cultures. Secondly, we wanted to compare theoretical and clinical academic grades with EI separately, but the student scoring system used in the university did not facilitate this. Lastly, further studies on EI and CD can include other variables, such as family, nursing curriculum content, culture, values in clinical environments etc.

As regards the present study, the findings now need to be replicated and validated in a more diverse sample of nursing students. It would also be useful to conduct longitudinal studies in order to establish causal relationships between the variables. Finally, qualitative studies on EI and CD among nursing students need to be examined in greater depth.

On the strength of the findings from this study, the Nursing Faculty where the research was completed recently revised its curriculum based on student-centered learning principles, reflective learning, and emotive competency. One or two courses and elective courses were added to the curriculum for each semester to increase the students' self-awareness, self-worth, personal and professional communication skills, in order to protect their mental health and to improve their social skills. In future, the effects of this revised program should be measured to determine any changes in the EI and CD of the students.

Implications for Nursing Education

The identification and prevention of negative influences associated with EI and CD in nursing students should be regarded as a priority. The relationship between EI and CD suggests that an interventional program on either CD or EI would benefit students' well-being. When nursing educators want students to develop their EI, it is necessary to determine CD in them, as CD may prevent the development of EI. Conversely, improving EI may be beneficial in reducing CD in students.

Additionally, it was hoped that the findings from this study would add to the discussion of both EI and CD together and develop them in training programs throughout the nursing curriculum. EI should be included in the selection criteria of nursing students to meet the expectations of the people who are receiving nursing care. As discussed above, the area of EI and CD still remains open to extensive empirical investigation.

CONCLUSION

Based on the findings which found decreases in EI and increases in CD throughout the nursing education, and which found a relationship between EI and CD and a relationship between EI and academic grades, nursing programs should be reviewed and new strategies should be planned to help students become more healthy and effective nurses. These findings reveal areas for improvement in the current nursing education to become more healthy and effective healthcare providers. The increases in EI and the deterioration in CD may have implications for the well-being of nursing students and the quality of working life within nursing. Therefore, available opportunities should be taken to provide support to nursing students in the faculty and nurses in healthcare settings. It can be suggested that EI should be included in the selection criteria as an approach to prevent problems in this regard and to meet the expectations of the people who are receiving nursing care.

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ETHICS

Ethics Committee Approval: Ethical approval for this study was obtained from the Ankara University Ethics Committee (approval number: 129-566).

Informed Consent: The students were asked to provide written consent to participate in this study and complete the questionnaires and allow access to their academic grade records.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.A., A.S., Design: G.A., A.S., Data Collection and/or Processing: G.A., Analysis and/or Interpretation: G.A., A.S., D.G., Literature Search: G.A., Writing: G.A., A.S., D.G.

DISCLOSURES

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REFERENCES

1. Mayer JD, Salovey P, Caruso DR. Emotional intelligence: Theory findings and implications. Psychological Inquiry. 2004; 15(3): 197-215.
2. Por J, Barribal L, Fitzpatric J, Roberts J. Emotional intelligence: its relationship to stress, coping, well-being and professional performance in nursing students. Nurse Educ Today. 2011; 31(8): 855-60.
3. Codier E, Odell E. Measured emotional intelligence ability and grade point average in nursing students. Nurse Educ Today. 2004; 34(4): 608-12.
4. Foster K, Fethney J, McKenzie H, Fisher M, Harkness E, Kozlowski D. Emotional intelligence increases over time: A longitudinal study of Australian pre-registration nursing students. Nurse Educ Today. 2017; 55: 65-70.
5. Hughes-Hammer C, Martsolf DS, Zeller RA. Depression and codependency in women. Archives of Psychiatric Nursing. 1998a; 12(6): 326-34.
6. Martsolf DS, Sedlak CA, Doheny MO. Codependency and related health variables. Archives of Psychiatric Nursing. 2000; 14(3): 150-8.
7. Belyea DL. 2011 The effect of an educational intervention on the level of codependency and emotional intelligence among graduate counseling students. Wayne State University, Dissertations. Retrieved from https://digitalcommons.wayne.edu/oa_dissertations/209/
8. Augusta Landa JM, López-Zafra E. The impact of emotional intelligence on nursing: An overview. Psychology. 2010; 1(1): 50-8.

9. Freshwater D, Stickley T. The heart of the art: Emotional intelligence in nurse education. Nurse Inquiry. 2004; 11(2): 91-8.
10. Holston EC, Taylor JY. Emotional intelligence in nursing students: Describing emotional intelligence in the last 2 years of a BSN program. International Journal of Advances in Psychology. 2016; 5: 11-22.
11. Dugué M, Sirost O, Dosseville F. A literature review of emotional intelligence and nursing education. Nurse Educ Pract. 2021: 54.
12. Fernandez R, Salamonson Y, Griffiths R. Emotional intelligence as a predictor of academic performance in first-year accelerated graduate entry nursing students. Journal of Clinical Nursing. 2012; 21: 3485-92.
13. Akerjordet K, Severinsson E. Emotionally intelligent nurse leadership: A literature review study. J Nurs Manag. 2008; 16(5): 565-77.
14. Rankin B. Emotional intelligence: Enhancing values-based practice and compassionate care in nursing. Journal of Advanced Nursing. 2013; 69(12): 2717-25.
15. Lewis GM, Nevilleb C, Ashkanasy NM, Emotional intelligence and affective events in nurse education: A narrative review. Nurse Educ Today. 2017; 53: 34-40.
16. Sharon D, Grinberg K. Does the level of emotional intelligence affect the degree of success in nursing studies? Nurse Educ Today. 2018; 64: 21-6.
17. Dear GE, Roberts CM, Lange L. Defining codependency: An analysis of published definitions. In S. Shohov (Ed.), Advances in Psychology Research, 2004; 34: 63-79. Huntington, NY: Nova Science Publishers.
18. Caffrey RA, Caffrey PA. Nursing: Caring or codependent. Nursing Forum. 1994; 29: 12-6.
19. Hopkins LM, Jackson W. Revisiting the issue of codependency in nursing: Caring or caretaking? Canadian Journal of Nursing Research. 2002; 34(4): 35-46.
20. Hughes-Hammer C, Martsolf DS, Zeller RA. Development and testing of the Codependency Assessment Tool. Arch Psychiatr Nurs. 1998b: 17(6): 326-34.
21. Cermak TL. Children of alcoholics and the case for a new diagnostic category of codependency. Alcohol Health Health and Research World. 1984; 8(4): 38-42.
22. Reyome ND, Ward KS, Witkiewitz K. Psychosocial variables as mediators of the relationship between childhood history of emotional maltreatment, codependency, and self-silencing. Journal of Aggression, Maltreatment & Trauma. 2010; 19(2): 159-79.
23. Schutte NS, Malouff JM, Hall LE, Haggerty DJ, Cooper JT, Golden C, Dornheim L. Development and validity of a measure of emotional intelligence. Personality and Individual Differences. 1998; 25: 167-77.
24. Ançel G, Açıkgöz I, Ayhan AGY. The relationship between problematic internet using emotional intelligence and some sociodemographic variables. Journal of Anatolian Psychiatry. 2015; 16(4): 255-63.
25. Ançel G, Kabakçi E. Psychometric properties of Türkish form of Codependency Assessment Tool. Archives of Psychiatric Nursing. 2009; 23(6): 441-53.
26. Ciarrochi JV, Deane F, Anderson S. Emotional intelligence moderates the relationship between stress and mental health. Personality and Individual Differences. 2002; 32(2): 197-209.
27. Schutte NS, Malouff JM, Simunek M, McKenley J, Hollander S. Characteristic emotional intelligence and emotional well-being. Cognition and Emotion. 2002; 16(6): 769-85.
28. Gorgas DL, Greenberger S, Bahner DP, Way DP. Teaching emotional intelligence: A control group study of a brief educational intervention for emergency medicine residents, West J Emerg Med. 2015; 16(6): 899-906.
29. Mattingly V, Kraiger K. Can emotional intelligence be trained? A meta-analytical investigation. Human Resource Management Review. 2019; 29(2): 140-55.
30. Benson G, Ploeg J, Brown B. A cross-sectional study of emotional intelligence in baccalaureate nursing students. Nurse Educ Today. 2010; 30(1): 49-53.
31. Harkness D. To have and to hold: Codependency as a mediator or moderator of the relationship between substance abuse in the family of origin and adult-offspring medical problems, Journal of Psychoactive Drugs. 2003; 35(2): 261-70.
32. Bacon I, McKay E, Reynolds F, McIntyre A. The Lived experience of codependency: An interpretative phenomenological analysis. International Journal of Mental Health and Addiction. 2020; 18: 754-71.
33. Abadi FKA, Vand MM, Aghaee H. Models and interventions of codependency treatment, systematic review. Jurnal UMP Social Sciences and Technology Management. 2015; 3(2): 572-83.
34. Bibi S, Saqlain S, Mussawar B. Relationship between emotional intelligence and self esteem among Pakistani University students. J Psychol Psychother. 2016; 6(4): 279.

RESEARCH ARTICLE

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The Impact of Taking Math Courses on Nursing Students' Skills to Calculate Drug Dosages: A Comparative Study

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Abstract

BACKGROUND/AIMS: This study evaluated the impact of taking math courses on nursing students' skills to calculate drug dosages.

MATERIALS AND METHODS: Two different groups of undergraduate nursing students constituted the sample of this comparative descriptive study. The first group was composed of 66 students who attended a fundamentals of nursing course. The second group was composed of 70 students who attended a fundamentals of nursing course and a basic mathematics course after a change in the nursing curriculum. Data were collected using a personal information form and a drug dosage calculation skills test (DDCST).

RESULTS: Those students who attended the math course obtained significantly higher scores on the DDCST compared to those who did not attend the math course. Students who did not like math or had a lower cumulative grade point average received lower scores on DDCST.

CONCLUSION: These findings suggest that departments of nursing may cooperate with the faculty of education and include basic mathematics courses in the curricula of nursing departments to increase the abilities of nursing students to calculate drug dosages. New strategies may be developed to improve the mathematical skills of nursing students.

Keywords: Nursing students, nursing education, math course, drug dosage calculation

INTRODUCTION

Drug administration is one of the most important functions of nursing, and it requires technical skills and a comprehensive knowledge.[1,2] Safe drug administration is one of the most important responsibilities of nurses.[3] Therefore, nurses should have sufficient skills in medication safety and drug dosage calculations.[4] Drug administration and medication safety are key subjects during the first year of nursing education.[1] Skills to calculate drug dosage are highly important for patient safety.[5]

Despite the development of new methods, tools and systems to ensure safety in drug administration, serious problems in drug administration may still occur. Nurses and nursing students should have the mathematical skills to calculate the correct drug dosage in an effective and safe manner.[6] Weaknesses in mathematical skills may harm patients via the miscalculation of drug dosages. Although the subject of drug dosage calculation is included in the nursing curriculum, problems with drug dosage calculation may occur in clinical practice. Weaknesses in mathematical skills are one of the main reasons for the miscalculation of drug dosages.[3,7-9] Analysis of the curricula in different countries reveals examples of nursing undergraduate curriculum with courses on mathematics.[10]

Medication errors are the most common type of errors which affect patient safety. Nurses hold the responsibility to maintain patient safety

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during medication administration. They need to take the necessary measures in order to maintain patient safety and success in medication administration.[11] A study on Turkish nurses found that 66.6% of the nurses had witnessed at least one medication error during the prior 12 months.[12]

Recent studies have examined the miscalculation of drug dosage by nurses and attempted to reveal the reasons for these miscalculations. These studies evaluated the mathematical and drug dosage calculation skills of nursing students and stressed the importance of the development of these skills in nursing education.[3,8,13] Some of these studies found that the nursing students had problems and felt anxious about basic math.[14] Negative learning experiences of the nursing students influenced their mathematical skills, and so math education in small groups was proposed for undergraduate students in nursing departments.[15]

Correct drug calculation during clinical practice and the safe administration of medications are the most important qualifications for nurses. The education of nursing students using an appropriate curriculum is key for safe clinical practices. An analysis of the nursing curriculum in Turkish universities revealed the absence of basic math courses in nursing education. The student group who participated in this research was heterogeneous in math education. Math courses were added to the nursing curriculum due to the low success rates of the students in drug dosage calculations. The present study compared the drug calculation skills scores of nursing students who did not take the math course with those students who attended the math course, which was subsequently added to the nursing curriculum. This study revealed the effects of the introduction of a basic mathematics course to the nursing curriculum on the drug dosage calculation skills of nursing students. These study findings may contribute to the revision of the nursing curriculum in order to improve safe drug administration. Within this context, this study aimed to analyze the impact of math lectures on the drug dose calculation skills of nursing students. The research questions included the following:

1. Do math lectures have an impact on drug dose calculation skills of nursing students?

2. Is there a relationship between the descriptive characteristics of nursing students and their drug dosage calculation skills?

MATERIALS AND METHODS

The present study was a comparative descriptive study to evaluate the effects of a basic mathematics course on the drug dosage calculation skills of nursing students. This study was performed on first-year and second-year undergraduate students of the nursing department of a private university in North Cyprus. A total of 184 students, including 100 students who were enrolled in the fundamentals of nursing course during the 2016-2017 academic year and 84 students who took the same course during the 2018-2019 academic year after the amendment of the curriculum, constituted the population of this study. A total of 136 students who attended the course and agreed to participate in this research constituted the study sample.

This study was performed in the nursing department of the faculty of health services at a private university. The duration of the nursing undergraduate program at this university is four years. The department gives courses on social and basic medical sciences in addition to basic nursing courses. Although the child health and disease nursing course in the third year also deals with drug dosage calculations, this subject is primarily the subject of the fundamentals of nursing course taught in the first year. The unit of the Fundamentals of Nursing course entitled "administrations of medications" includes 16 hours of instruction and teaches the basics of drug dosage calculation in approximately six hours.

Data Collection

This study was performed with undergraduate nursing students who had two different nursing curricula at the same university. Data were collected in two different periods, May, 2017 and December, 2018.

Group 1: Students in the first group took the fundamentals of nursing course in the spring semester of the first year. Drug dosage calculation was taught in approximately six hours within the context of the fundamentals of nursing course. Students were informed about the aim and scope of this research after their course, and their written consent was obtained. Students who agreed to participate were asked to complete the Drug Dosage Calculation Skills Test (DDCST) in 40 minutes without help or the use of calculators. Fourteen students who had not attended the lectures on drug dosage calculation and 20 students who found the test hard and left the study were excluded from this study. The study ultimately included 66 students in the first group.

Group 2: The nursing curriculum was amended in the 2017-2018 academic year, and a course, entitled Basic Mathematics for Social Sciences, was added. Unlike the first group, students in the second group took a basic mathematics course for 42 hours in 14 weeks during the first semester and took the fundamentals of nursing course after their basic mathematics course. The lectures on drug dosage calculation which were taught to the second group within the context of the Fundamentals of Nursing course did not differ from the first group. Ten students who had not attended the lectures and 4 students who refused to participate in this study were excluded. This study ultimately included 70 students in the second group.

Measures

We used a personal information form and the DDCST to collect the data.

Personal Information Form: This form was developed using the relevant literature[1,16,17] and was composed of questions on the sociodemographic characteristics of the nursing students, including age, gender, and parental educational status.

Drug Dosage Calculation Skills Test: The DDCST was prepared by Karabağ Aydin and Dinç[16] to evaluate the drug dosage calculation skills of nursing students. This test was prepared consistently with expert opinions, and item analysis was performed after a pilot study to evaluate the clarity of the test. The test included 25 questions, and each correct answer was given four points. The Cronbach's α of the DDCST was 0.67. We obtained permission to use the DDCST from the authors via e-mail.

Statistical Analysis

Frequency analysis was used to evaluate the distribution of the attendance to math courses according to the demographic characteristics of the participant students. The chi-squared test was used to compare the sociodemographic characteristics of the students who attended or did not attend the basic mathematics course. Means

and standard deviation were used to analyze the DDCST scores of the students. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to analyze the normality of the distribution of the DDCST scores, and the scores exhibited a non-normal distribution. Therefore, the Mann-Whitney U test was used for independent variables with two categories, and the Kruskal-Wallis test was used for independent variables with more than two categories.

Ethical Considerations

We obtained institutional permission from the head of the nursing department and research ethics approval from the research and publication ethics Eastern Mediterranean University Board of the university where this study was conducted (approval number: 2017/43-7). Written informed consent was obtained from all the participants.

RESULTS

Descriptive Characteristics of the Nursing Students

A total of 41.18% of the participants were between 18-19 years old, and 59.56% were female. The mothers of 32.35% of the participants and the fathers of 26.47% of the participants were graduates of primary school. A total of 40.44% of the participants were graduates of general high schools, and 60.29% were enrolled in nursing departments with an undergraduate placement exam. In addition, 30.88% of the participants had a cumulative grade point average (CGPA) lower than 2.00, and 35.29% had low success rates. Furthermore, 60.29% of the participants liked math. A total of 30.15% expressed that they did not use calculators, and 54.41% sometimes used calculators during mathematical calculations. A total of 44.85% of the participants considered themselves insufficient during drug dosage calculations.

Effects of the Math Course on DDCST Scores

The DDCST scores of those participants who had taken the basic mathematics course (=50.69±19.91) were significantly higher than those students who had not taken this course (=12.24±11.74) ($p<0.05$) (Table 1).

Comparison of the Descriptive Characteristics of the Students using the DDCST Scores

Table 2 reveals no statistically significant differences between the age, parental education, type of high school and perceptions about the success of the students who had taken the basic mathematics course and their scores on the DDCST ($p>0.05$). However, we found a statistically significant difference between the DDCST scores of those students who had taken the basic mathematics course and their gender, type of exams passed in order to enter the nursing department, academic success, calculator usage and their self-evaluations about their own drug dosage calculation skills ($p<0.05$). Accordingly, the DDCST scores of the male nursing students were statistically higher than their female counterparts ($p<0.05$). Students who had entered the nursing department using the EMU Entrance Exam had lower DDCST scores ($p<0.05$). Students with a CGPA below 2.00 obtained lower DDCST scores. However, students who liked mathematics and did not use calculators to solve mathematical problems had higher DDCST scores. Participants who considered their drug dosage calculation skills as sufficient also obtained higher DDCST scores.

DISCUSSION

Problems with drug dosage calculations have been on the agenda of researchers for a long time because miscalculations may harm patients.[18] Nurses and nursing students should have sufficient mathematical skills to calculate correct drug dosages. Poor skills in basic mathematics results in the miscalculations of drug dosages.[9,19] Our study found that the DDCST scores of those students who had taken a basic mathematics course were higher than for those who had not taken this course. In contrast to our findings, Alteren and Nerdal[7] found that the scores obtained from a basic math course did not significantly affect drug dosage calculation skills. However, Karabağ Aydin and Dinç[16] found a positive relationship between the arithmetic skills of nursing students and their DDCST scores. Similarly, Coyne et al.[3] found that strategies to increase the mathematical skills of nursing students increased their drug dosage calculation skills. McMullan et al.[20] also found a statistically significant positive relationship between the mathematical skills of their participants and their drug dosage calculation skills. Røykenes and Larsen[9] found that participants who perceived their mathematical skills as insufficient considered the drug dosage calculation tests stressful. Two studies on Turkish nursing students found that the mathematical and drug dosage calculation skills of their participants were low.[5,21] The students in our study entered the nursing department using different entrance exams and they were graduates of different types of high schools. The students had different mathematical skills depending on their type of high school. Therefore, we suggest that students who did not take math courses may obtain lower scores from drug dosage calculation tests. The findings of this study reveal the need for an amendment to nursing curricula with the addition of basic arithmetic skills for the administration of medications.

The DDCST scores of the participants increased from 12.24% to 50.69% with the inclusion of the basic mathematics course to the nursing curriculum. The introduction of a basic mathematics course also influenced the scores obtained by the students on their final exams. The average final exam scores of the control group who did not take the basic mathematics course was 51 during the 2017-2017 academic year. The average final score increased to 61.06 during the 2018-2019 academic year after the introduction of the basic mathematics course. The average DDCST score of the nursing students in the study of Karabağ Aydin and Dinç[16] was 71.55±12.29. The lower DDCST scores prior to the introduction of the math course in our study may have occurred due to a number of reasons. Nursing students should have obtained high scores from the math section of their university entrance exams, and so undergraduate students of nursing departments would have already

Table 1. Comparison of the drug dosage calculation skills test scores of those students who had taken and those who had not taken a math course

Group	n	$\bar{x}$	s	M	Min.	Max.	SO	Z	p
Took math course	70	50.69	19.91	54	12	84	97.54	-8.881	0.001*
Did not take math course	66	12.24	11.74	12	0	52	37.70		
Total	136	32.03	25.31	24	0	84	-	-	-

*p<0.05.

Table 2. Comparison of the descriptive characteristics of students who had received the math course with their scores obtained from the drug dosage calculation skills test

	n	$\bar{x}$	s	M	SO	X^2/Z	p
Age							
18-19	24	44.50	20.74	40.00	29.44	3,627	0.163
20-21	32	53.25	17.04	56.00	37.47		
22 and above	14	55.43	23.21	62.00	41.39		
Gender							
Female	35	44.11	20.15	48.00	28.74	-2.787	0.005*
Male	35	57.26	17.59	64.00	42.26		
Maternal education							
Illiterate	16	56.00	14.68	62.00	39.84	6,845	0.144
Primary school	19	51.16	20.77	56.00	36.71		
Secondary school	8	57.00	28.02	66.00	43.56		
High school	21	48.57	18.60	48.00	33.02		
University or above	6	34.00	16.73	30.00	18.00		
Paternal education							
Illiterate	9	55.56	15.29	60.00	39.50	3,692	0.449
Primary school	19	53.47	21.34	64.00	39.11		
Secondary school	10	52.40	20.87	48.00	36.85		
High school	18	50.67	21.61	56.00	35.86		
University or above	14	42.57	17.79	42.00	26.61		
Type of high school							
General high school	28	47.71	22.12	50.00	33.18	2,021	0.568
Vocational high school	9	48.00	21.82	40.00	33.67		
Anatolian high school (elite high school)	28	52.29	18.25	52.00	36.41		
Other	5	63.20	6.57	68.00	46.70		
Type of university entrance exam							
Eastern mediterranean entrance exam	19	36.21	19.62	28.00	21.68	17,492	0.001*
Undergraduate placement exam	43	53.58	17.37	56.00	37.80		
Vertical transfer examination	8	69.50	9.06	72.00	55.94		
CGPA							
1.99 and below	23	40.52	20.55	40.00	25.63	8,526	0.014*
2.00-2.99	35	54.97	16.47	56.00	39.21		
3.00 or above	12	57.67	21.81	64.00	43.58		
Perceived success							
Low	21	47.24	19.50	48.00	31.52	2,143	0.342
Medium	45	51.29	20.40	56.00	36.34		
High	4	62.00	14.79	68.00	46.88		
Attitudes towards mathematics							
Likes	38	55.16	18.58	56.00	40.08	-2.058	0.040*
Does not like	32	45.38	20.41	48.00	30.06		
Usage of calculators							
Uses	12	38.33	21.81	34.00	23.58	10,613	0.005*
Does not use	17	61.65	16.19	68.00	47.76		
Uses occasionally	41	49.76	18.72	52.00	33.90		
Evaluation of drug dosage calculation							
Adequate	6	63.33	20.46	70.00	50.42	7,042	0.030*
Partially adequate	35	54.51	16.27	56.00	38.41		
Inadequate	29	43.45	21.77	48.00	28.90		

*p<0.05, **Super high school, college, private high school.

achieved a certain threshold of skills in math in Turkey. However, the students in the present study entered the nursing department using different entrance exams. A total of 27.14% of the students entered the department using the EMU entrance exam despite having lower math scores. The fact that this study was only performed on nursing students who received the fundamentals of nursing course may have influenced our findings because those students who took the pediatric nursing course received information on drug dosage calculations and gained more practice regarding this subject, which may have positively influenced their DDCST scores.

Our study found that the DDCST scores of the male participants were higher than the females ($p<0.05$). However, another study of Turkish nursing students found no impact of gender on drug dosage calculation skills.[5] A randomized controlled study to develop the drug dosage calculation skills of nurses found that male nurses had fewer miscalculations and benefited more from their education.[18]

Existing studies suggest that limited math experience leads to lower math scores and higher anxiety levels.[9] Students with more math experience are better at drug dosage calculations.[22] The participants in our study who liked math and had sufficient knowledge of drug dosage calculations obtained higher scores on the DDCST. Røykenes and Larsen[9] found that those students who evaluated their math knowledge as low felt higher stress during drug dosage calculations. Various studies also stressed the relationship between drug dosage calculation skills and other factors, such as math skills and anxiety, in solving mathematical problems.[3] Taking the findings in the literature into consideration, we may conclude that the DDCST scores of the nursing students who liked math are higher.

Study Limitations

Firstly, this study was only performed on students who took the fundamentals of nursing course. This factor constitutes a limitation because the pediatric nursing course, which also includes the subject of drug dosage calculation, may have influenced the results of our study. Secondly, we used classical methods to teach drug dosage calculations. The use of other methods to teach dosage calculation and randomized controlled trials may change the research findings, which constitutes the second limitation of the study.

CONCLUSION

Curricula for undergraduate nursing programs should be prepared in order to provide qualifications for nurses so that they may work in clinical environments and be prepared for life-long learning. Mathematical and drug administration skills of nursing students play a key role during their preparation for clinical practice. The administration of medications, which is highly important for patient safety, holds an important place in the nursing curriculum. Nursing educators should prepare a supportive environment for the students using different methods in order to increase the math skills of the nursing students. Continuous education should be maintained to develop the mathematical and drug dosage calculation skills of nursing students. We suggest that nursing curricula should be amended to improve the mathematical skills of the nursing students at the undergraduate level. In addition, we suggest that the basic math skills of the students who will study nursing should be improved before they enter the faculty.

MAIN POINTS

- Safe drug administration is one of the most important responsibilities of nurses.
- Skills to calculate drug dosage are highly important for patient safety.
- Students who attended a math course obtained significantly higher scores on the DDCST.
- Departments of nursing may cooperate with the faculty of education and include basic mathematics courses in the curricula of nursing departments.

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ETHICS

Ethics Committee Approval: We obtained institutional permission from the head of the nursing department and research ethics approval from the research and publication ethics Eastern Mediterranean University Board of the university where this study was conducted (approval number: 2017/43-7).

Informed Consent: Written informed consent was obtained from all the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.C., H.F.K. Design: S.C., H.F.K., Supervision: H.F.K., Resources: H.F.K., S.C., Materials: S.C., H.F.K., Data Collection and/or Processing: S.C., H.F.K., Analysis and/or Interpretation: H.F.K., S.C., Writing: S.C., H.F.K., Critical Review: S.C., H.F.K.

DISCLOSURES

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REFERENCES

1. Karaca A, Açıkgöz F. Nursing Students' Drug Dose Calculation Skills and Drug Administration Errors. J Anatolia Nursing and Health Sciences 2014; 17(2): 110-6.
2. Ardahan-Akgül E, Özgüven-Öztornacı B, Doğan Z, Yıldırım-Sarı H. Determination of senior nursing students' mathematical perception skills and pediatric medication calculation performance. Florence Nightingale Hemsire Derg. 2019; 27(2): 166-72.
3. Coyne E, Needham J, Rands H. Enhancing student nurses' medication calculation knowledge; integrating theoretical knowledge into practice. Nurse Educ Today. 2013; 33(9): 1014-9.
4. Foss B, Mordt Ba P, Oftedal BG, Løkken A. Medication calculation: the potential role of digital game-based learning in nurse education. Comput Inform Nurs. 2013; 31(12): 589-93.

5. Yapucu Guneş U, Baran L, Yılmaz D. Mathematical and Drug Calculation Skills of Nursing Students in Turkey. International Journal of Caring Sciences. 2016; 9(1): 220-7.

6. Grugnetti AM, Bagnasco A, Rosa F, Sasso L. Effectiveness of a Clinical Skills Workshop for drug-dosage calculation in a nursing program. Nurse Educ Today. 2014; 34(4): 619-24.

7. Alteren J, Nerdal L. Relationship between High School Mathematics Grade and Number of Attempts Required to Pass the Medication Calculation Test in Nurse Education: An Explorative Study. Healthcare (Basel). 2015; 3(2): 351-63.

8. Eastwood KJ, Boyle MJ, Williams B, Fairhall R. Numeracy Skills Of Nursing Students. Nurse Educ Today. 2011; 31(8): 815-8.

9. Røykenes K, Larsen T. The relationship between nursing students' mathematics ability and their performance in a drug calculation test. Nurse Educ Today 2010; 30(7): 697-701.

10. Marks R, Hodgen J, Coben D, Bretscher N. Nursing Students' experiences of learning numeracy for professional practice. Adults Learning Mathematics International Journal. 2015; 11(1): 43-58.

11. Tanık M, Sarıbay E, Baba D. Nurses' compliance with drug application steps and its place in Health Quality. Journal of Social And Humanities Sciences Research. 2018; 5(17): 230-40.

12. Aydın SS, Akın S, Işıl Ö. Evaluating the Knowledge Levels of Nurses Regarding Medication Errors and the Views of Nurses on Reporting Medication Errors. Hemşirelikte Eğitim ve Araştırma Dergisi 2017; 14(1): 14-24.

13. Özyazıcıoğlu N, Aydın Aİ, Sürenle S, Çinar HG, Yılmaz D, Arkan B, et al. Evaluation of students' knowledge about paediatric dosage calculations. Nurse Educ Pract. 2018; 28: 34-9.

14. Bagnasco A, Galaverna L, Aleo G, Grugnetti AM, Rosa F, Sasso L. Mathematical calculation skills required for drug administration in undergraduate nursing students to ensure patient safety: A descriptive study: Drug calculation skills in nursing students. Nurse Educ Pract. 2016; 16(1): 33-9.

15. Røykenes K. "My math and me": Nursing students' previous experiences in learning mathematics. Nurse Educ Pract .2016; 16(1): 1-7.

16. Karabağ Aydin AK, Dinç L. Effects of Web-Based Instruction on Nursing Students' Arithmetical and Drug Dosage Calculation Skills. CIN - Comput Inform Nurs. 2017; 35(5): 262-9.

17. Ayık G, Altuğ Özsoy S, Çetinkaya A. Medication Errors of Nursing Students. Florence Nightingale J Nurs. 2011;18 (3): 136-43.

18. Simonsen BO, Daehlin GK, Johansson I, Farup PG. Improvement of drug dose calculations by classroom teaching or e-learning: a randomised controlled trial in nurses. BMJ Open 2014; 4(10): e006025.

19. Choudhary R, Malthus C. The impact of targeted mathematics/numeracy tutorials on maths anxiety, numeracy and basic drug calculation exam marks. Journal of Academic Language & Learning 2017; 11(1).

20. McMullan M, Jones R, Lea S. Patient safety: numerical skills and drug calculation abilities of nursing students and Registered Nurses. J Adv Nurs. 2010; 66(4): 891-9.

21. Taskiran N, Sari D, Akbiyik A. Nursing students' opinions related to drug dose calculation skills and drug administration errors. J Nurs Care 2016; 5: 4.

22. Newton SE, Moore G, Harris M, Pittiglio L. The effect of context on nursing student math aptitude. J Prof Nurs 2010; 26(6): 341-5.

RESEARCH ARTICLE

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Investigation of Urinary Findings in Urticaria Patients

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Abstract

BACKGROUND/AIMS: Urticaria is a common disease in the population which presents with wheals, angioedema or both. There are many stimuli in the etiopathogenesis of urticaria and infections are considered among the first triggers.

MATERIALS AND METHODS: The urinalysis results of patients were reported and the relationship between these findings and both laboratory and clinical spectrum was presented.

RESULTS: In the urinalysis results of the patients, bacteriuria was found in 100 (42.6%), pyuria in 69 (29.4%) and pyuria and bacteriuria in 60 (25.5%). Ninety-one (91%) of those patients with bacteriuria (p=0.000), 65 (94%) of those patients with pyuria (p=0.000), and 59 (98.3%) of those patients with bacteriuria and pyuria were female (p=0.000). Also, the leukocyte values of those patients with bacteriuria were significantly higher than those without bacteriuria (p=0.041). For the group of patients with pyuria, the leukocyte and neutrophil values were significantly higher than for those without pyuria (p=0.006; p=0.036, respectively). Lastly, the leukocyte values of those patients with bacteriuria and pyuria were significantly higher than those without bacteriuria and pyuria (p=0.013).

CONCLUSION: In female patients with a diagnosis of urticaria, the rates of bacteriuria and/or pyuria were found to be significantly high, and there was also a statistically significant high mean leukocyte value in those patients with bacteriuria and/or pyuria, suggesting that inflammation in the urinary tract may be an important stimulus in its etiology.

Keywords: Urticaria, bacteriuria, pyuria, urinalysis, angioedema

INTRODUCTION

Urticaria is a common disease in the population, which presents with wheals, angioedema or both. Urticaria develops due to edema in the superficial dermis and suddenly appears clinically and then spontaneously disappears within the same day. Angioedema develops due to edema in the deep dermis, subcutaneous tissue or mucous membranes.[1] Coexistence with angioedema is observed in approximately half of the cases of urticaria.[2] If urticaria and/or angioedema attacks last less than 6 weeks, it is called acute urticaria, while if it lasts longer than 6 weeks and there are at least two attacks per week, it is called chronic urticaria.[3] Acute urticaria is observed in 20% of the population and chronic urticaria is observed in 5% of the population.[4] 1-30% of acute urticaria patients can progress to chronic urticaria. According to the mechanism of urticaria formation, it is divided into two groups, as either spontaneous urticaria or inducible urticaria.[1]

Acute urticaria etiology includes 40% acute infections and 10% drug intolerance.[2] Cystitis and tonsillitis are the most common bacterial infections associated with acute urticarial. Also various viral and parasitic

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agents have been associated with acute urticaria.[5] There are many reports regarding the benefits of eliminating infectious processes.[6] It has been reported that *Helicobacter pylori* infection of the gastrointestinal tract, bacterial infections of the nasopharynx (recurrent sinusitis and tonsillitis), dental sepsis, urinary tract infections, and cutaneous fungal infections are associated with chronic urticaria which needs be treated in these patients.[7-9] In this study, we aimed to investigate the association between urinalysis, laboratory findings and the clinical spectrum of patients with acute and chronic urticaria.

MATERIALS AND METHODS

Retrospectively, all patients over the age of 18 with a diagnosis of urticaria who were followed up in our outpatient clinic between January, 2017 and January, 2020 were included in this study. Ethical approval was obtained from the Ethical Committee of the Near East University Hospital for the study (approval number: 2021/90-1326). Pregnant women, female patients who were in the menstrual period at the time of admission, and patients who described genital discharge were not included in this study. The patients were questioned regarding age, gender, duration of urticaria, presence of angioedema accompanying urticaria, systemic diseases, drug usage in the previous two weeks, a history of infection in the previous two weeks, a history of chronic infection, the presence of atopy, the presence of dermographism, and the presence of dysuria. Regarding laboratory findings, hemogram, high-sensitivity C-reactive protein (hs-CRP), total immunoglobulin E (IgE) levels, and urinalysis results were obtained and the urine culture results of those patients with bacteriuria were also obtained. Leukocyte, neutrophil, lymphocyte, eosinophil, neutrophil lymphocyte ratio values and biochemically hs-CRP and total IgE levels in the hemogram were reported numerically. The presence of pyuria was accepted as a polymorphonuclear leukocyte count >10 white blood cells/high power field (WBC/HPF) in the urine. Leukocyte esterase positivity and bacteriuria in urine were evaluated as positive or negative. The urine culture results of those patients with bacteriuria were obtained. Cases with significant levels of squamous epithelial cells (≥15/HPF) in urine samples were not included in this study because they were considered to be contaminated.

Statistical Analysis

The data analysis was carried out using SPSS version 23.0 (IBM SPSS Corp.; Armonk, NY, USA). Independent samples t-test was used to compare the two groups. Also, frequencies and percentages were obtained for the qualitative variables and the chi-square test was used to determine statistical significance for categorical variables. In this study, p-values ≤0.05 were considered statistically significant.

RESULTS

Our study included a total of 235 urticaria patients, where 157 (66.8%) were female and 78 (33.2%) were male. The patients were aged between 18 and 74 years and their mean age was 31.6±12.8 years [mean ± standard deviation (SD)]. The duration of the disease was 1 day to 20 years. The patients were further categorized as either acute or chronic urticarial. One hundred and fifty-nine (67.7%) of the patients (1.13±0.09 weeks) (mean ± SD) were diagnosed as acute urticaria, and 76 (32.3%) (85.02±18.07 weeks) (mean ± SD) as chronic urticaria. Isolated urticaria was detected in 48 (20.4%) of the patients included in this study, and urticaria and angioedema were detected in 187 (79.6%) of them. 58 (24.7%) of the patients had atopy history and 27 (11.5%) had dermographism. 23 of the patients (9.8%) had a history of accompanying systemic disease, 16 of the patients (6.8%) had thyroiditis and 7 (3%) had anemia.

Infection history in the previous two weeks was determined in 54 (23%) of the patients included in this study. A significant relationship was found between the history of infection in the previous two weeks and the acute urticaria and chronic urticaria patient groups (χ^2=12.031, p=0.001). The distribution of infection was dental infection in 1 patient, pilonidal sinus infection in 1 patient, and upper respiratory tract infection in 52 patients. 47 (87%) of the patients with a positive history of infection were diagnosed with acute urticaria, and 7 (13%) of them were diagnosed with chronic urticaria. In addition, 66 patients (28.0%) had a history of medicinal drug use within the previous two weeks, 38 patients (16.2%) were using non-steroidal anti-inflammatory drugs, 27 patients (11.5%) were using antibiotics and 1 patient (0.4%) was using antidepressants. A significant relationship was found between the groups with acute urticaria and chronic urticaria in terms of medicinal drug use within the previous two weeks (χ^2=4.242, p=0.045). Fifty-one (77.6%) of the patients who had a history of medicinal drug use within the previous two weeks were diagnosed with acute urticaria, and 15 (22.4%) were diagnosed with chronic urticaria. In the urinalysis results of the patients included in this study, bacteriuria was found in 100 (42.6%), pyuria in 69 (29.4%), and pyuria with bacteriuria in 60 (25.5%). In 3 (3%) patients with bacteriuria, positive urine culture was detected, with *Escherichia coli* being found in 2 patients and *Serratia marcescens* in 1 patient. Leukocyte esterase positivity was detected only in 2 (2%) patients with bacteriuria.

Bacteriuria existence was determined in 67 patients (67%) with acute urticaria, and 33 patients (33%) with chronic urticaria. There was no significant association between the acute urticaria and chronic urticaria patient groups in terms of of bacteriuria existence (χ^2=0.035, p=0.888). 46 of the patients (66.7%) with pyuria were diagnosed with acute urticaria, and 23 (33.3%) of them were diagnosed with chronic urticaria. In the comparison of pyuria existence, there was no significant association between the two groups (χ^2=0.044, p=0.879). Fourty of the patients (66.7%) with bacteriuria and pyuria coexistence were diagnosed with acute urticaria, and 20 (33.3%) of them were diagnosed with chronic urticaria. Bacteriuria and pyuria coexistence were compared in the two patient groups and no significant association was found (χ^2=0.036, p=0.874) (Table 1). In addition, there was a significant association between those patients with bacteriuria and those patients who had pyuria (χ^2=80.538, p=0.000), as 60 (60%) of the patients with bacteriuria had pyuria simultaneously.

Regarding gender, the results were statistically significantly higher in female patients than male patients due to the evaluation of bacteriuria (91%) and pyuria (94%) existence separately, and bacteriuria and pyuria coexistence (98.3%) (p=0.001) (Table 1).

Twenty-three (23%) of the patients with bacteriuria had a history of atopy, and no significant association was found between bacteriuria and atopy history (χ^2=0.265, p=0.607). No statistically significant association was found between bacteriuria and dermographism (χ^2=1.079, p=0.299). Dermographism was found in 14 (14%) patients with bacteriuria. Atopy history was present in 13 (18.8%) of the patients with pyuria, and no

significant association was found between pyuria and atopy history (χ^2=1.792, p=0.245). Dermographism was found in 9 (13%) of the patients with pyuria, and no significant association was found between pyuria and dermographism (χ^2=0.232, p=0.656). There was atopy in 12 (20%) of the patients with bacteriuria and pyuria coexistence, and no significant association was found between bacteriuria and pyuria coexistence and atopy history (χ^2=0.950, p=0.388). In addition, dermographism was present in 8 (13.3%) of the patients with bacteriuria and pyuria coexistence, and no statistically significant association was found between bacteriuria and pyuria coexistence and dermographism (χ^2=0.269, p=0.641) (Table 1).

Dysuria was described in 12 (5.1%) of the total number of patients included in this study, 10 (10%) of the patients with bacteriuria, 7 (10.1%) of the patients with pyuria, and 7 (11.7%) of the patients with bacteriuria and pyuria coexistence. A significant association was found between bacteriuria and dysuria (χ^2=8.603, p=0.003), where 10 (10%) of the patients with bacteriuria had dysuria simultaneously. There was a significant association between pyuria and dysuria (χ^2=5.118, p=0.044), where 7 (10.1%) of the patients with pyuria had dysuria concurrently (Table 1). A significant association was found between bacteriuria and pyuria coexistence and dysuria (χ^2=7.156, p=0.014), as 7 (11.7%) of the patients with bacteriuria and pyuria coexistence had dysuria at the same time.

When the laboratory results of the patient groups with bacteriuria and/or pyuria were examined, there was no significant difference between the groups in terms of the values of lymphocyte, eosinophil, neutrophil lymphocyte ratio, hs-CRP, and total-IgE since all p-values >0.05, as can be seen in Table 2.

On the other hand, there was a significant difference in the leukocyte value between the patient groups with bacteriuria (p=0.041). There was no significant difference in the neutrophil value between those patient groups with or without bacteriuria (p=0.112). There was a significant difference in the neutrophil (p=0.036) values between those patients with or without pyuria and also there was a significant difference in the leukocyte values between the patient groups with pyuria (p=0.006). Also, there was a significant difference in the leukocyte (p=0.013) values between those patients with and those without the coexistence of bacteriuria and pyuria, as seen in Table 2.

DISCUSSION

Urticaria is a skin disease which significantly impairs quality of life, especially when it becomes chronic. In the literature, the approximate rates of the urticaria cases were 40% urticaria, 40% urticaria and angioedema simultaneously, and 20% isolated angioedema.[4] In our study, the rate of cases was found to be higher than in the literature, as isolated urticaria was identified in 48 (20.4%) of the patients, and urticaria and angioedema simultaneously were detected in 187 (79.6%) of them. In studies, acute urticaria is observed equally in both genders in the young age group, but chronic urticaria is more common in middle-aged women.[4] In our study, there was a female dominance as 157 (66.8%) of the cases were female in the acute and chronic urticaria groups.

Urticaria can develop idiopathically, however, in chronic urticaria patients, the risk of accompanying autoimmune diseases, such as thyroid diseases, type 1 diabetes, systemic lupus erythematosus and rheumatoid arthritis is quite high.[4,7] In our study, thyroiditis (6.8%) and anemia (3%) were present as chronic systemic diseases accompanying urticaria cases.

While medicinal drugs may be the primary cause of acute urticaria, they are also observed as a triggering or exacerbating cause in chronic urticaria. Drug-related urticaria is particularly observed in association with nonsteroidal anti-inflammatories and antibiotics.[2] It was reported in one study that urticaria and angioedema are the most common clinical manifestations among hypersensitivity reactions due to the use of nonsteroidal anti-inflammatory drugs.[10] In our study, 66 (28.0%) of the patients had a history of drug usage within the previous two weeks, and 51 (77.6%) of them were diagnosed with acute urticaria. Compatible with the literature, in our study, 38 patients (16.2%) were using non-steroidal anti-inflammatory drugs while 27 patients (11.5%) were using antibiotics at the time they were diagnosed with urticaria.

Although the relationship between acute urticaria and infection has been explained more clearly, it is also suggested that infections in chronic urticaria play a triggering and exacerbating role in the course of the disease rather than being the primary cause.[5,7] In our study, a significant relationship was found between the history of infection within the previous two weeks and both acute urticaria and chronic urticaria patients (χ^2=12.031, p=0.001). 54 (23%) of the patients had a history of infection within the previous two weeks; specifically, there

Table 1. Demographic characteristics and clinical findings between bacteriuria, pyuria, and both bacteriuria and pyuria groups, respectively

		Patients with bacteriuria			Patients with pyuria			Patients with bacteriuria and pyuria		
		χ^2	p		χ^2	p		χ^2	p	
Gender	Female	91 (91%)	**45.941**	**0.001**	65 (94%)	**33.058**	**0.001**	59 (98.3%)	**36.110**	**0.001**
	Male	9 (9%)			4 (6%)			1 (1.7%)		
Duration	Acute	67 (67%)	0.035	0.888	46 (66.7%)	0.044	0.879	40 (66,7%)	0.036	0.874
	Chronic	33 (33%)			23 (33.3%)			20 (33.3%)		
Angioedema		19 (39.6%)	0.218	0.641	16 (33.3%)	0.459	0.484	15 (31.25%)	1.037	0.308
Atopy		23 (23%)	0.265	0.607	13 (18.8%)	1.792	0.245	12 (20%)	0.950	0.388
Dermographism		14 (14%)	1.079	0.299	9 (13%)	0.232	0.656	8 (13.3%)	0.269	0.641
Dysuria		10 (10%)	**8.603**	**0.003**	7 (10.1%)	**5.118**	**0.044**	7 (11.7%)	**7.156**	**0.014**

*statistically significant values are shown in bold.

Table 2. Independent Samples t-test results for the laboratory results between bacteriuria, pyuria, and both bacteriuria and pyuria groups, respectively

	Patients without bacteriuria	Patients with bacteriuria			Patients without pyuria	Patients with pyuria			Patients without bacteriuria and pyuria	Patients with bacteriuria and pyuria		
	M (SD)		t	p	M (SD)		t	p	M (SD)		t	p
Neutrophil (10^3/uL)	5.78 (3.54)	6.55 (3.63)	-1.60	0.112	5.78 (3.50)	6.87 (3.71)	-2.11	**0.036***	5.85 (3.51)	6.83 (3.76)	-1.81	0.071
Lymphocyte (10^3/uL)	2.06 (0.92)	2.23 (0.87)	-1.36	0.174	2.06 (0.87)	2.30 (0.94)	-1.84	0.068	2.07 (0.88)	2.30 (0.93)	-1.73	0.085
Eosinophil (10^3/uL)	0.19 (0.91)	0.10 (0.17)	1.09	0.327	0.18 (0.83)	0.09 (0.14)	0.84	0.402	0.17 (0.80)	0.10 (0.15)	0.66	0.508
Neutrophil lymphocyte ratio	3.49 (3.29)	3.77 (3.92)	-0.56	0.574	3.53 (3.66)	3.80 (3.47)	-0.51	0.611	3.62 (3.74)	3.60 (3.18)	0.03	0.973
hs-CRP (mg/dL)	0.56 (0.87)	0.59 (0.94)	-0.28	0.783	0.58 (0.92)	0.55 (0.86)	0.178	0.859	0.58 (0.92)	0.54 (0.86)	0.34	0.735
Leukocyte (10^3/uL)	8.56 (3.86)	9.60 (3.66)	-2.06	**0.041***	8.55 (3.73)	10.05 (3.80)	-2.748	**0.006***	8.63 (3.71)	10.06 (3.89)	-2.50	**0.013***
Total IgE (IU/mL)	137.84 (65.63)	150.67 (98.25)	-0.42	0.672	140.32 (53.89)	150.48 (99.77)	-0.30	0.767	137.75 (47.79)	159.49 (31.95)	-0.61	0.544

M: mean, SD: standard deviation, *statistically significant values are shown in bold.

was a history of dental infection in 1 patient, pilonidal sinus infection in 1 patient, and upper respiratory tract infection in 52 patients. Forty-seven (87%) of the patients with a history of infection within the previous two weeks were diagnosed with acute urticaria, and 7 (13%) of them were diagnosed with chronic urticaria.

Asymptomatic bacteriuria is defined as the presence of bacteria in properly collected urine samples of patients without signs of urinary tract infection, with or without pyuria. It is especially detected in the elderly and in females and treatment is not recommended, except for some special conditions.[11] Although the predominant consensus is that asymptomatic bacteriuria is a local organ-specific condition, there are opinions that it stimulates a generalized immune response.[12] In our study, the existence of bacteriuria and pyuria in female patients were significantly higher than in male patients. It is reported that the prevalence of urinary tract infections is significantly higher in women than in men until the age of 60 years and older.[13] Some of the reasons for urinary tract infections in women may be the shorter distance between the urethra and the anus, frequent coitus and the use of spermicides.[14] Therefore, it is understandable that women have urticaria more frequently than men as urinary infections are seen more frequently in women and they are known to be a triggering factor.

The gold standard for the diagnosis of urinary tract infection is the detection of the pathogen by the urine culture method, accompanied by clinical symptoms. Pyuria (leukocyturia) describes an increase in the number of polymorphonuclear leukocytes in the urine (usually >10 WBC/HPF) or leukocyte esterase positivity. The presence of pyuria is an indicator of genitourinary system infection, but it is not an absolute indicator for urinary tract infection and does not require treatment. However, the absence of pyuria excludes urinary tract infection.[9]

Reports have shown that urinary tract infection is a trigger in acute and chronic urticaria and urticarial complaints regressed after the treatment of the urinary tract infection with antibiotics.[5,15] Zotter et al.[16] reported that, in patients with hereditary angioedema with C1-inhibitor deficiency, the frequency and number of attacks were higher in those patients with bacteriuria compared to those without bacteriuria. Kadhim et al.[9] reported that urinary tract infections were found at a significantly higher rate in urticaria patients compared with the control group in their study. There was also a statistically significant relationship between urticaria and both pyuria and positive urine culture, and they reported pyuria in 19.8% of urticaria patients and positive in urine culture in 8.2% of them. Additionally, it was reported that 32.6% of the patients with pyuria and 28.9% of the patients with urine culture were asymptomatic.[9] In our study, the presence of pyuria was detected in 69 (29.4%) of the urticaria patients and a positive urine culture result was found in 3% of those patients with bacteriuria. In addition, dysuria was determined in 7 (10.1%) patients with pyuria and dysuria was determined in 2 (66.7%) out of 3 patients with positive urine culture results. A significant relationship was found between bacteriuria and the presence of dysuria (χ^2=8.603, p=0.003), and 10 (10%) patients with bacteriuria had dysuria at the same time. There was a significant relationship between pyuria and dysuria (χ^2=5.118, p=0.044), where 7 (10.1%) of the patients with pyuria had dysuria simultaneously. A significant relationship was found between bacteriuria and pyuria association and dysuria (χ^2=7.156, p=0.014), as 7 (11.7%) of the patients with bacteriuria and pyuria had dysuria as well.

The leukocyte values of those patients with bacteriuria were significantly higher than those without bacteriuria. For the group of patients with pyuria, the leukocyte and neutrophil values of those patients with pyuria were significantly higher than those without pyuria. Also, the leukocyte values of those patients with bacteriuria and pyuria were significantly higher than those without bacteriuria and pyuria (Table 2). For these reasons, our study supports the hypothesis that pyuria and/or bacteriuria may play a role in the etiology of urticaria by triggering an inflammatory response.

CONCLUSION

In order to define the role and importance of bacteriuria and/or pyuria in the etiology of urticaria, it is clear that studies with larger numbers of cases and controls are needed. Especially in female patients diagnosed with urticaria, the rates of bacteriuria and/or pyuria were found to be significantly higher, and the statistically significantly higher number of leukocytes in patients with bacteriuria and/or pyuria suggests that inflammation in the urinary tract may be an important stimulus in the etiology of urticaria. These results may pave the way for studies to be conducted to evaluate the urticaria treatment response rates with urinary infection treatments to be given to urticaria patients with bacteriuria and/or pyuria.

MAIN POINTS

• Although the etiopathogenesis has not been clearly explained, many infections are reported as being triggering factors for urticaria.

• Studies have shown that urinary tract infection is a triggering factor in urticaria and that urticaria complaints regress after urinary tract infection treatment.

• According to the findings of this study, it is suggested that asymptomatic bacteriuria and/or pyuria may also be a significant triggering factor for urticaria.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Ethical Committee of the Near East University Hospital for the study (approval number: 2021/90-1326).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.M., Design: D.M., Data Collection and/or Processing: D.M., S.M., N.S., Analysis and/or Interpretation: D.M., S.M., N.S., Literature Search: D.M., S.M., N.S., Writing: D.M. S.M.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Radonjic-Hoesli S, Hofmeier KS, Micaletto S, Schmid-Grendelmeier P, Bircher A, Simon D. Urticaria and angioedema: an update on classification and pathogenesis. Clin Rev Allergy Immunol. 2018; 54: 88-101.
2. Kocatürk Göncü E, Aktan Ş, Atakan N, Bülbül Başkan E, Erdem T, Koca R, et al. The Turkish Guideline for the Diagnosis and Management of Urticaria-2016. Turkderm - Arch Turk Dermatol Venerology. 2016; 50: 82-98.
3. Ruiz-Villaverde R, Moreno-Ramírez D, Galán-Gutierrez M, de Troya M, Reyes-Alcázar V, Alcalde M, et al. Clinical pathway for patients with acute or chronic urticaria: A consensus statement of the Andalusian section of the Spanish Academy of Dermatology and Venereology (AEDV). Actas Dermosifiliogr. 2016; 107: 482-8.
4. Fine LM, Bernstein JA. Guideline of Chronic Urticaria Beyond. Allergy Asthma Immunol Res. 2016; 8: 396-403.
5. Gotua M, Kulumbegov B, Chanturidze N, Devidze M, Lomidze N, Rukhadze M. Association between urticaria and infections (review). Georgian Med News. 2019; 288: 97-101.
6. Aguilar N, Lugo-Reyes, Mendez NHS, Mendieta E. Chronic urticaria and infections. World Allergy Organ J. 2012; 5: 201.
7. Dionigi PC, Menezes MC, Forte WC. A prospective ten-year follow-up of patients with chronic urticaria. Allergol Immunopathol (Madr). 2016; 44: 286-91.
8. Magen E, Mishal J. Possible benefit from treatment of Helicobacter pylori in antihistamine-resistant chronic urticaria. Clin Exp Dermatol. 2013; 38: 7-12.
9. Kadhim KA, Al Junaiyeh HA, Naif A, Ali Y. Urinary tract ınfection in spontaneous urticaria among Thi-Qar patients. Indian Journal of Public Health Research & Development. 2020; 11: 2067-72.
10. Brockow K. Time for more clinical research on non-steroidal antiinflammatory drug-induced urticaria/angioedema and anaphylaxis. Clin Exp Allergy. 2013; 43: 5-7.
11. Cortes-Penfield NW, Trautner BW, Jump RLP. Urinary tract infection and asymptomatic bacteriuria in older adults. Infect Dis Clin North Am. 2017; 31: 673-88.
12. Yu Y, Zielinski MD, Rolfe MA, Kuntz MM, Nelson H, Nelson KE, et al. Similar neutrophil-driven inflammatory and antibacterial responses in elderly patients with symptomatic and asymptomatic bacteriuria. Infect Immun. 2015; 83: 4142-53.
13. Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010; 7: 653-60.
14. Geerlings SE. Clinical presentations and epidemiology of urinary tract ınfections. Microbiol Spectr. 2016; 4.
15. Lehloenya R, Christians S. A Case of Chronic Urticaria Complicated by Raoultella Ornithinolytica Urinary Tract Infection, Bronchospasm and Angioedema. The World Allergy Organization Journal. 2012; 5 (Suppl 2): S204.
16. Zotter Z, Veszeli N, Kőhalmi KV, Varga L, Imreh É, Kovács G, et al. Bacteriuria increases the risk of edematous attacks in hereditary angioedema with C1-inhibitor deficiency. Allergy. 2016; 71: 1791-1793.

RESEARCH ARTICLE

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Isolation of Pyogenic Microorganisms from Infected Wounds in the General Surgery and Orthopedic & Traumatology Departments of the Near East University Hospital: A Retrospective Study

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Abstract

BACKGROUND/AIMS: Wound infection is characterized as the presence of a wound environment characterized by microorganisms in adequately large numbers, or of adequate virulence to aggregate an immune response locally and/or systemically. The aim of this study, conducted in a university hospital in North Cyprus, was to determine the microorganisms that cause pus formation in wound infections.

MATERIALS AND METHODS: One hundred and eighty-five samples were analyzed for this study from the period of September, 2015 to August, 2019. The samples were analyzed in the Near East University Hospital Microbiology Laboratory, North Cyprus. The samples were collected from two different departments. The sensitivity pattern of the organisms was determined by the BD Phoenix instrument. The SPSS version 22 was used for statistical analysis.

RESULTS: The orthopedic unit had a total of 123 patient samples while the general surgery unit had a total of 62 patient samples. Culture was positive in 56 (45.5%) of the 123 samples taken from the orthopedic clinic. There was no significant difference between gender and wound infection in the samples taken from the orthopedic clinic (p=0.640). The total number of outpatients was 15 (12.2%) and the number of inpatients was 108 (87.8%) in the orthopedic department. In the general surgery department, there were a total of 62 patient samples and a total of 41 (66.1%) were culture positive. The most commonly seen bacteria was *Escherichia coli* (22.6%).

CONCLUSION: With the aim to determine a summarized analysis of wound microbiology, and the current opinions and controversies regarding wound treatment, this retrospective study attempted to assess the microbiological aspects which are important to the administration of microorganisms in wounds.

Keywords: Microorganisms, wound infection, resistance

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INTRODUCTION

Wound infection is characterized as the presence of a wound environment characterized by microorganisms in adequately large numbers, or of adequate virulence to aggregate an immune response locally and/or systemically.

A break in skin integrity can allow bacteria to enter the body and proliferate. Absent of the protective barrier of the skin, sensitive tissues in the wound bed may lead to microorganism colonization. The proliferation of microorganisms in a wound can disrupt wound healing as it can cause local tissue damage.[1] The subcutaneous or underlying tissue provides a moist, nutritious environment, which facilitates microbial colonization and generation. Wound colonization is poly-microbial, which means potentially pathogenic microorganisms are present, thus any wound is at risk of becoming infected.[2]

Staphylococcus aureus (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) are the most common pyogenic bacteria associated with wound infections. These two bacteria together account for up to 20-40% of all nosocomial, post-surgery and burn infections. *Enterococci* and *Enterobacter* are other microorganisms which have also been associated with wound infections, especially after abdominal surgery in immunocompromised patients.[3] The above mentioned risks and antibiotic resistance make wound infections a global problem. The antimicrobial resistance factors include changes in microbial ecology, genetics and the non-selective use of antimicrobial agents. Methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant *Enterococci* (VRE) are two medically relevant examples.[4]

The aim of this study was to determine the microorganisms which cause pus formation in wound infections. The present study was conducted in North Cyprus between September, 2015 and December, 2019.

MATERIALS AND METHODS

One hundred and eighty-five samples were analyzed for this study from the period of September, 2015 to August, 2019. The samples were analyzed in the Near East University Hospital Microbiology Laboratory, North Cyprus. These samples were collected from two different departments (general surgery and orthopedic departments). These samples only included wound and pus culture tests. Demographic information (age, sex) was obtained from the patients' medical records. The sensitivity pattern of the pyogenic organisms was determined against commonly used antibiotics using a BD Phoenix instrument. The samples were assigned accordingly and were subject to analysis in the Microbiology Laboratory at the Near East University Hospital, Nicosia, North Cyprus. Near East University Ethics Committee approval (approval number: 2020/76) was obtained for this study.

Statistical Analysis

After the data were collected, they were analyzed using SPSS (Statistical Package for the Social Sciences) version 22 and the results were compared with the literature. Since our study was single-centered, it does not reflect the whole of North Cyprus and this is seen as a limitation. Therefore, we think that multi-center studies should be conducted.

RESULTS

The orthopedic unit had a total of 123 patient samples, while the general surgery unit had a total of 62 patient samples from the period of September, 2015 to August, 2019 (Table 1).

Out of the 123 samples cultured from the orthopedic department, 56 (45.5%) were found to be culture positive, while 67 (54.5%) were culture negative. Out of the 123 patients from the orthopedic unit, the minimum age was 21 years, the maximum was 87 years and the mean age of the patients in the orthopedic department was 65 years. The number of male patients was 40 (32.5%) and females was 83 (67.5%). No significant difference was found between gender and wound infection (p=0.640). The total number of outpatients was 15 (12.2%) and inpatients was 108 (87.8%) in the orthopedic department. No significant difference was found between the outpatients and inpatients in terms of wound infections (p=0.517). The predominant bacteria was *Escherichia coli* (*E. coli*) (11.3%) followed by *P. aeruginosa* (8.1%), *S. aureus* (8.1%), coagulase negative *Staphylococci* (CoNS) (4.8%), *Enterococcus faecium* (*E. faecium*) (2.4%), *Enterococcus faecalis* (2.4%), *Candida* species (1.6%), *Citrobacter* species (1.6%), *Acinetobacter baumannii* (*A. baumannii*) (1.6%), *Proteus* species (1.6%), *Enterobacter* species (0.8%), *Klebsiella pneumoniae* (*K. pneumonia*) (1.1%) and *Burkholderia cepacia* (0.8%) (Figure 1). For the Gram-negative bacteria, *A. baumannii* (n=2) showed resistance to almost all the antibiotics and was found to have sensitivity only to trimethoprim-sulfamethoxazole (SXT) and tigecycline. *P. aeruginosa* (n=10) was found to have high resistance to aztreonam (ATM) (80%). *Enterobacteriacae* (n=20) was found to have the highest resistance to SXT (63%).

In the general surgery department, there were a total of 62 patient samples considered in this study and a total of 41 (66.1%) were culture positive. The minimum age was 19 years, the maximum age was 89 years and the mean age of the patients was 52.37±20.99 years. The number of males was 23 (37.1%) and the number of females was 39 (62.9%). No significant difference was found between the genders and

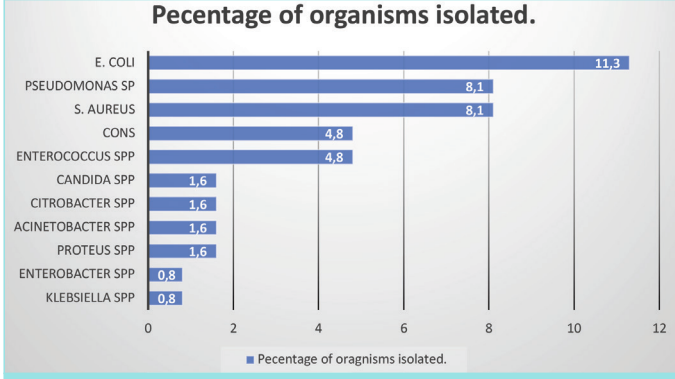

Figure 1. Percentage of organism isolated from the orthopedic department.

Table 1. Percentage of patients from the two different departments

	Number	Percentage (%)
Orthopedic	123	66.5
General surgery	62	33.5
Total	185	100.0

wound infections (p=0.907). The total number of outpatients was 30 (48.4%) and inpatients was 32 (51.6%) in the general surgery department. No significant difference was found between the outpatients and the inpatients in terms of wound infections (p=0.652). The predominant bacteria type was *E. coli.* (22.6%), followed by *P. areuginosa* (9.7%), CoNS (9.7%), *Proteus* species (4.8%), *S. aureus* (4.8%), *Citrobacter* species (4.8%), *K. pneumoniae* (3.2%), *E. faecium* (1.6%), *Candida* species (1.6%), *A. baumannii* (1.6%), and *Enterobacter cloacae* (1.6%) (Figure 2).

For the Gram-negative bacteria, *A. baumannii* (n=1) was resistant to almost all the antibiotics and sensitivity to tigecycline (100%). *P. aeruginosa* (n=6) was found to have the highest resistance to ATM (50%). *Enterobacteriacae* (n=23) was found to have the highest resistance to amoxicillin/clavulanate (100%). The Gram-positive bacteria sensitivity and resistance pattern in CoNS (n=6) was found to have the highest resistance to ciprofloxacin (CIP) (33%) and SXT (33%). *S. aureus* (n=3) had high resistance to CIP (33%). *E. faecium* (n=1) had high resistance to CIP (100%) and erythromycin (100%).

DISCUSSION

Wound infections are the main problem for nosocomial infections despite the continuous progress in surgery and antibiotic prophylaxis. Therefore, they important for morbidity and mortality.[5,6] Wound infection is a main concern among health care practitioners.[7] Whatever the cause, wounds have an important but often unrecognized effect on those who suffer from them and on the health care system. The phenomenon of wounds has been called the "silent epidemic".[8]

This study showed that the most frequently isolated microorganism type from both departments participating in this study was *E. coli,* which had the highest percentages. Also, in the orthopedic department, the gram-positive bacteria isolated showed that the percentage of MRCN was 3/6 (50%), MRSA was 5/10 (50%), and VRSA was 1/10 (10%). Infections in wounds are aerobic or facultative pathogens, for example *S. aureus*, *P. aeruginosa*, or beta-hemolytic *Streptococci*. There is reported to be a large prevalence of *S. aureus* in wounds.[8,9] According to studies on wound infections, the responsible bacteria found in colonized wounds is one-third anaerobic bacteria, however, the responsible bacteria found in infected wounds is 50% anaerobic bacteria. Aerobic and anaerobic pathogens may lead to infection with more than one type of the bacteria (poly-microbial), therefore, broad-spectrum antibiotics may be effective in the administration of infected wounds. Our result showed that only clindamycin or metronidazole with an aminoglycoside

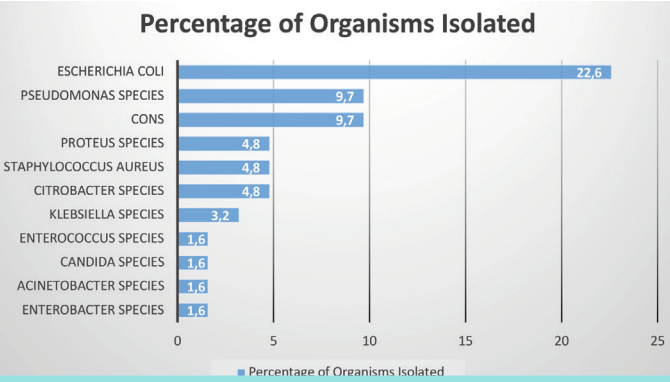

Figure 2. Percentage of organisms isolated from the general surgery department.

(e.g., gentamicin) or a cephalosporin (e.g., cefuroxime or cefotaxime) was confirmed to be highly effective. In the United States, cefoxitin or cephamycin are used as a single agent for the treatment of already established infections and not as prophylactics. However, new classes of antibiotics, such as ureidopenicillins, carbapenems, and B-lactam/B-lactamase inhibitor combinations have increased the choice for prophylactic and therapeutic treatment.[10] Since *S. aureus* is the most commonly isolated microorganism seen in complicated infections of wounds, the most common treatments are with cephalosporin, macrolides, clindamycin, and semi-synthetic penicillin (oxacillin).[10] If strains of MRSA are complicated, then vancomycin and teicoplanin are another choice for treatment.[9] In another study, poly-microbial growth was reported from 59.6% of cultures and 61.5% of multidrug-resistant organisms. Our results are similar to other studies.[11,12] In selecting antibiotics for the treatment of wound infections, we need to have an understanding of the normal flora, the antimicrobial patterns of the microorganisms, and antimicrobial agents. The factors involved in the wound from colonization to infection and even up to healing can help practitioners to clarify clinical findings and microbiological investigations of wounds. In term of topical antiseptics, bacterial resistance persists, but new antimicrobial agents are broadly effective and have a low incidence of resistance.[13]

Furthermore, the microbiology of wounds has been actively researched in recent years, but there is still much to be learned and discovered about the microbial mechanisms these pyogenic microorganisms use to induce infection and prevent wound healing.[10,14]

CONCLUSION

As a result, debate and theories regarding microbial involvement in wound healing is likely to continue.

With the aim of giving a summarized analysis of wound microbiology, together with the current opinions and controversies regarding wound evaluation and treatment, this retrospective study attempted to address certain microbiological aspects which are important to the management of microorganisms in wounds.[15]

MAIN POINTS

- Wound infection is characterized as the presence of a wound environment characterized by microorganisms in adequately large numbers, or of adequate virulence to aggregate an immune response locally and/or systemically.
- The risk factors stated in this study and antibiotic resistance problems have made wound infections a global problem.
- Antimicrobial resistance factors include changes in the microbial ecology, genetics and the non-selective use of antimicrobial agents. MRSA, and VRE are two relevant examples.
- The aim of this work was to determine those microorganisms which cause pus formation in wound infections in North Cyprus.

ETHICS

Ethics Committee Approval: Near East University Ethics Committee approval (approval number: 2020/76) was obtained for this study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Conception: E.G., N.Ç., K.S., Design: E.G., N.Ç., K.S., Supervision: H.E., E.E., N.Ç., K.S., Fundings: H.E., E.E., Data Collection and/or Processing: H.A., E.G., Analysis and/or Interpretation: E.G., Literature Review: M.G., Writing: M.G., Critical Review: M.G., K.S.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Siddiqui AR, Bernstein JM. Chronic wound infection: Facts and controversies. Clin Dermatol. 2010; 28: 519-26.
2. Dai T, Huang Y, Sharma K, Hashmi T, Kurup D, Hamblin MR. Topical antimicrobials for burn wound infections. Recent Pat Antiinfect Drug Discov. 2010; 5: 124-51.
3. Kotz P, Fisher J, McCluskey P, Hartwell D, Dharma H. Use of a new silver barrier dressing, ALLEVYN Ag in exuding chronic wounds. Int Wound J. 2019; 6: 186-94.
4. Al-Waili N, Salom K, Al-Ghamdi A. Honey for wound healing, ulcers, and burns; data supporting its use in clinical practice. ScientificWorldJournal. 2011; 11: 766-87.
5. Tesfahunegn Z, Asrat D, Woldeamanuel Y, Estifanos K. Bacteriology of surgical site and catheter related urinary tract infections among patients admitted in Mekelle Hospital, Mekelle, Tigray, Ethiopia. Ethiopian Med J. 2009; 47: 117-22.
6. Ashby E, Haddad S, O'Donnell E, Wilson AP. How will surgical site infection be measured to ensure "high quality care for all"?. J Bone Joint Surg Br. 2010; 92: 1294-9.
7. Alexander MF. Wound infection. In: Nursing Practice Hospital and Home, the Adult. Alexander MF, Fawcett JN, Runciman PJ, (editors). New York: Churchill Livingstone. 1994; p. 703.
8. Smith & Nephew Foundation. Skin breakdown-the silent epidemic. Smith & Nephew Foundation, Hull; 2007.
9. Mayhall CG. Surgical infections including burns. In: R. P. Wenzel Prevention and control of nosocomial infections (2nd edition). The Williams & Wilkins Co. Baltimore. 1993; p. 614-64.
10. Surucuoglu S, Gazi H, Kurutepe S, Ozkutuk N, Ozbakkaloglu B. Bacteriology of surgical wound infections in a tertiary care hospital in Turkey. East Afr Med J. 2005; 82: 331-6.
11. Otokunefor V, Datubo-Brown DD. Bacteriology of wound infections in the surgical wards of a teaching hospital. West Afr J Med. 1990; 9: 285-90.
12. Uçkay I, Sax H, Harbarth S, Bernard L, Pittet D. Multi-resistant infections in repatriated patients after natural disasters: lessons learned from the 2004 tsunami for hospital infection control. J Hosp Infect. 2008; 68: 1-8.
13. Wilson P, Gibbons C, Raeves C, Hogson B, Liu M, Plummer D, et al. Surgical wound infection as a performance indicator: agreement of common definitions of wound infection in 4773 patients. BMJ. 2004; 329: 720-2.
14. Nichols RL. Current strategies for prevention of surgical site infections. Curr Infect Dis Rep. 2004; 6: 426-34.
15. Collier M. Recognition and management of wound infections. World Wide Wounds. (accessed 20.09.2020). (2004). Available from: https://bit.ly/1KwbFwT

RESEARCH ARTICLE

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The Determination of the Psychological Resilience, Academic Achievement and Academic Self-Efficacy of Nursing Students

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Abstract

BACKGROUND/AIMS: It is considered that students who have strong psychological resilience and believe that they can overcome academic difficulties are more successful academically. The aim of this study was to determine the psychological resilience, academic achievement and academic self-efficacy of nursing students.

MATERIALS AND METHODS: This descriptive and cross-sectional research study was completed with a total of 454 nursing students between September, 2017 and January, 2018. The data were collected using the Personal Information Form, the Resilience Scale for Adults, and the Academic Self-Efficacy Scale.

RESULTS: There was a positive but weak significant correlation between the students' psychological resilience and their academic self-efficacy.

CONCLUSION: Studies aimed at increasing students' psychological resilience will have an impact on the academic self-efficacy of students.

Keywords: Academic self-efficacy, psychological resilience, academic achievement, nursing student

INTRODUCTION

Individuals may encounter many difficulties and traumatic situations throughout their lives. The reactions of these individuals who experience these difficulties and their coping skills are different from each other. Some individuals experience psychological problems in traumatic and stressful circumstances, whereas others can get over the effects of these negative circumstances in a short time and return to their normal lives quickly. This can be explained through the concept of psychological resilience which indicates how an individual adapts to difficulties or finds the strength to overcome them.[1] The concept of psychological resilience includes individual characteristics and is affected by many factors in the developmental process. These may include negative life events, chronic diseases, familial problems, economic difficulties and violence.[2] It has been suggested that healthy individuals who have encountered a negative experience try to solve further negative experiences using similar methods.[3] The perception of self-efficacy is important for psychological resilience. Self-efficacy is one's belief that one is able to cope with the difficulties one may face. It affects the behaviors of individuals and their belief that they can achieve success. Academic self-efficacy, an important sub-dimension of self-efficacy, refers to the individual's belief that they will be successful in attaining the desired goal of a given academic subject or task. Students with high academic self-efficacy make an effort to become more motivated, are more solution-oriented when faced with problems, and are able to regather their strength faster after a negative outcome.[4]

In the literature, academic achievement has been defined as the assessment made by teachers of students' responses to the lessons taught in schools, their exam scores, their scores for practical activities, and how the scores obtained express their achievement.[5] Students' academic

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achievements are associated with mental, affective, environmental and social factors.[6] In order to be considered academically successful, students should not only have a good grade point average but also be habituated to daily study and be able to transfer what they have learned into daily life.

The undergraduate period is a transitional period. During this period, young people are both in search of an identity and also trying to cope with the difficulties of university life. Starting university is a new beginning, with new goals, and it brings with it many issues, such as leaving one's family, establishing new friendships in a different environment, dealing with the fear being alone, experiencing economic difficulties, having to adapt to going to lectures and feeling concern about one's academic achievements. Nursing students may encounter many other difficult circumstances in addition to the ones mentioned above, including experiencing clinical practice in a hospital for the first time, communicating with patients, participating in the care of patients, and not knowing how to cope with their patients' problems. In this situation, students may experience inefficacy, despair and severe anxiety in both clinical and academic settings. In addition, they may experience stress and uneasiness while trying to cope with these concerns.[7]

It is considered that students who have strong psychological resilience and believe that they can overcome academic difficulties are more successful academically. In this context, it is thought to be important to improve the factors which affect the resilience of nursing students and academic self-efficacy; ensure students' awareness and enable support systems to increase their resilience.

MATERIALS AND METHODS

Sample and Setting

This descriptive and correlation type of study was conducted in North Cyprus, between September, 2017 and January, 2018. The population of the present study comprised 650 students who were enrolled in a faculty of nursing. The study aimed to reach the whole universe by not selecting samples. Four hundred and fifty-four students who were studying in the faculty of nursing during the fall semester of the 2017-2018 academic year, and who volunteered to participate were included in this study. The percentage of participation in this research was 70%.

Data Collection Instruments

To collect the data, the Personal Information Form determining the sociodemographic characteristics of the students, the Resilience Scale for Adults (RSA), and the College Academic Self-Efficacy Scale (CASES) were used.

Personal Information Form

The Personal Information Form consists of 13 questions related to the sociodemographic characteristics of the students. The form includes questions relating to age, gender, marital status, year of study, family type, whether their parents were alive, family attitude, income level, social support, place of residence, employment status, whether they had voluntarily chosen to study in the department and their academic average scores.

Academic achievement: The university where the study was conducted has a requirement to earn a minimum of 2.00 general academic average to graduate from the faculty of nursing. Therefore, the study accepted the threshold of the general academic average as 2.00 and students who earned 2.00 or above were determined to be successful.

Resilience Scale for Adults

This scale was developed by Friborg et al.[8] and its Turkish validity and reliability study was conducted by Basım and Çetin.[9] The scale consists of six dimensions: *perception of self* (Cronbach's α=0.72), *social competence* (α=0.77), *family cohesion* (α=0.81), *social resources* (α=0.83), *planned future* (α=0.75) and *structured style* (α=0.68). The RSA includes a total of 33 items and is a 5-point Likert-type scale. The higher the score, the higher the psychological resilience and the lower the score, the lower the resilience. In this study, the Cronbach's alpha coefficient of the scale was calculated to be 0.86.

College Academic Self-Efficacy Scale

The CASES was developed by Owen and Froman[10] and its Turkish validity and reliability study was conducted by Ekici.[11] The scale is formed of the three sub-dimensions called *social status*, *cognitive applications* and *technical skills*. The CASES includes a total of 33 items and is a 5-point Likert-type scale. The Cronbach alpha reliability coefficient for the total scale was found to be 0.86; it was 0.88 for the *social status* dimension; 0.82 for the *cognitive applications* dimension and 0.90 for the *technical skills* dimension. In this study, the Cronbach's alpha coefficient of the scale was calculated to be 0.90.

Procedure

Data were collected in the classroom environment before or after lectures. The students were informed about the purpose and scope of this study and it was determined whether they would volunteer to participate in this study. The questionnaires were handed out to those students who agreed to participate in this study. The participants completed the questionnaires in approximately 15 minutes.

Ethical Considerations

Ethics committee approval was received for this study from Near East University Ethics Committee (approval number: 424, date: 29.06.2017). This study was carried out in accordance with the principles of the Helsinki Declaration. The purposes and methods of this study were explained to the students. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

The Statistical Package for the Social Sciences 18.0 software program was used to analyze the data in a computer environment. The data were evaluated using descriptive statistics [eg, median (standard deviation), range, percentage] and the test of normality and paired sample t-tests were used to compare variables. Pearson correlation analysis was performed to examine the relationship between psychological resilience and academic self-efficacy. The statistical significance level, α, was accepted to be 0.05.

RESULTS

37% of the nursing students were aged 20 years or below and the mean age of the students was 21.38±2.19 years. It was determined that, of the nursing students, 59.7% were female, 97.8% were single and 31.1%

were in their fourth year of study. Of the nursing students, 70% lived in a nuclear family, 51.3% had a democratic family, and 68.7% had an income equal to their expenses. It was determined that 74.2% of the students received social support from their families, that 46.9% of them lived with their friends, and that 79.7% of them had chosen to study in the department of nursing (Table 1).

The distribution of the students' mean scores for the RSA and CASES are given in Table 2. The mean subscale scores of the students for the RSA were 14.16±3.18 for *structural style*; 14.96±3.42 for *future perception*; 23.09±4.82 for *family cohesion*; 21.79±4.38 for *personal competence*; 21.50±4.47 for *social competence* and 24.92±4.57 for *social resources*. The mean total RSA score was 120.46±20.02. When the mean subscale scores of the students for CASES were examined, the mean *social status* score was 31.57±6.57; the mean *cognitive operations* score was 64.95±11.53; and the mean *technical skills* score was 13.14±3.19. The mean total CASES score was determined to be 109.86±19.25. The general academic average of students was 2.25.

The RSA Family Cohesion sub-scale average scores of the nursing students were found to be higher in female students compared to the male students (22.45±4.59), and the difference between the groups was significant ($p<0.005$). Similarly, the RSA total average scores were also found to be higher in female students compared to the male students (23.53±4.93), and this difference between the gender and psychological resilience was statistically significant ($p<0.005$).

The RSA total average scores of the fourth-grade class students were higher than the students of other grades (123.66±19.62), and the difference between the class levels and psychological resilience of the students was statistically significant ($p<0.005$). Post-hoc advanced analysis determined that this significance derived from the difference between the average scores of the third and fourth-grade classes.

This study showed that there was a statistically significant difference between family attitudes and the RSA total average scores of the nursing students ($p<0.005$). The RSA *family cohesion* sub-scale average scores of those students with highly tolerant families were higher (25.36±4.41), and there was a statistically significant difference between the groups ($p<0.005$). Post-hoc advanced analysis determined that this significant difference derived from the difference between the democratic family and tolerant family average scores.

This study found that there was a statistically significant difference between the social support and RSA total average scores of the nursing students ($p=0.001$), and all of the sub-scale average scores with the exception of the *social competence* sub-scale. Post-hoc advanced analysis determined that this significant difference in the RSA total average scores derived from the difference between the average scores of the family and friend groups.

This study found a statistically significant difference between the class levels and CASES total average scores of the students ($p<0.005$). Post-hoc advanced analysis determined that this significant difference between the CASES total average scores and the class levels of students derived from the difference between the average scores of the third and fourth-grade classes.

The CASES total average scores of the students who chose the nursing department willingly (111.04±18.80) was found to be higher than the other students. This study also found that there was a statistically

Table 1. Distribution of the characteristics of the nursing students' education (n=454)

Characteristics	n	%
Age		
17- 20	168	37.0
21-22	146	32.2
Over 23 years	140	30.8
Mean age	454	21.38±2.19
Gender		
Female	271	59.7
Male	183	40.3
Marital status		
Married	10	2.2
Single	444	97.8
Academic year		
1st	76	16.7
2nd	116	25.6
3rd	121	26.7
4th	141	31.1
Family type		
Nuclear	318	70.0
Extended	120	26.4
Broken	16	3.5
Mother		
Alive	442	97.4
Not alive	12	2.6
Father		
Alive	434	95.6
Not alive	20	4.4
Family attitude		
Democratic	223	51.3
Carefree	9	2.8
Strict	83	18.3
Inconsistent	10	2.2
Perfectionist	21	4.6
Overprotective	57	12.6
Permissive	41	9
Income status		
Income less than expenses	86	18.9
Income equal to expenses	312	68.7
Income more than expenses	56	12.3
Social support		
Family	337	74.2
Friend	107	23.5
Other	10	2.1
Current place of residence		
With friends in dormitory	108	23.8
With friends at home	213	46.9
With family at home	122	26.9
Alone at home	11	2.4
Employment status		
Employed	65	14.3
Unemployed	389	85.7
Choosing the department willingly		
Yes	392	79.7
No	92	20.3

*Frequency, number, and percentage were used

significant difference between choosing the nursing department willingly and the CASES total average scores (p<0.005).

The general academic averages of the nursing students who were older than 23 years were found to be higher than the other age groups (2.37±0.44), and this difference between the age and the general academic averages of students was statistically significant (p<0.005).

According to the gender variable, this study found that the GPAs of the female students were higher than the male students (2.34±0.49), and this difference between the gender and the general academic averages of the students was statistically significant (p<0.005).

The GPAs of the fourth-grade class students were higher than the other students (2.41±0.42), and this difference between the class levels and the general academic averages of the students was statistically significant (p<0.005). Post-hoc advanced analysis determined that this significant difference between the GPA average scores and the class levels derived from the difference between the average scores of the third and fourth-grade classes.

This study revealed that those students who had nuclear families had higher GPAs (2.29±0.48) compared to those students with different family structures, and this difference between the family structure and the general academic averages of the students was statistically significant (p<0.005). Post-hoc advanced analysis determined that the significant difference between the GPA average scores and the family structures derived from the difference between the average scores of the nuclear and fragmented family structures.

The GPAs of the students who stayed in a dormitory were also found to be higher than the other students (2.47±0.43), and this difference between the place of residence and the general academic averages of the students was found to be statistically significant (p<0.005).

When the correlation of the RSA with the CASES and students' general academic average scores were examined, it was found that there was a positive, significant but weak correlation between all of the subscale scores of both scales (p<0.001), except for the correlation between the *family cohesion* subscale of the RSA and the *social status* subscale of the CASES (r=0.054; p=0.247) (Table 3).

There was a positive, significant, but weak correlation between the *structural style* subscale of the RSA and the general academic average score (p<0.001). A negative, weak correlation was determined between the mean *personal competence* subscale score of the RSA and the general academic average (r=-0.001) (Table 3).

There was a positive, significant, but weak correlation between the mean total scores of the RSA and the CASES (r=0.263; p<0.001). There was no significant correlation between the mean total RSA score and the general academic average score (p=0.024); however, there was a positive, significant, but weak correlation between the CASES and the general academic average (r=0.260; p<0.001) (Table 3).

Table 2. Mean RSA and CASES scores of the nursing students (n=454)

Scales	Mean ± SD	Minimum and maximum scores
Resilience Scale for Adults		
Perception of self	21.79±4.38	6-30
Perception of future	14.96±3.42	4-20
Structural style	14.16±3.18	4-20
Social competence	21.50±4.47	6-30
Family cohesion	23.09±4.82	6-30
Social resources	24.92±4.57	7-35
Total score	120.46±20.02	33-165
College Academic Self-Efficacy Scale		
Social status	31.57±6.57	10-50
Cognitive operations	64.95±11.53	19-95
Technical skills	13.14±3.19	4-20
Total score	109.86±19.25	33-165

SD: Standard deviation, RSA: Resilience Scale for Adults, CASES: College Academic Self-Efficacy Scale

DISCUSSION

In this study, findings related to the psychological resilience, academic achievement and academic self-efficacy levels of the students in a department of nursing and the correlation between them were discussed in line with the literature. It was found that the differences between the students' gender, year of study, family structure, family attitudes, social support, whether they had willingly chosen to study in the department and their psychological resilience were statistically significant. Studies have shown that female students have higher psychological resilience than male students.[12,13] Likewise, in our study, female students were found to have greater psychological resilience. This may be due to the fact that women have better skills in coping with stress and solving problems, that they are more likely to seek help for problem areas, and due to other factors contributing to psychological resilience. In the study conducted by Şahin and Buzlu[14] with university students, it was stated that, as the years of study increased, students became better at communicating with and relating to the people in their environment, and thus their psychological resilience increased. Students beginning university may face many problems in the first year, such as being away from their families, feeling scared of being alone, having to establish themselves in a new environment, facing economic difficulties and feeling concerned about their academic success, and they may experience stress and difficulties while trying to cope.[15,16] Similar to the literature, it can be thought that the increases in psychological resilience as the years of study increased in our study may be due to the students maturing and gaining independence and increased self-awareness about themselves and their environment, and an increased knowledge and experience of their profession.

It was determined that the significant difference between family attitudes and the psychological resilience of the students resulted from the difference in the mean score for democratic family attitude. A democratic family attitude is a decisive and reassuring parental attitude. Parents with this attitude show unconditional love and respect to their children, the needs of the children are met and managed, and they are able to ensure the development of a sense of responsibility in their children. When previous studies were examined, it was determined that a democratic family attitude increased psychological resilience, self-efficacy, and self-esteem in students.[17,18] If students feel that they are not alone and that they are important, they are more likely to perceive their future positively, to have increased psychological resilience, and to adapt more easily to negative results when they encounter difficult experiences.[19] In the study conducted by Malkoç and Yalçın[20], it was

stated that students' psychological well-being increased as the social support from their family and friends increased. The findings of our study are similar to those in the literature and it can be said that the social support provided by family and friends protects the physical and mental health of the students and increases their psychological resilience.

It was determined that relationship between the students' year of study, whether they had willingly chosen to study in the department and their academic self-efficacy was statistically significant. Studies have stated that academic self-efficacy increases as the year of study of students increases.[21,22] It can be suggested that students' academic self-efficacy becomes stronger due to the fact that the longer they have studied for, the greater their academic knowledge becomes, the more they become involved in clinical practices, and the more their skills develop.

In the study conducted by Egelioğlu et al.[23] with nursing students, it was found that there was a significant correlation between having willingly chosen the department of nursing and the academic achievement score. The choice of profession indicates a commitment to a field in which one believes one will achieve success. A student's choice of a profession can be affected by many factors such as their individual characteristics and their familial and environmental situations and this is reflected in the student's success during and after their period of education and in a feeling of academic efficacy. The significant difference between the students' academic self-efficacy and whether they had willingly chosen their department supports the findings in the literature.

The relationships between age, gender, grade, family structure, place of residence and the general academic average score and the general academic achievement of the nursing students were found to be significant. The reason for the significant relationship between age and academic achievement in our study may be due to the fact that students' professional knowledge increased as their age increased and that students were focused on their academic achievement after graduation. Studies have found a significant correlation between age and academic achievement.[24,25] It has been stated in the literature that female students are more successful than the male students and that personal characteristics directly related to academic achievements, such as self-esteem, self-efficacy, good time management, satisfaction with life and psychological well-being are more often found in female students than in male students.[26] Given that female students showed a high degree of psychological resilience and academic self-efficacy in our study as well, it is thought that their academic achievements may have been affected by these two positive factors.

In parallel with the results of this study, other studies have demonstrated that as the year of study increases, academic achievement also increases.[27,28] At the beginning of their university life, students may encounter difficulties in adapting to conditions such as a new location, lectures and their physical environment. As the years of study progress, students' perspectives on events change, their professional knowledge and skills increase, problems in adapting decrease, and their academic achievement thus increases.

The literature indicates that having a nuclear family contributes to students' academic achievement and their post-graduate working life. Nuclear families provide the necessary environment, motivation and social support in order to provide a good education to their children. This also increases students' academic achievement.

One of the most important problems of students who start university is finding accommodation and the first choice of accommodation for students and their families are usually dormitories. Students staying in a dormitory socialize with people from other cultures, their social environment expands, they share knowledge with their friends, they study as a group, they have a suitable studying environment, they do not have any transport problems, they participate in the lectures and they benefit from events and libraries on campus. This enables students to achieve success in their lectures.[29] In our study, the academic achievement of those students who stayed in dormitories was at a high level. This may be because the physical conditions of the dormitories were good, they were on the university campus and close to the libraries, they had suitable study areas and students from the same department were able to study together.

In this study, a positive, weak, but significant correlation was found between the total psychological resilience and total academic self-efficacy scores of the nursing students. Nursing students encounter many stressors related to academic and clinical settings during their undergraduate education. Difficulty in coping with these stressors may cause a loss of motivation, self-control, stress and a lack of self-confidence, and may affect learning. It has been stated in the literature that students with high psychological resilience experience less concern and have more belief that they can overcome any difficult circumstances they encounter.[1] Likewise, academic self-efficacy, which expresses the individual's belief that he/she can successfully achieve academic goals,

Table 3. Cross-scale correlation analysis

CASES	Social status		Cognitive operations		Technical skills		CASES total score		General academic average	
	r	p	r	p	r	p	r	p	r*	p
RSA										
Structural style	0.199	**<0.001**	0.225	**<0.001**	0.172	**<0.001**	0.250	**<0.001**	0.161	**<0.001**
Perception of future	0.194	**<0.001**	0.284	**<0.001**	0.196	**<0.001**	0.273	**<0.001**	0.052	0.267
Family cohesion	0.054	0.247	0.182	**<0.001**	0.130	**<0.006**	0.159	**<0.001**	0.044	0.348
Perception of self	0.230	**<0.001**	0.256	**<0.001**	0.262	**<0.001**	0.274	**<0.001**	**-0.001**	0.988
Social competence	0.161	**<0.001**	0.147	**<0.002**	0.225	**<0.001**	0.175	**<0.001**	0.083	0.076
Social resources	0.113	**<0.001**	0.171	**<0.001**	0.177	**<0.001**	0.170	**<0.001**	0.038	0.424
RSA total score	0.184	**<0.001**	0.261	**<0.001**	0.240	**<0.001**	0.263	**<0.001**	0.072	0.124
CASES total score	0.846	**<0.001**	0.940	**<0.001**	0.740	**<0.001**	-	-	0.260	**<0.001**

RSA: Resilience Scale for Adults, CASES: College Academic Self-Efficacy Scale.

is strongly linked to psychological resilience. The results of our study are consistent with those in the literature. The weak correlation between the two variables may be attributed to the lack of support programs for psychological resilience and academic self-efficacy for nursing students.

This study determined that there was a positive, significant, but weak correlation between academic self-efficacy and the general academic average scores and that academic self-efficacy had a statistically significant relationship with academic achievement. In other studies which have examined academic self-efficacy and academic achievement, it has been found that there was a high correlation between these two concepts and that achievement stimulated academic self-efficacy.[30,31]

Students who have high self-efficacy make more effort to complete assigned tasks, perform better academically compared to students with low self-efficacy and do not procrastinate with regard to their academic work.[32] Similar to another study, this study found that students' belief in their own academic success was reflected in their academic achievements.

In our study, no significant correlation was found between the total psychological resilience score and the general academic average score and it was determined that psychological resilience had no statistically significant relationship to academic achievement. Academic life contributes greatly to the development of students as a result of the knowledge and experiences they acquired as well as to their motivation and strength to cope with negativity. On the other hand, the fact that academic education is a long and dynamic process which may be affected by many different factors can also lead students to experience issues much of the time. This may affect the students' resilience. A correlation between psychological resilience and academic achievement was not found in our study; however, there are studies showing that there is a positive correlation between these two elements.[33,34]

CONCLUSION

This study found a significant, positive and weak correlation between the psychological resilience and academic self-efficacy of nursing students. In addition, no significant correlation was determined between the students' psychological resilience and their general academic average scores. Moreover, it was determined that there was a positive, significant, but weak correlation between academic self-efficacy and the general academic average scores of the students.

In line with the results of our study, further studies should be conducted to investigate whether increasing students' psychological resilience will have an effect on their academic self-efficacy. Psychological resilience, academic self-efficacy and general academic average scores were found to be affected by many factors including gender, year of study, family structure, family attitude, social support, place of residence, and whether the department had been willingly chosen. It is important to evaluate students in terms of these variables. It is also important to plan awareness-based training for the areas in which students need to be strengthened.

MAIN POINTS

- Students' psychological resilience and academic self-efficacy are an important issue which affects their achievements.
- Our study showed a significant, positive, and weak correlation between the psychological resilience and the academic self-efficacy of nursing students.
- It is also important to plan awareness-based training for those areas in which students need to be strengthened.

ETHICS

Ethics Committee Approval: Ethics committee approval was received for this study from Near East University Ethics Committee (approval number: 424, date: 29.06.2017).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.T.A., M.M., Design: N.T.A., M.M., Supervision: M.M., Fundings: N.T.A., M.M., Materials: N.T.A., Data Collection and/or Processing: N.T.A., Analysis and/or Interpretation: N.T.A., Literature Search: N.T.A., Writing: N.T.A., M.M., Critical Review: M.M.

DISCLOSURES

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REFERENCES

1. Sidheek KPF, Satyanarayana VA, Sowmya HR, Chandra PS. Using the Kannada version of the connor davidson resilience scale to assess resilience and its relationship with psychological distress among adolescent girls in bangalore, India. Asian J Psychiatr. 2017; 30: 169-72.
2. Southwick SM, Bonanno GA, Masten AS, Panter-Brick C, Yehuda R. Resilience definitions, theory, and challenges: interdisciplinary perspectives. Eur J Psychotraumatol. 2014; 5.
3. Masten AS, Barnes AJ. Resilience in children: developmental perspectives. Children. 2018; 5(7): 98.
4. Artino AR. Academic self-efficacy: from educational theory to instructional practice. Perspect Med Educ. 2012; 1(2); 76-85.
5. Mirkamali SM, Khabare K, Mazari E, Farhadi Amjad F. The role of mental health on academic performance of university students; with the meditation of academic achievement motivatio. JSRP. 2015; 6(2): 101-9.
6. Sharma D, Sharma S. Relationship between motivation and academic achievement. IJASR. 2018; 4(1): 1-5.
7. Jonsén E, Melender HL, Hilli Y. Finnish and swedish nursing students' experiences of their first clinical practice placement a qualitative study. Nurse Educ Today. 2013; 33(3): 297-302.
8. Friborg O, Hkemdal O, Rosenvinge JH, Martinussen MA. New rating scale for adult resilience: What are the central protective resources behind healthy adjustment? Int J Methods Psychiatr Res. 2003; 12(2): 65-76.
9. Basım HN, Çetin F. The reliability and validity of the resilience scale for adults Turkish version. Turk Psikiyatri Derg. 2011; 22(2): 104-14.
10. Owen S, Froman RD. Development of a callege academic self- efficacy scale. Paper presented at the annual meeting of the national council on measurement in education. New Orleans LA; 1988.

11. Ekici G. Academic self-efficacy scale: the study of adaptation to Turkish, validity and reliability. H.U. Education Journal. 2012; 43: 174-85.
12. Cassidy S. Resilience building in students: The role of academic self-efficacy. Front Psychol. 2015; 6: 1781.
13. Mwangi CN, Ireri AM. Relationship between academic resilience and academic achievement among secondary school students in kiambu county, Kenya. Int J Sch Cog Psychol. 2015: 1-5.
14. Şahin G, Buzlu S. The mediating role of perceived stress on relationship of resilience with self efficacy social support and the effective coping skills in nursing students. Journal of Anatolia Nursing and Health Sciences 2017; 20: 122-36.
15. Berg P, Carol P. Turning classroom failure ınto student success: the value of ıntegrating resiliency building activities in the academic classroom. MTR. 2017; 2(4): 299-311.
16. Smith GD, Yang F. Stress, resilience and psychological wellbeing in Chinese undergraduate nursing students. Nurse Educ Today. 2017; 49: 90-5.
17. Chee WC. Lose at the starting line, win at the finishing line": The narratives behind beating academic adversity. Soc Indic Res. 2017; 45(2): 741-53.
18. Bingöl TY, Batik MV, Hoşoğlu R, Fırıncı-Kodaz A. Psychological Resilience and Positivity as Predictors of Self-Efficacy. Asian J Distance Educ. 2019; 5(1): 63-9.
19. Pines EW, Rauschhuber ML, Norgan GH, Cook JD, Canchola L, Richardson C, et al. Stress resiliency, psychological empowerment and conflict management styles among baccalaureate nursing students. J Adv Nurs. 2012; 68(7): 1482-93.
20. Malkoç A, Yalçın İ. Relationships among resilience, social support, coping, and psychological well-being among university students. TPCGJ. 2015; 5(43): 35-43.
21. Jiang Z. Emotional intelligence and career decision-making self-efficacy: national and gender differences. JEC. 2017; 51(3): 112-24.
22. Jonsén E, Melender HL, Hilli Y. Finnish and swedish nursing students' experiences of their first clinical practice placement a qualitative study. Nurse Educ Today. 2013; 33(3): 297-302.
23. Egelioğlu N, Arslan S, Bakan G. The effect of satisfaction status of nursing students on their academic achievement. Journal of Research and Development in Nursing 2011; 10(1): 114-24.
24. Baba I, Aliata IM, Patrick AB. Demographic factors and students' academic achievement in tertiary ınstitutions in ghana: A study of wa polytechnic. JEP. 2013; 14(30): 76-80.
25. Yazıcı H, Albayrak E, Reisoğlu S. Personality, academic self-efficacy, academic locus of control and academic procrastination among university students. MAKU Journal of Faculty of Education. 2016; 38: 90-102.
26. Alshammari F, Saguban R, Pasay-An EA, Alshammari L. Factors affecting the academic performance of student nurses: A cross-sectional study. JNEP. 2018; 8(1): 60-8.
27. Jamshid K, Mohammadi B, Mohammadi Z, Parviz MK, Poursaberi R, Mohammed MM. Academic satisfaction and academic achievement among students at kermanshah university of medical sciences: Academic year 2015-2016. Res Dev Med Educ. 2017; 6(2): 72-9.
28. Tayfur C, Ulupınar S. The effect of perceived social support on the academic achievement of health college students. J Psy Nurs. 2016; 7(1): 1-6.
29. Ammigan R, Jones E. Improving the student ecperience: Learning from a comparative study of international student satisfaction. JSIE. 2018; 22(4): 283-301.
30. Alhadabi A. Karpinski AC. Grit, self-efficacy, achievement orientation goals, and academic performance in University students. Int J Adolesc Youth. 2019; 25: 519-35.
31. Shoukat A, Zubair H, Fahad M, Hamid K, Awais A. Factors contributing to the students academic performance: A case study of ıslamia university sub-campus. Am Educ Res J. 2013; 1(8): 283-9.
32. Tiyuri A, Saberi B, Miri M, Shahrestanaki E, Bayat B, Salehiniya H. Research self-efficacy and its relationship with academic performance in postgraduate students of tehran university of medical sciences in 2016. J Educ Health Promot. 2018; 10(7): 11.
33. Abolmaali K, Mahmudi R. The prediction of academic achievement based on resilience and perception of the classroom environment. SJEDU. 2013; 1(1): 7-12.
34. Novotný JS, Křeménková L. The relationship between resilience and academic performance at youth placed at risk. Československá Psychologi. 2016; 60(6): 553-66.

RESEARCH ARTICLE

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Pain, Anxiety, Depression, Fatigue, Sleep Quality, and Health-Related Quality of Life in the Mothers of Children with Autism Spectrum Disorder and the Mothers of Typically Developing Children: A Case-Control Study

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Abstract

BACKGROUND/AIMS: The special needs for children with autism spectrum disorder (ASD) increase the burden of caregiving, which may cause several negative effects on the caregiver. The aim of this study was to compare the care burden, pain, anxiety, depression, fatigue, sleep quality, and health-related quality of life (HRQOL) in the mothers of children with ASD against those with typically developing children.

MATERIALS AND METHODS: Children with ASD (n=35) and their mothers (n=35), and typically developing children (n=35) and their mothers (n=35) were recruited into this case-control study. The pain, anxiety/depression, fatigue, sleep quality, and HRQOL of the mothers were assessed.

RESULTS: There was no significant difference in most of the demographic characteristics of the children and their mothers ($p>0.05$). The mothers of those children with ASD had a significantly greater care burden and anxiety levels, and more impaired sleep quality and HRQOL ($p<0.05$). A non-significant difference was observed in depression, fatigue, and pain between the mothers of children with ASD and those with typically developing children ($p>0.05$).

CONCLUSION: It was found that the mothers of children with ASD had a higher care burden and anxiety levels, and lower sleep quality and HRQOL compared to the mothers of typically developing children. However, there was no significant difference between the two groups in terms of pain, fatigue, or depression levels.

Keywords: Autism spectrum disorder, mother, caregiver, children, pain, quality of life

INTRODUCTION

Developmental disabilities include various cognitive and physical disorders which occur in early childhood and remain throughout life.[1] Developmental disabilities such as autism spectrum disorder (ASD) have an increasing prevalence.[2] These children with developmental disabilities commonly require significant help while performing many activities of daily living.[2] These elevated special needs generate significant changes in family dynamics and increase the burden on caregiving which is commonly given by their biological mothers.[3-5]

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The caregiver's problems can affect the continuous interaction between them and their children.[6] Therefore, it is important to know a caregiver's health status in order to provide better treatment to an impaired child. Previous studies showed that the caregivers of children with intellectual and developmental disabilities have higher levels of anxiety and depression compared to the caregivers of children without such disabilities or the general population.[1,7-9] There is cumulative evidence that the caregivers of such children have a lower health-related quality of life (HRQOL).[2,4,5,10]

Chronic pain is commonly co-morbid with a depressive or anxiety disorder which can exacerbate the pain perception.[11,12] Although it is known that the caregivers of children with developmental disabilities experience more anxiety and depression,[1,7-9] the interaction between these problems and other related issues such as pain, fatigue, and sleep quality is not clear. A previous study investigated the HRQOL in the caregivers of children with intellectual disability using the 5-level EQ-5D which includes five dimensions related to the level of perceived problems, including pain/discomfort and anxiety/depression.[10] It was reported that 49.7% of the caregivers had pain/discomfort problems and 54.3% of them had anxiety/depression problems.[10] However, that study focused on pain/discomfort and anxiety/depression problems related to HRQOL without assessing them directly.[10] However, direct assessments are required in order to obtain a better understanding. For example, a recent study reported that having intellectual disability in children with cerebral palsy increases pain and disability related to the lower back and neck in the caregivers.[13] Our study aimed to compare the care burden, pain, anxiety, depression, fatigue, sleep quality, and HRQOL in those mothers of children with ASD and the mothers of typically developing children. We hypothesized that the mothers of children with ASD would have significantly greater levels of care burden, pain, anxiety, depression, and fatigue; and lower levels of sleep quality and HRQOL compared to the mothers of typically developing children.

MATERIALS AND METHODS

Study Design and Participants

This study had a case-control design. Children diagnosed as having an ASD according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders-5[14] and their primary caregivers were recruited from a special education and rehabilitation center located in Nicosia, The Turkish Republic of North Cyprus. Typically developing children (without a physician-diagnosed chronic disease) and their primary caregivers living in the same city were recruited from the friends, families, and neighborhoods of the researchers. The inclusion criteria for the caregivers were being the biological mother and primary caregiver of the child. We included only the mothers since mothers are generally the primary caregivers of the children due to certain cultural considerations. Those mothers with a physician-diagnosed chronic disease (neurological, systemic, metabolic, etc.), a history of operation within the prior 6 months, or those who were pregnant were excluded.

The required sample size was calculated as 54 participants with their children (27 for each group) in order to achieve an effect size of 0.78, a power of 80%, and an alpha error probability of 0.05 using G*Power (Ver. 3.1.9.4, Dusseldorf University, Germany).[15,16]

This study was approved by the Ethics Review Board of Near East University (approval number: 2019/65-715, date: 22.01.2019) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki (as revised in Brazil, 2013). All mothers gave informed consent for themselves and their children before entering this study.

Outcome Measures

Demographic characteristics [gender, body mass index (BMI), education level, and the number of children] of the mothers and their children were obtained.

The Zarit Burden Interview (ZBI) was used to assess the distress experienced by the caregivers due to caring for their children. The ZBI consists of 22 items having a 5-point scale, where higher scores indicate a higher burden. The ZBI was found to be a valid and reliable scale to be used within the Turkish population.[17]

The McGill Pain Questionnaire (MPQ) was used to assess the pain experience of the caregivers.[18] The MPQ includes three parts. In the first part, the participants mark their painful sites. The second part is a verbal descriptive scale related to the intensity level of their current pain. The third part consists of 72 descriptive adjectives related to pain. A cumulative total score is calculated, and higher scores indicate more pain experience. The Turkish version of the MPQ was found to be a reliable and valid measure.[19]

The Nordic Musculoskeletal Questionnaire (NMQ) was used to determine the prevalence of pain in different body regions within the prior year and week. The NMQ has a dichotomous option for each body part and gives a prevalence rate for each body region rather than a cumulative score.[20,21] The NMQ was translated into Turkish, and this version was found to be reliable and valid.[20]

The Fatigue Severity Scale (FSS) was used to assess fatigue severity.[22] The FSS includes 9 items with a 7-point scale and higher scores represent greater fatigue severity. The Turkish version of FSS was found to be reliable and valid.[22] A cut-off score of 4 or more is considered indicative of problematic fatigue.[23]

The Hospital Anxiety and Depression Scale (HADS) was used to assess the level of anxiety and depressive symptoms. It consists of two subscales: HADS-Anxiety and HADS-Depression with each subscale having 7 items with a response-scale with four alternatives (from 0 to 3).[24,25] The Turkish version of the HADS was also found to be a valid and reliable measure.[26] The cut-off points of the Turkish version were 10 for HADS-Anxiety and 7 for HADS-Depression.[26]

The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality.[27] The PSQI has 19 items with a 0-3 interval scale and lower scores indicate healthier sleep quality. The Turkish version of the PSQI was found to be valid and reliable.[28]

The Nottingham Health Profile (NHP) was used to assess HRQOL.[29] The NHP consists of 38 items with yes/no answer options and each section score is weighted. The NHP has 6 different subscale scores and the higher the score, the lower the HRQOL. The Turkish version of the NHP was found to be valid and reliable.[30]

Statistical Analysis

The Kolmogorov-Smirnov test and histograms were used to investigate the normal distribution of data. Mann-Whitney U test and chi-squared test were conducted to compare differences between the study groups.

Effect sizes were calculated as Cohen's d.[31] Statistical significance was set at $p<0.05$. Statistical analyses were conducted using the IBM SPSS Statistics for Windows (Version 24.0. Armonk, NY: IBM Corp.).

RESULTS

In total, 70 mothers and 70 children participated in this study. No significant differences were observed in age, BMI, number of children, and education levels between the mothers of children with ASD and those with typically developing children ($p>0.05$) (Table 1). There were significantly more males in those children with ASD ($p<0.05$). No significant difference was observed in age, BMI, and education level between those children with ASD and the typically developing children ($p>0.05$) (Table 2).

The mothers of children with ASD had significantly greater ZBI, PSQI, HADS-Anxiety, NHP-Energy, NHP-Emotional reaction, and NHP-Social isolation scores compared to the mothers of the typically developing children ($p<0.05$). No significant differences were observed in the remaining study variables ($p>0.05$). Table 3 presents the comparison statistics of care burden, pain, fatigue, sleep quality, anxiety, depression, and HRQOL between the mothers of children with ASD and those with typically developing children.

The most common musculoskeletal pain sites during the prior year and prior week were the upper back and neck in both the mothers of children with ASD and those with typically developing children. No significant difference was observed in the presence of musculoskeletal pain sites during the prior year or prior week between the mothers of children with ASD and those with typically developing children ($p>0.05$). The details are presented in Table 4.

DISCUSSION

The study hypothesis was that the mothers of children with ASD would have significantly greater levels of care burden, pain, anxiety, depression, and fatigue; and lower levels of sleep quality and HRQOL compared to the mothers of typically developing children. The main findings were that the mothers of children with ASD had greater care burden, greater anxiety levels, lower sleep quality, and lower HRQOL.

Although the mothers of children with ASD had greater anxiety levels, there was no significant difference between the number of individuals with anxiety determined by published cut-off values between the mothers of children with ASD and the mother of typically developing children.[26] This finding should be interpreted with caution. The mothers of children with ASD had relatively high anxiety (14.3%) and depression (42.9%) prevalence in our study. However, mothers with typically developing children also had relatively high anxiety (8.6%) and depression (37.1%) prevalence. Almansour et al.[32] found that the caregivers of children with ASD had significantly more anxiety/depression disorders compared to controls; with 32% of the caregivers of children with ASD having anxiety/depression, whereas the controls had 2%. Ingersoll et al.[33] reported similar results that 44% of the mothers of children with ASD had depression and this ratio was 30% in their control subjects. Similarly, other studies also reported significant differences between the caregivers of children with ASD and controls in terms of depression/anxiety.[34,35] The depression/anxiety rates in the mothers of children with

Table 1. The demographic characteristics of the mothers of children with ASD and typically developing children

	Mothers of children with ASD (n=35)	Mothers of typically developing children (n=35)	p
Age (years)[a]	35 (31-41)	34 (29-41)	0.879
BMI (kg/m^2)[a]	22.4 (20.8-25.5)	23 (20.8-28.7)	0.385
Number of children[a]	2 (1-2)	2 (1-2)	0.497
Education level			
Secondary school[b]	17 (48.6)	6 (17.1)	0.775
High school[b]	10 (28.6)	13 (37.1)	
University[b]	8 (22.9)	16 (45.7)	

[a]Median (interquartile range), analyzed with Mann-Whitney U test. [b]Number of participants, analyzed with chi-squared test. ASD: autism spectrum disorder, BMI: body mass index.

Table 2. The demographic characteristics of the children with ASD and typically developing children

	Children with ASD (n=35)	Typically developing children (n=35)	p
Age (years)[a]	7 (5-9)	8 (4-12)	0.331
Gender			
Female[b]	9 (25.7)	17 (48.6)	**0.048***
Male[b]	26 (74.3)	18 (51.4)	
BMI (kg/m^2)[a]	19.0 (16.6-24.1)	18.5 (15-21.6)	0.312
Education level			
Preschool[b]	17 (48.6)	11 (31.4)	0.054
Primary school[b]	15 (42.9)	15 (42.9)	
Secondary school[b]	3 (8.6)	8 (22.9)	
High school[b]	0	1 (2.9)	

*$p<0.05$. [a]Median (interquartile range), analyzed with Mann-Whitney U test. [b]Number of participants, analyzed with chi-squared test. ASD: autism spectrum disorder, BMI: body mass index.

Table 3. Comparison of care burden, pain, fatigue, sleep quality, anxiety, depression, and health-related quality of life between the mothers of children with ASD and those with typically developing children

	Mothers of children with ASD (n=35)	Mothers of typically developing children (n=35)	p	U/χ^2	d
ZBI[a]	25 (18-31)	12 (6-22)	**<0.001***	292.5	1.0
MPQ[a]	44 (27-65)	38 (30-50)	0.250	514.5	0.29
FSS[a]	40 (23-50)	30 (14-44)	0.113	477.5	0.39
Presence of problematic fatigue[b]	19 (54.3)	14 (40.0)	0.231	1.433	0.29
HADS-Anxiety[a]	7 (5-8)	5 (3-7)	**0.014***	403.5	0.61
Presence of anxiety[b]	5 (14.3)	3 (8.6)	0.452	0.565	0.18
HADS-depression[a]	6 (4-8)	6 (4-8)	0.763	587.0	0.07
Presence of depression[b]	15 (42.9)	13 (37.1)	0.626	0.238	0.11
PSQI[a]	13 (11-14)	12 (10-13)	**0.019***	414.0	0.58
NHP					
Pain[a]	18.7 (9-33.8)	17.1 (0-36)	0.582	566.0	0.13
Energy[a]	37 (0-61)	0 (0-39.2)	**0.049***	454.0	0.46
Sleep[a]	12.6 (0-27.3)	0 (0-12.6)	0.071	476.5	0.39
Mobility[a]	0 (0-21.4)	0 (0-22)	0.877	600.5	0.04
Emotional reaction[a]	16.8 (10.5-24.4)	0 (0-14)	**<0.001***	315.0	0.92
Social isolation[a]	0 (0-22)	0 (0-0)	**0.011***	439.0	0.50

*p<0.05. [a]Median (interquartile range), analyzed with Mann-Whitney U test. [b]Number of participants, analyzed with chi-squared test. ASD: autism spectrum disorder, ZBI: Zarit Burden Interview, MPQ: McGill Pain Questionnaire, FSS: Fatigue Severity Scale, HADS: Hospital Anxiety and Depression Scale, PSQI: Pittsburgh Sleep Quality Index, NHP: Nottingham Health Profile.

Table 4. Comparison of the presence of musculoskeletal pain sites during the prior year and prior week between the mothers of children with ASD and those with typically developing children

	Musculoskeletal pain sites during the prior year							Musculoskeletal pain sites during the prior week						
	Mothers of children with ASD (n=35)		Mothers of typically developing children (n=35)					Mothers of children with ASD (n=35)		Mothers of typically developing children (n=35)				
Anatomical region	**n**	**%**	**n**	**%**	**p**	**χ^2**	**d**	**n**	**%**	**n**	**%**	**p**	**χ^2**	**d**
Neck	18	51.4	22	62.9	0.334	0.933	0.23	13	37.1	12	34.3	0.803	0.062	0.06
Shoulders	16	45.7	17	48.6	0.811	0.057	0.06	6	17.1	11	31.4	0.163	1.942	0.34
Elbows	4	11.4	2	5.7	0.393	0.729	0.21	3	8.6	1	2.9	0.303	1.061	0.25
Wrists/hands	11	31.4	6	17.1	0.163	1.942	0.34	5	14.3	4	11.4	0.721	0.128	0.09
Upper back	22	62.9	23	65.7	0.803	0.062	0.06	14	40	18	51.4	0.337	0.921	0.23
Lower back	16	45.7	19	54.3	0.473	0.541	0.18	10	28.6	9	25.7	0.788	0.072	0.06
Hips/thighs	7	20	4	11.4	0.324	0.971	0.24	1	2.9	2	5.7	0.555	0.348	0.14
Knees	9	25.7	10	28.6	0.788	0.072	0.06	1	2.9	5	14.3	0.088	2.917	0.42
Ankles/feet	10	28.6	9	25.7	0.788	0.072	0.06	7	20	7	20	>0.999	<0.001	<0.001

ASD: autism spectrum disorder.

ASD in our study were similar to previous studies. However, due to the high rate of depression/anxiety in the mothers of typically developing children, this difference did not reach a significance level. This difference might be related to outcome measures, cut-off values, and sample sizes. In addition, cultural differences can also play a notable role on this difference as the aforementioned studies were conducted in China, Singapore, Saudi Arabia, and the USA.[32-35] On the other hand, a study conducted in Iran reported no significant difference between the mothers of children with ASD and controls in terms of depression levels, whereas anxiety/insomnia levels were significantly different.[36] We also found that anxiety and sleep quality were significantly different, whereas depression levels were not. We believe that these similar results can be attributed to the similarities between the two studies, such as similar geography and a similar study sample (32 mothers of children with ASD and 29 mothers of children without ASD).[36]

We expected that if the mothers of children with ASD had greater anxiety/depression, they would have greater pain experience. However, since there was no large difference in anxiety/depression, the pain scores (direct assessment and related to HRQOL) were not significantly different. In addition, no significant difference was observed in the musculoskeletal pain sites between the mothers of children with ASD and those with typically developing children. However, one should keep in mind that this finding does not mean that these problems are non-

significant in this population as, in our study, 62.9% of the mothers of children with ASD reported upper back pain, 51.4% reported neck pain, and 45.7% reported lower back and shoulder pain. In a previous study, although pain symptoms were not directly assessed, it was reported that 49.7% of the caregivers of children with intellectual disability had pain/discomfort problems.[10] Health professionals working with children with ASD should consider referring their mothers for further assessment and rehabilitation programs for musculoskeletal pain management.

There is cumulative evidence that the caregivers of children with developmental disorders have lower HRQOL.[2,4,5,10] Our results are consistent with these previous reports. We found that most of the sub-domains of HRQOL (energy, emotional reaction, and social isolation) were significantly lower in the mothers of children with ASD compared to the mothers of typically developing children. On the other hand, there was a non-significant difference in the pain, sleep, and mobility subdomains of HRQOL. Indeed, one could expect this due to the observed significant difference in sleep quality, the mothers of children with ASD would have an impaired sleep sub-domain of HRQOL. The median of the sleep sub-domain was 12.6 in the mothers of children with ASD, whereas it was 0 in the mothers of typically developing children. This non-significant difference might be related to the small sample size. However, the observed small effect size suggests that this non-significant difference would be similar in a large sample size. Therefore, the results show that statistically significant sleep quality impairment does not cause a significant decrease in the sleep subdomain of HRQOL in the mothers of children with ASD.

Study Limitations

There are many limitations to our study. Firstly, although we conducted a priori sample size calculation, our sample size was relatively small. Secondly, we only included mothers, which diminishes the generalizability of our findings. The inclusion of other family members such as fathers, grandmothers, grandfathers, and siblings would reflect the family impact better. Lastly, due to the cross-sectional design of our study, we cannot give information about changes over time or show possible factors contributing towards the assessed variables which are mostly time-dependent and context-dependent conditions. Therefore, future longitudinal studies are required. Despite these limitations, our study had strength in assessing pain, fatigue, and sleep quality directly.

CONCLUSION

Our results may provide valuable information regarding sample size calculations for future studies.

The mothers of children with ASD had a greater care burden, higher anxiety levels, lower sleep quality and lower HRQOL related to energy, emotional reaction, and social isolation compared to the mothers of typically developing children. However, the mothers of children with ASD did not have significantly different pain, fatigue, or depression levels compared to the mothers of typically developing children. However, one should keep in mind that these problems were relatively high in both groups.

MAIN POINTS

• The special needs for children with ASD increase the burden of caregiving.

• The mothers of children with ASD have a greater care burden and higher anxiety levels, lower sleep quality, and lower HRQOL.

• The levels of pain, fatigue, and depressive symptoms are not significantly different between the mothers of those children with and those without ASD.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Review Board of Near East University (approval number: 2019/65-715, date: 22.01.2019) and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki (as revised in Brazil, 2013).

Informed Consent: All mothers gave informed consent for themselves and their children before entering this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.S., T.K., A.G., Design: E.S., T.K., A.G., Supervision: T.K., A.G., Data Collection and/or Processing: E.S., T.K., A.G., Analysis and/or Interpretation: E.S., T.K., A.G., Literature Search: E.S., T.K., A.G., Writing: E.S., T.K., A.G., Critical Review: E.S., T.K., A.G.

DISCLOSURES

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REFERENCES

1. Scherer N, Verhey I, Kuper H. Depression and anxiety in parents of children with intellectual and developmental disabilities: A systematic review and meta-analysis. PLoS One. 2019; 14(7): e0219888.
2. Barros ALO, de Gutierrez GM, Barros AO, Santos MTBR. Quality of life and burden of caregivers of children and adolescents with disabilities. Spec Care Dentist. 2019; 39(4): 380-8.
3. Volkmar F, Siegel M, Woodbury-Smith M, King B, McCracken J, State M; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2014; 53(2): 237-57.
4. Isa SN, Ishak I, Ab Rahman A, Mohd Saat NZ, Che Din N, Lubis SH, et al. Health and quality of life among the caregivers of children with disabilities: A review of literature. Asian J Psychiatr 2016; 23: 71-7.
5. Ten Hoopen LW, de Nijs PFA, Duvekot J, Greaves-Lord K, Hillegers MHJ, Brouwer WBF, et al. Children with an Autism Spectrum Disorder and Their Caregivers: Capturing Health-Related and Care-Related Quality of Life. J Autism Dev Disord. 2020; 50(1): 263-77.
6. Rodriguez G, Hartley SL, Bolt D. Transactional Relations Between Parenting Stress and Child Autism Symptoms and Behavior Problems. J Autism Dev Disord. 2019; 49(5): 1887-98.
7. Falk NH, Norris K, Quinn MG. The factors predicting stress, anxiety and depression in the parents of children with autism. J Autism Dev Disord. 2014; 44(12): 3185-203.

8. Machado Junior SB, Celestino MI, Serra JP, Caron J, Ponde MP. Risk and protective factors for symptoms of anxiety and depression in parents of children with autism spectrum disorder. Dev Neurorehabil. 2016; 19(3): 146-53.
9. Barker ET, Hartley SL, Seltzer MM, Floyd FJ, Greenberg JS, Orsmond GI. Trajectories of emotional well-being in mothers of adolescents and adults with autism. Dev Psychol. 2011; 47(2): 551-61.
10. Arora S, Goodall S, Viney R, Einfeld S, Team M. Health-related quality of life amongst primary caregivers of children with intellectual disability. J Intellect Disabil Res. 2020; 64(2): 103-16.
11. de Heer EW, Gerrits MM, Beekman AT, Dekker J, van Marwijk HW, de Waal MW, et al. The association of depression and anxiety with pain: a study from NESDA. PLoS One. 2014; 9(10): e106907.
12. Woo AK. Depression and Anxiety in Pain. Rev Pain. 2010; 4(1): 8-12.
13. Gokcin Eminel A, Kahraman T, Genc A. Physical workload during caregiving activities and related factors among the caregivers of children with cerebral palsy. Irish Journal of Medical Science (1971 -). 2021; 190: 701-9.
14. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5®): American Psychiatric Pub; 2013.
15. Kaya K, Unsal-Delialioglu S, Ordu-Gokkaya NK, Ozisler Z, Ergun N, Ozel S, et al. Musculo-skeletal pain, quality of life and depression in mothers of children with cerebral palsy. Disabil Rehabil. 2010; 32(20): 1666-72.
16. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007; 39(2): 175-91.
17. Özlü A, Yıldız M, Aker T. Zarit Bakıcı Yük Ölçeğinin Şizofreni Hasta Yakınlarında Geçerlilik ve Güvenilirlik Çalışması. Archives of Neuropsychiatry/ Noropsikiatri Arsivi. 2009; 46.
18. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain. 1975; 1(3): 277-99.
19. Oksuz E, Malhan S, Tulunay FC. Turkish McGill Pain Questionnaire: reliability and validation. Value in Health. 2007; 10(6): A467.
20. Kahraman T, Genç A, Göz E. The Nordic Musculoskeletal Questionnaire: cross-cultural adaptation into Turkish assessing its psychometric properties. Disabil Rehabil. 2016; 38(21): 2153-60.
21. Kuorinka I, Jonsson B, Kilbom A, Vinterberg H, Biering-Sørensen F, Andersson G, et al. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. Appl Ergon. 1987; 18(3): 233-7.
22. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989; 46(10): 1121-3.
23. Lerdal A. Fatigue Severity Scale. In: Michalos AC, editor. Encyclopedia of Quality of Life and Well-Being Research. Dordrecht: Springer Netherlands; 2014. p. 2218-21.
24. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes. 2003; 1: 29.
25. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67(6): 361-70.
26. Aydemir Ö, Guvenir T, Kuey L, Kultur S. Validity and reliability of Turkish version of hospital anxiety and depression scale. Turkish Journal of Psychiatry. 1997; 8(4): 280-7.
27. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2): 193-213.
28. Agargun MY, Kara H, Anlar Ö. The reliability and validity the Pittsburgh Sleep Quality Index. Turkish Journal of Psychiatry. 1996; 7(2): 107-11.
29. Hunt SM, McKenna SP, McEwen J, Backett EM, Williams J, Papp E. A quantitative approach to perceived health status: a validation study. J Epidemiol Community Health. 1980; 34(4): 281-6.
30. Kücükdeveci AA, McKenna SP, Kutlay S, Gürsel Y, Whalley D, Arasil T. The development and psychometric assessment of the Turkish version of the Nottingham Health Profile. Int J Rehabil Res. 2000; 23(1): 31-8.
31. Lenhard W, Lenhard A. Calculation of effect sizes. Dettelbach, Germany: Psychometrica; 2016. Available from: https://www.psychometrica.de/effect_size.html
32. Almansour MA, Alateeq MA, Alzahrani MK, Algeffari MA, Alhomaidan HT. Depression and anxiety among parents and caregivers of autistic spectral disorder children. Neurosciences. 2013; 18(1): 58-63.
33. Ingersoll B, Meyer K, Becker MW. Increased rates of depressed mood in mothers of children with ASD associated with the presence of the broader autism phenotype. Autism Res. 2011; 4(2): 143-8.
34. Gong Y, Du Y, Li H, Zhang X, An Y, Wu BL. Parenting stress and affective symptoms in parents of autistic children. Sci China Life Sci. 2015; 58(10): 1036-43.
35. Lai WW, Goh TJ, Oei TP, Sung M. Coping and Well-Being in Parents of Children with Autism Spectrum Disorders (ASD). J Autism Dev Disord. 2015; 45(8): 2582-93.
36. Riahi F, Izadi-Mazidi S. Comparison between the mental health of mothers of children with autism and control group. Iran J Psychiatry Behav Sci. 2012; 6(2): 91-5.

RESEARCH ARTICLE

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The Prevalence of Cognitive Impairment in Famagusta-North Cyprus Residents Over 65 Years of Age

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Abstract

BACKGROUND/AIMS: Dementia is one of the major causes of disability and dependency among elderly and the fifth cause of death worldwide. With screening and identifying disease at early stages, new treatment plans and specific care in patients' lives overall benefit society in financial and social aspects. The main aim of this study is to detect prevalence of cognitive impairment (CI) among Famagusta residents in North Cyprus aged 65 and above, and also to identified its associate risk factors.

MATERIALS AND METHODS: This study is a population based, cross-sectional study. Simple random sampling was applied to the population. Sample size was calculated as 143. Along with demographics involving risk factors of dementia, CI was assessed by the Mini-Mental State Examination and Mini Cog Test scores. Daily life activity impairment was evaluated with Functional Activities Questionnaire and depression with Short Geriatric Depression Scale. SPSS was used for analysis and chi-square was used for hypothesis test ($p<0.05$).

RESULTS: In total,135 participants were included in analysis from 4 age groups (65-69/70-74/75-79/80+). The mean age of the participants was 73.17±6.421 and females comprised 70.4%. Overall, 40% of the whole population had CI and 20.7% had depression. It was observed to be more frequent among older age groups ($p<0.001$) and females ($p=0.007$). Lower education was found to be associated with CI and 60.8% of individuals with 6 or less years of education had CI ($p=0.011$).

CONCLUSION: This study has shown that prevalence of CI, including MCI and possible dementia cases are quite high. Considering the growing elderly population, cognitive screening tests and preventive measures of modifiable risk factors are required as public health measures.

Keywords: Cognitive impairment, dementia, Cyprus, epidemiology, prevalence

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INTRODUCTION

Dementia is a chronic condition identified as a progressive decline in memory and other cognitive abilities, which are orientation, comprehension, calculation, language, and judgement.[1]

Dementia is one of the major causes of disability and dependency among the elderly worldwide.[2] It is associated with an increased risk of death and a decreased quality of life.[3]

There are various disorders and factors which lead to dementia, which results in an irreversible neuronal loss and a reduction of cognitive functioning. The most common type is Alzheimer's disease (AD). However, frontotemporal, Lewy body dementia and vascular dementia are also common types.[4]

Before dementia develops, there is a critical period which is known as "Mild Cognitive Impairment (MCI)". MCI is described as an "*intermediate stage of cognitive impairment that is often, but not always, a transitional phase to dementia*".[5] The main difference between dementia and MCI is that the former interferes with daily activities.[6] It is reported that 15% of all MCI cases turn into dementia.[7-9] It is important to detect MCI in order to slow down its progression to dementia.

The risk factors for dementia can be divided into two groups as non-modifiable and modifiable. Older age is the main risk factor and being female is also among the non-modifiable risk factors for dementia. There are many reasons behind the higher likelihood of dementia in females. The most identifiable cause is the tendency of women to live longer than men and consequently, the risk of dementia increases with age.[10] Concerning modifiable risk factors, the vascular risk factors are hypertension, hyperlipidemia, diabetes mellitus, stoke history and coronary heart disease. The presence of multiple vascular risk factors, which means more than three, increases the probability of developing any type of dementia.[10] In addition, the education span of individuals is considered to be one of the main risk factors for dementia development. A systematic review states that lower education levels are associated with an increase in the development of dementia[11] and meta-analysis revealed that this risk can be reduced by 7% for each additional year in education.[12]

High income countries (HIC) and low-income countries (LIC) show different behaviors in terms of dementia prevalence. Even though the prevalence of dementia in LIC was double the prevalence in HIC in 2015, it was projected that LIC will experience a massive growth in dementia prevalence and it will reach a level of approximately 4 times higher than that of HIC prevalence by 2050.[13]

Every day, there is an increase in the number of people diagnosed with dementia all around the world. According to studies, it was seen that the incidence of dementia doubled with every 5.9-year increase in age, from 3.1/1,000 person years at age 60-64, to 175.0/1,000 person years at age 95+. Initially, researchers arrived at the conclusion that dementia was more common in HIC based on the data for 'diagnosed cases' alone. However, it was not until later that they realized that there seemed to be an underestimation in the figures for middle income counties (MIC) and LIC due to the vast majority of population with dementia being undiagnosed. 7.7 million new cases of dementia are anticipated each year worldwide, implying one new case every 4.1 seconds, which shows the scale of this issue/disease.[14]

According to World Health Organization, there are 50 million dementia sufferers and 60-70% of them are sub-classified as AD. Overall dementia is the fifth cause of death in the world and it is projected that there will be a further increase in the prevalence of dementia from 82 million to 152 million between the years 2030-2050. Raising awareness and early diagnostic criteria are seen to be effective in fighting the prevalence of this disease.

The importance of our study is that, currently, there are no official data about the situation in Cyprus. Alzheimer Europe estimated a total of 11,250 dementia patients in Cyprus in 2012, which represents 1.07% of the total population (1,047,311).[15] Our study is necessary to understand the trends in Cyprus regarding dementia and MCI. Further development on our research would lead to a better understanding of the problem around our country and could inform the structuring of government health policies aimed at the aged population. Additionally, early detection of cognitive impairment (CI) with screening tests could mitigate the condition and help slow progression and reduce mortality. Reversible causes of CI, which are potentially treatable can be identified and treated as well.[16] With screening and identifying this disease in its early stages, new treatment plans and specific care in patients' lives overall benefit society in both its financial and social aspects. Also, the significance of periodic check-ups and follow-ups for cognitive health of the elderly population must be emphasized as well as the importance of public health policies which can be shaped accordingly.

In light of the literature, the main aim of this study was to define the prevalence of CI, MCI and depression in Famagusta residents over 65, and also to identify the severity of CI and its associated risk factors. In addition, the goal was to offer follow-up and/or referral of individuals with scores lower than the threshold levels.

MATERIALS AND METHODS

A population based, cross sectional study was carried out among those residents of Famagusta who were aged ≥65 years between September, 2019 and June, 2020. This study was approved by the Health Subcommittee of Eastern Mediterranean University Research and Publication Ethics Board (approval number: ETK00-2020-0039).

According to the Turkish Republic of North Cyprus State Planning Organization from the 2011 population census, there were 3,170 people aged ≥65 years living in Famagusta and the distribution of the population according to the age groups of 65-69, 70-74, 75-79, 80+ were 36% (1,139), 25% (785), 19% (614) and 20% (632), respectively. The sample size of this study was calculated to be 143 with a 99% confidence level. The Delphi consensus was a study showing that the prevalence of dementia changes with different age ranges and regions of the world. Famagusta was found to be in the Euro A Region. Age standardized prevalence was calculated and applied as 6% using the information from the study.[17]

The residents aged ≥65 years were divided into 4 different age groups, 65-69, 70-74, 75-79, 80+ and the number of surveys required to collect data from each age group was calculated depending on the distribution of the population. By simple random sampling, the participants of this study were selected randomly from the population registries of the Municipality of Famagusta. If the selected participants refused to participate in this study, they were replaced by randomly

selected substitute participants. Participants with mental retardation, communication problems (i.e., aphasia) or perceptual problems (i.e., blindness or deafness) were excluded from this study.

The research team consisted of a neurologist as a supervisor, and seven third year medical students. A door-to-door survey was conducted. An informed voluntary consent form was filled out by all the participants.

A demographic questionnaire was prepared by the team to identified the age, sex, years of education, vascular risk factors, regular drugs and self-declaration of forgetfulness of the participants.

CI was assessed by the validated Turkish versions of the standardized Mini-Mental State Examination (sMMSE),[18] "*Clock drawing*",[19] daily life activities with Functional Activities Questionnaire (FAQ)[20] and depression with Short Geriatric Depression Scale.[21] In addition to this, a modified version of sMMSE (sMMSE-il) was used for illiterate participants.[22]

The MMSE cut-off score for CI was accepted as lower than or equal to a score of 24 out of 30. Scores were further classified; between 20 to 24 as mild, 13 to 19 as moderate and equal to or lower than 12 as severe CI.

In "*clock drawing*", the participants were awarded either 0 if they could not draw, or 2 if they could draw a clock. Also, "*clock drawing*" was a component of MiniCog score which is accepted as another cognitive screening score with a "*three-word recall*" score. The total score is calculated out of 5 by adding the score from the clock drawing test and the number of words recalled from the "*three-words recall*" test ranging from 0 to 3.

FAQ was used to assess the daily life activities of the participants. For those people aged 50-69, having equal or more than 5, and aged above 70 having equal or more than 9 points respectively indicates functional activities impairment.

The Short Geriatric Depression Scale was used to assess the occurrence and the severity of depression in the elderly. The severity categorization was carried out as follows; scores between 0 to 4 indicate no depression, 5 to 8 indicate mild, 9 to 11 indicate medium level, 12 to 15 indicate heavy depression.

Statistical Analysis

The IBM SPSS version 22.0 was used for data entry and analysis. The chi-square test was used as a hypothesis test for the data analysis which determined whether there was an association between two categorical variables and $p<0.05$ was considered significant.

RESULTS

After the exclusion criteria were checked in all the data collected, our research ended up with a total number of n=135, which corresponded to a 94.4% response rate.

70.4% (n=95) of the participants were female and 29.6% (n=40) of the participants were male. Their mean age was 73 years with a standard deviation of 6. The minimum age was 65 years and the maximum age was 97 years in our study population. The age groups were divided into 4 different groups as 65-69, 70-74, 75-79, and 80+. The ratios of the participants in each age group were 37.1% (n=50), 24.4% (n=33), 24.4% (n=33) and 14.1% (n=19), respectively.

8.4% (n=11) of the participants were illiterate, 44.3% (n=58) had been educated for 1-6 years which was the highest percentage, 35.6% (n=48) had been educated for 7-12 years and 10.7% (n=14) had received education of more than 12 years. Most of the population over 65 were living with their spouse with 51.9% (n=69) in Famagusta. The ratios of people living with their children or grandchildren, their spouse and children, or their spouse and caregiver were 15.8% (n=21), 15% (n=20), and 0.8% (n=1) respectively.

In diseases with vascular risk factors, the study population had a single risk factor percentage of 33.8% (n=44). This was followed by three or more risk factors with 29.2% (n=38), two risk factors with 26.2% (n=34), and none with 10.8% (n=14).

In this study, 40% (n=54) of the participants had CI. Analysis revealed that CI was associated with gender (p=0.007), age (p=0.000028) and education level (p=0.011). CI was more common among female participants than males, with 47.4% (n=45) of female participants having CI whereas only 22.5% (n=9) of the male participants had CI. As the number of years of education increased, CI decreased, with the lowest percentage of CI seen in the 12+ years of education group with a percentage of 5.9% (n=3). Regarding the association between age groups and CI, it was found that as age increased, CI became more common. It was found that there was no association between the number of vascular risk factors and CI.

In the group with CI, the influence on daily life activities determined by FAQ coincides exactly with their own declaration. Furthermore, of the 54 people with CI, 34 of them had no impairment in their daily life activities determined by FAQ. This group was the possible MCI group and constituted 25.2% of the total population.

The characteristics of the subjects and associations with CI are summarized in Table 1.

In the age groups, both CI and depression ratios were compared with each other (Figure 1). In the first age group aged between 65-69 years, the CI ratio was 34.0% and the depression ratio was 14.0%. Between the ages 70-74 years, the CI ratio and depression ratio were 42.4% and 24.2% respectively. In the third group which consisted of a population aged between 75-79 years, it had a 33.3% CI ratio and a 21.2% depression ratio. Lastly, in the 80 years and older age group, both the CI proportion and the depression proportion were the highest among the three groups at 63.2% and 31.6%, respectively.

In our population, with respect to the scores found in MMSE, the CI severity levels were found to be proportionally present (Figure 2). 60.0% of the population had no CI, 31.9% had mild CI, 7.4% had moderate CI and 0.7% had severe CI.

DISCUSSION

Dementia is a worldwide problem. Dementia prevalence increases dramatically with age, especially for those over 65 years of age. In 2014, it was estimated that 5 million people were living with dementia and this is expected to be nearly 14 million by 2060.[23]

Dementia presents in LIC, MIC and also in HIC. However, the prevalence of dementia is variable. It is lower in HIC compared to the dementia prevalences of LIC and MIC. In addition to this, in 2015, the dementia prevalence was only 2 times higher in LIC compared to HIC. However,

by 2050, it is projected that the dementia prevalence will be four times higher in LIC and MIC.[13] Cyprus is an island in the Mediterranean Sea, divided into two parts, North and Southern Cyprus. North Cyprus is an MIC.[24] Therefore, North Cyprus is a high risk country for dementia.

Although dementia is a huge public health concern, no previous study was carried out in either North or Southern Cyprus. Due to this reason, this study was designed. This study only involved Famagusta city in North Cyprus, however, country-wide dementia prevalence data is also planned to be collected. Our study showed that nearly half of the Famagusta population who were over than 65 years old have CI.

In this study, one of the data collection tools was MMSE. This tool is the most commonly used screening test for the detection of CI in the elderly population. This test has both higher specificity and sensitivity compared to other tests. The cut-off point for the mini MMSE was set at 24 points. Scores below or equal to 24 points were grouped as mild, moderate or severe CI. These cut-off points were determined according to numerous studies in which it was reported that the cut-off points were 23/24 and 24/25. According to 14 studies, it was seen that the MMSE cut-off values of 23/24 or 24/25 had 88.3% sensitivity and 86.2% specificity.[25] It is evident that the MMSE test is a commonly used and reliable test for population surveys for CI. In addition to MMSE, the

Table 1. Demographics of the participants with respect to cognitive impairment

Characteristic of subjects	Total (n=135)	Cognitive impairment (n=54, 40%)	No cognitive impairment (n=81, 60%)	p-value
Gender, n (%)				0.007
Female	95 (70.4)	45 (83.3)	50 (61.7)	
Male	40 (29.6)	9 (16.7)	31 (38.3)	
Age groups, n (%)				0.000028
65-69	50 (37.1%)	17 (34.0)	33 (66.0)	
70-74	33 (24.4%)	14 (42.4)	19 (57.6)	
75-79	33 (24.4%)	11 (33.3)	22 (66.7)	
80+	19 (14.1%)	12 (63.2)	7 (36.8)	
Education groups, n (%)				0.011
Illiterate	11 (8.4)	5 (9.8)	6 (7.5)	
1-6 years	58 (44.3)	31 (60.8)	27 (33.8)	
7-12 years	48 (35.6)	12 (23.5)	36 (45.0)	
12+ years	14 (10.7)	3 (5.9)	11 (13.8)	
Total	131 (100.0)	51 (100.0)	80 (100.0)	
People living with, n (%)				
Alone	22 (16.5)	10 (18.9)	12 (15.0)	
Spouse	69 (51.9)	23 (43.4)	46 (57.5)	
His/her children or grandchildren	21 (15.8)	10 (18.9)	11 (13.8)	
Spouse and children	20 (15.0)	9 (17.0)	11 (13.8)	
Spouse and caregiver	1 (0.8)	1 (1.9)	0 (0.0)	
Total	133 (100.0)	53 (100.0)	80 (100.0)	
Diseases of vascular risk factors, n (%)				0.930
None	14 (10.8)	6 (11.5)	8 (10.3)	
One risk factor	44 (33.8)	18 (34.6)	26 (33.3)	
Two risk factors	34 (26.2)	12 (23.1)	22 (28.2)	
Three or more risk factors	38 (29.2)	16 (30.8)	22 (28.2)	
Total	130 (100.0)	52 (100.0)	78 (100.0)	
Declared forgetfulness by themselves or relatives, n (%)				
Yes	48 (35.6)	20 (37 .0)	28 (34 .6)	
No	87 (64 .4)	34 (63.0)	53 (65.4)	
Total	135 (100.0)	54 (100.0)	81 (100.0)	
Functional daily life impairment, n (%)				
Yes	28 (20.7)	20 (37.0)	8 (9.9)	
No	107 (79.3)	34 (63.0)	73 (90.1)	
Total	135 (100.0)	54 (100.0)	81 (100.0)	

Mini-Cog Test was also carried out with the participants and the similar results of the Mini-Cog Test supported our MMSE results.

Depression can overlap and interfere with the results of cognitive tests. However, since the prevalence of depression was found to be low overall, this lends support to the impact of depression being non-significant and so the results of the cognitive tests can be more objectively evaluated as CI.

The only study about the epidemiology of dementia in Turkey was carried out in İstanbul, sharing a population with similar socioeconomic characteristics with our study and the validated Turkish MMSE was used as a screening tool. It was found that the prevalence of CI was 50% above 70 years of age in that population survey. With further diagnostic methods in clinics, it indicated that the prevalence of dementia was 20.0%.[26] Our population's educational status and our country's economic status are similar to that research. Also, our population's CI

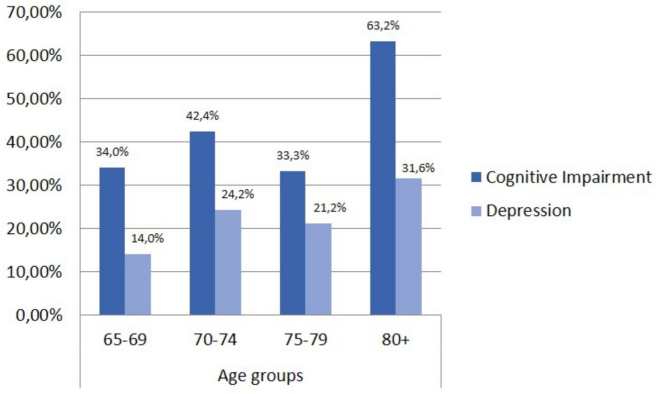

Figure 1. Cognitive impairment and depression frequency in age groups.

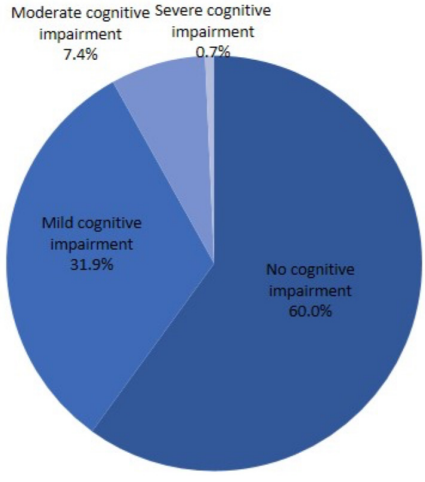

Figure 2. Cognitive impairment presence and severities in the study population.

prevalence was found to be 40% above 65 years old, which is quite similar with the other research. Highly variable prevalence rates have been reported for dementia, ranging from 8.5% to 59.4% around the world.[27] This high variability may be seen because of the different risk factor characteristics of participants and the different socioeconomic status of countries. Our prevalence was within this range.

Concerning the association between age groups and CI, it was revealed that as age increases, CI becomes more common. In addition to that, CI was found to be more common among females than males. Furthermore, CI was seen more commonly in the low education groups, and a significant association between low levels of education was observed, which is similar to previous epidemiological studies.[10,28]

Data on the presence of vascular risk factors were dependent on the participants' own declarations. This might explain detecting no association between vascular risk factors and CI as some participants were not aware of their vascular risk factors or were underdiagnosed. Previous studies point out that vascular risk factors disrupt cognitive functions.[29]

Dementia estimates in North Cyprus ware calculated to be around 2,700 based on worldwide prevalence.[17] To the best of our knowledge, this is the first study ever, not only in North Cyprus but also in Cyprus as a whole to determine the prevalence of CI and MCI.

Overall, this study indicated that 40% of the study population had CI and 25.2% had possible MCI. It is of great importance to follow up those patients with possible MCI annually.

Interestingly, 63% of the individuals with CI determined by valid tests had no declaration of forgetfulness either from themselves and/or from their relatives. Therefore, it is important to screen this age group periodically. Most recently, the American Academy of Neurology has recommended physicians to carry out annual cognitive function assessments for memory problems on individuals aged 65 and older, because increasing age is the major risk factor for cognitive decline.[30] Patients may not realize their developing cognitive deficits or think they are a part of normal aging. Thus, routine checking is necessary.

Study Limitations

The limitations of this study can be mentioned as different external factors which may have affected cognitive tests at that time, such as the hour of the day, the previous night's sleep, vitamin deficiencies and/or metabolic status. Additionally, the participants of this study were selected randomly from the Municipality of Famagusta population registries from those residents aged ≥65 years. These registries include the majority of the residents aged ≥65 years in Famagusta but not all. Data collection between genders were biased towards females because of two reasons: The Municipality of Famagusta population registries contained more females than males, and also, as participation to our study depended on willingness, females tended to volunteer more to become participants in our study. Another limitation of our study was the fact that some data was based on the patients' own declarations.

CONCLUSION

To conclude, dementia is one of the major global health problems. This neuropsychiatric progressive disease becomes more prevalent with age. Consequently, it has become a global concern. Dementia impacts

not just the individual, but also the families and societies at large as it interferes with their daily activities and it reduces productivity.

40% of the participants surveyed in our research suffer from CI. Additionally, 25.2% of the study population had possible MCI and 20.7% suffered from depression.

Our study showed that CI is more common in women, the elderly and those who had received little or no education.

Future studies can be conducted in other cities to find out the general CI prevalence in North Cyprus.

MAIN POINTS

- Nearly half of the study population have cognitive impairment.
- Cognitive impairment has associations with older age, the female gender and lower education.
- Considering the growing elderly population, cognitive screening tests are required as public health measures.

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ETHICS

Ethics Committee Approval: This study was approved by the Health Subcommittee of Eastern Mediterranean University Research and Publication Ethics Board (approval number: ETK00-2020-0039).

Informed Consent: An informed voluntary consent form was filled out by all the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.E.Y., E.C.Ö., F.O.S.A., İ.F.Z., O.A., R.İ., S.C., A.E., Design: E.C.Ö., B.E.Y., F.O.S.A., İ.F.Z., O.A., R.İ., S.C., A.E., Supervision: A.E., Materials: B.E.Y., E.C.Ö., F.O.S.A., F.O.S.A., İ.F.Z., O.A., R.İ., S.C., A.E., Data Collection and/or Processing: B.E.Y., E.C.Ö., F.O.S.A., İ.F.Z., O.A., R.İ., S.C., A.E., Analysis and/or Interpretation: B.E.Y., E.C.Ö., F.O.S.A., İ.F.Z., O.A., R.İ., S.C., A.E., Literature Search: B.E.Y., E.C.Ö., F.O.S.A., İ.F.Z., O.A., R.İ., S.C., A.E., Writing: B.E.Y., E.C.Ö., F.O.S.A., İ.F.Z., O.A., R.İ., S.C., A.E.

DISCLOSURES

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REFERENCES

1. Diagnostic and Statistical Manual of Mental Disorders: DSM-5 (5th edition). Washington DC; 2014.
2. Alzheimer's Disease International. Policy Brief for G8 Heads of Government. The Global Impact of Dementia 2013-2050. London, UK; 2013.
3. Formiga F, Ferrer A, Chivite D, Alburquerque J, Olmedo C, Mora J, et al. Predictors of cognitive decline in 85-year-old patients without cognitive impairment at baseline: 2-year follow-up of the octabaix study. Am J Alzheimers Dis Other Demen. 2013; 28(2): 147-53.
4. Kumar A, Sidhu J, Goyal A, Tsao JW. Alzheimer Disease. [Updated 2020 Mar 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499922/
5. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med. 2014; 275(3): 214-28.
6. McKhann GM, Knopman DS, Chertkow H, Hyman B, Jack C, Kawas C, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011; 7(3): 263-9.
7. Petersen RC, Lopez O, Armstrong MJ, Getchius T, Ganguli M, Gloss D, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018; 90(3): 126-35.
8. Alzheimer's Association. 2018 Alzheimer's disease facts and figures. Alzheimer's & Dementia, 218; 14: 367-429.
9. Roberts RO, Knopman DS, Mielke MM, Cha RH, Pankratz VS, Christianson TJ, et al. Higher risk of progression to dementia in mild cognitive impairment cases who revert to normal. Neurology. 2014; 82(4): 317-25.
10. Fernández Martínez M, Castro Flores J, Pérez de Las Heras S, Mandaluniz Lekumberri A, Gordejuela Menocal M, Zarranz Imirizaldu JJ. Risk factors for dementia in the epidemiological study of Munguialde County (Basque Country-Spain). BMC Neurol. 2008; 8: 39.
11. Sharp ES, Gatz M. Relationship between education and dementia: an updated systematic review. Alzheimer Dis Assoc Disord. 2011; 25(4): 289-304.
12. Xu W, Tan L, Wang HF, Tan MS, Tan L, Li JQ, et al. Education and Risk of Dementia: Dose-Response Meta-Analysis of Prospective Cohort Studies. Mol Neurobiol. 2016; 53(5): 3113-23.
13. Prince MJ, Wimo A, Guerchet MM, Ali GC, Wu YT, Prina AM, Alzheimer's Disease International. World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. London: Alzheimer's Disease International; 2015.
14. Dementia: a public health priority. World Health Organization; 2020 accessed 9 June 2020). Available from: https://www.who.int/mental_health/publications/dementia_report_2012/en/
15. Alzheimer Europe - Policy in Practice - Country comparisons - 2013: The prevalence of dementia in Europe - Cyprus. Alzheimer-europe.org. 2019. (accessed 8 November 2019). Available from: https://www.alzheimer-europe.org/Policy-in-Practice2/Country-comparisons/2013-The-prevalence-of-dementia-in-Europe/Cyprus/(language)/eng-GB
16. Morley JE, Morris JC, Berg-Weger M, Borson S, Carpenter BD, Del Campo N, et al. Brain health: the importance of recognizing cognitive impairment: an IAGG consensus conference. J Am Med Dir Assoc. 2015; 16(9): 731-9.
17. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005; 366(9503): 2112-17.
18. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Reliablitiy and validity of the standardized mini mental state examination in the diagnosis of mild dementia in Turkish population. Turk Psikiyatri Dergisi. 2002; 13(4): 273-81.

19. Emek-Savaş DD, Yerlikaya D, Yener GG. Validity, reliability and turkish norm values of the clock drawing test for two different scoring systems. Turk J Neurol. 2018; 24: 143-52.

20. Selekler K, Cangöz B, Karakoç E. Adaptation And Norm Determination Study Of The Functional Activities Questionnaire (FAQ) On Turkish Adults (Ages 50 And Over). Turk J Neurol. 2004; 10(2): 102-7.

21. Durmaz B, Soysal P, Ellidokuz H, Isik AT. Validity and reliability of geriatric depression scale-15 (short form) in Turkish older adults. North Clin Istanb. 2018; 5(3): 216-20.

22. Babacan-Yıldız G, Ur-Ozcelik E, Kolukısa M, Işık AT, Gürsoy E, Kocaman G, et al. Validity and reliability studies of modified mini mental state examination (MMSE-E) for turkish ılliterate patients with diagnosis of alzheimer disease. Türk Psikiyatri Dergisi. 2016; 27(1): 41-6.

23. What Is Dementia? CDC 2019. (accessed 9 June 9 2020). Available from: https://www.cdc.gov/aging/dementia/index.html

24. Besim M, Sertoğlu K, Ekici A. Northern Cyprus Economy Competitiveness Report 2017-2018: Turkish Cypriot Chamber of Commerce; 2018.

25. Lin JS, O'Connor E, Rossom RC, Perdue LA, Burda BU, Thompson M, et al. Screening for Cognitive Impairment in Older Adults: An Evidence Update for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK174643/

26. Gurvit H, Emre M, Tinaz S, Bilgic B, Hanagasi H, Sahin H, et al. The prevalence of dementia in an urban Turkish population. Am J Alzheimers Dis Other Demen. 2008; 23(1): 67-76.

27. Rocca WA, Hofman A, Brayne C, Breteler MM, Clarke M, Copeland JR, et al. Frequency and distribution of Alzheimer's disease in Europe: a collaborative study of 1980-1990 prevalence findings. The EURODEM-Prevalence Research Group. Ann Neurol. 1991; 30(3): 381-90.

28. Paddick SM, Longdon A, Gray WK, Dotchin C, Kisoli A, Chaote P, et al. The association between educational level and dementia in rural Tanzania. Dement Neuropsychol. 2014; 8(2): 117-25.

29. Sahathevan R, Brodtmann A, Donnan GA. Dementia, stroke, and vascular risk factors; a review. Int J Stroke. 2012; 7(1): 61-73.

30. Foster NL, Bondi MW, Das R, Foss M, Hershey LA, Koh S, et al. Quality improvement in neurology: Mild cognitive impairment quality measurement set. Neurology. 2019; 93(16): 705-13.

RESEARCH ARTICLE

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The Protective Effects of *Momordica Charantia* Fruit Extract in Methotrexate Induced Liver Damage in Rats

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Abstract

BACKGROUND/AIMS: Methotrexate (MTX), a cytotoxic therapeutic agent, is used for the cure of malignancies and rheumatologic disorders. However, the significant side effects of MTX limits its use. In this study, we aim to assess the hepatoprotective properties of *Momordica charantia* (MC) against MTX-induced liver damaged in rats.

MATERIALS AND METHODS: Following one dose of MTX (20 mg/kg), the rats were given either distilled water or MC extract (300 mg/kg, po) for 5 days. After the dissection of the rats, the liver was removed to analyse tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), transforming growth factor β (TGF-β) and 8-hydroxy-2'-deoxy-guanosine (8-OhdG) levels and superoxide dismutase (SOD), catalase (CAT), and caspase-3 activities. The tissues were also examined histopathologically.

RESULTS: The hepatic TNF-α, IL-1β, TGF-β, 8-OhdG levels, and Caspase-3 activity in the MTX group were found to be significantly increased compared to the control group. However, MC extract was able to significantly decrease TNF-α, TGF-β, 8-OhdG levels, and Caspase-3 activity. Also, both the SOD and CAT activity of the MTX group decreased compared to the control group. Although only the SOD levels elevated significantly with MC treatment, the SOD and CAT activities of the MC treated group were similar to the control group. Supporting these biochemical parameters, MTX-induced histologic alterations in the liver were also ameliorated via MC treatment.

CONCLUSION: Our results demonstrated that MC has a protective role against MTX-induced hepatic tissue injury by reducing apoptosis, oxidative damage, and the expression of pro-inflammatory cytokines.

Keywords: Methotrexate, liver, *Momordica charantia*, oxidative stress, inflammation

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INTRODUCTION

Methotrexate (MTX) is a folate antagonist chemotherapeutic drug used for the cure of various types of cancer (for instance acute osteosarcoma, leukaemia, breast, lung, and stomach cancers) and also rheumatologic disorders.[1,2] The cytotoxic effect of MTX is based on the inhibition of the dihydrofolate reductase enzyme and thus inhibition of the purines and pyrimidines necessary for RNA and DNA synthesis. However, this cytotoxic effect is not only seen in the tumour cell but also in various organs such as the liver, kidney, ileum, and heart. Therefore, the side effects which occur in these organs limit the use of this drug.[2,3]

As mentioned in the introduction section, MTX causes cellular arrest by inhibiting RNA and DNA synthesis. This effect is the direct cytotoxic effect of MTX. On the other hand, it has been demonstrated that MTX induced hepatotoxicity is related to oxidative stress caused by the generation of reactive oxygen species (ROS).[4] ROS leads to mitochondria-related apoptosis[2,5,6] and fibrosis[7] in the liver cells. In MTX treated rats, mitochondrial dysfunction and the ROS induce cytokines to be released, such as tumour necrosis factor-alpha (TNF-α)[6,8] and interleukin-1β (IL-1β).[6,9]

Plants have been used for decades to treat various diseases and to prevent side effects of drugs. *Momordica charantia* (MC) fruits, widely grown in Asia and the Mediterranean region, have several bioactive compounds such as proteins, flavonoids, polysaccharides, triterpenoids, ascorbic acid, and steroids.[10-12] These compounds are known to have numerous biological impacts, for instance immunomodulators, antioxidants,[12-14] antidiabetic,[15] hepatoprotective,[14,16] anti-apoptotic,[17] and anti-inflammatory.[10,18] Qader et al.[13] demonstrated that MC extracts displayed no toxic effects in a 64 human lung cell fibroblast line. In CCl4 treated rats, the MC Ucche variety has been shown to decrease lipid peroxidation, protein oxidation, nitric oxide production, and increased reduced glutathione (GSH) content and catalase (CAT) activity in liver tissues and plasma.[14] Moreover, the amelioration of inflammation and tissue fibrosis by the Ucche variety was also shown histologically in these CCl4 treated rat liver tissues.[14] However, the protective effects of MC against the hepatotoxic effects of MTX on the liver is unknown.

In light of these data, we aimed to investigate whether aqueous MC extract is protective against MTX-induced liver damage by using biochemical and histological analysis.

MATERIALS AND METHODS

Materials

MC liquid aqueous extract was purchased from a local producer (Turkey).

Total Phenolic Compounds of the *Momordica Charantia* Extract

The whole phenolic compounds of the MC extract were determined as detailed by Gao et al.[19] with minor alterations described by Yıldırım et al.[20]

Activity Analysis of the *Momordica Charantia* Extract

In Vitro Antioxidant Activity

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging activities of the MC extract were determined similarly to Zou et al.[21].

In Vitro Anti-inflammatory Activity

The anti-inflammatory activity was measured similarly to Phosrithong and Nuchtavorn[22] with minor alterations detailed by Yıldırım et al.[20].

Animals

Twenty-four Wistar albino rats (male, 200-250 g) were used in this study. The rats were housed under standard conditions (22±2 °C, 60-63% humidity) with a 12 hour light-12 hour dark period. The rats were kept ad libitum. The study procedures were approved by the Marmara University, Animal Experiments Local Ethics Commission, İstanbul-Turkey (approval number: 66. 2019.mar). This study was performed in Marmara University Experimental Animals Implementations and Researches Centre (DEHAMER, İstanbul-Turkey).

Experimental Design

The rats were assigned into 3 groups (n=24) as the control group (C), the MTX group (MTX), and the MTX + MC group. Each group was comprised of 8 rats. Liver toxicity was performed with one dose of MTX injection (20 mg/kg/ip; pharmaceutics),[9] while the MTX + MC group received MC extract at a dose of 300 mg/kg/po for the 5 following days. The control and MTX groups were given distilled water for 5 days by oral gavage at the same volume (Figure 1).

Biochemical Analyses of the Liver Tissue

Pro-Inflammatory Cytokine Levels

The liver tissues were homogenized with 0.9% NaCl (Ultra Turrax homogenizer) and centrifuged at 1,500 xg at 4 °C for 10 min. The supernatants were collected and the TNF-α and IL-1β levels were evaluated with enzyme-linked immunosorbent assay (ELISA) kit (Abbkine Rat TNF-α ELISA Kit, Cat. number: KET9007, China); Abbkine Rat IL-1β ELISA Kit, Cat. number: KET9001, China).

Superoxide Dismutase and Catalase Activities

The Superoxide dismutase (SOD) and CAT activities of the liver were measured for anti-oxidative status evaluation. The tissues were homogenized with 0.9% NaCl and centrifuged at 1,500 xg at 4 °C for 10 minutes. The supernatants were collected and SOD and CAT level measurements were performed using the ELISA method in accordance with the manufacturer's prospectus using commercial kit (Abbkine Rat SOD ELISA Kit, Cat. No: KTE62765; Abbkine Rat Catalase ELISA Kit, Cat. number: KTE100847, China).

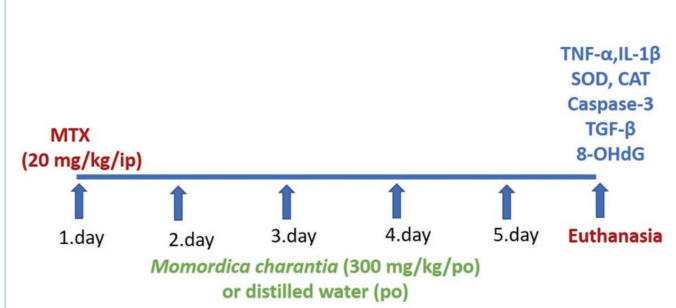

Figure 1. Summary of the experimental protocols.

Caspase-3 Activity and 8-hydroxy-2'-Deoxy-Guanosine (8-OhdG) Levels

The liver tissues were homogenized with 0.9% NaCl and centrifuged at 1,500 xg at 4 °C for 10 min. Caspase-3 activities in the collected supernatants were measured using a commercial kit via the manufacturer's procedure (Abbkine Rat Caspase-3 ELISA Kit, Cat. number: KTE100992, China).

The 8-OhdG levels were analysed as an indicator of oxidant DNA damage. DNA isolation was performed from the samples first (Invitrogen K182001). 8-OhdG levels were assessed with the aid of the DNA samples using the ELISA kit (8-OHdG ELISA Kit-Abbkine, Cat number: KTE100312, China).

Transforming Growth Factor-β Levels

TGF-β was measured as an indicator of fibrotic activity. Tissues were homogenized with 0.9% NaCl and centrifuged at 1,500 xg at 4 °C for 10 minutes. The upper phase was collected and the TGF-β levels in the samples were analysed using a commercial kit following the manufacturer's procedure using the ELISA method (Bioassay Technology Laboratory, Rat TGF-β ELISA Kit, Cat. number: E0778Ra, China).

Histological Procedure

The collected liver tissues were kept in 10% formaldehyde solution and they then underwent histologic preparation for light microscopic investigations. Concisely, the tissues were dehydrated by a series of alcohol solutions of increasing alcoholic concentrations (70%, 90%, 96%, and 100%) and cleared in xylene solution before being embedded in paraffin. The paraffin tissue blocks were sectioned to 5 µm in thickness by a rotary microtome (Leica RM2125RT) and mounted on glass slides. The hematoxylin and eosin dyed sections were analysed under a light microscope (Olympus BX51) and these sections were photographed using a digital camera system attached to the photomicroscope (Olympus DP72) for the evaluation of histopathological alterations.

Statistical Analysis

Statistical analysis was performed using Graphpad Prism 6.0 (Graphpad Software, San Diego, CA, USA). The biochemical data of groups were analysed by variance analysis (ANOVA) followed by Tukey multiple comparison tests. All data were expressed as mean ± standard error. Any variances were considered significant if $p<0.05$.

RESULTS

In Vitro Anti-Inflammatory/Antioxidant Activities and Total Compounds of MC

Low IC50 values (concentrations which eliminate 50% of the radical or stops the activity of the enzyme by 50%) indicate high activity. When Table 1 is examined, MC showed moderate antioxidant activities against DPPH and ABTS radicals with IC50 values of 3,132 and 2,463 mg/mL, respectively. In the anti-inflammatory activity experiment, MC exhibited good anti-lipoxygenase activity with an IC50 value of 0.045 mg/mL. In addition, the activities of the extract were lower than the standards in all activity experiments. Also, the total phenol ingredient of the MC extract was found to be 3,440 mg/g as gallic acid equivalent (Table 1).

Pro-Inflammatory Cytokine Levels

The TNF-α and IL-1β levels of the MTX group were found to be significantly higher than in the control group ($p<0.001$, $p<0.05$, respectively). MC treatment decreased TNF-α elevation ($p<0.05$) (Figure 2a). Although the IL-1β levels tended to decrease in the MTX + MC group, this was not statistically significant (Figure 2b).

SOD and CAT Activities

Both the SOD and CAT activities of the MTX group decreased compared to the control group ($p<0.001$). Although the SOD levels were significantly elevated with MC treatment ($p<0.05$), both were still lower than the control group (Figure 3a, b).

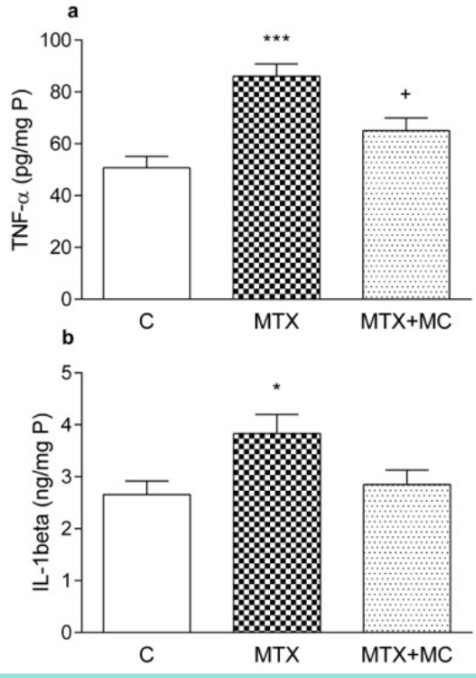

Figure 2. Tumour necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) levels of the groups. Each group consisted of 8 animals. *p<0.05, ***p<0.001: versus the control group, +p<0.05: versus the MTX group. C: Control group, MTX: Methotrexate group, MC: *Momordica charantia* extract group.

Table 1. Anti-inflammatory/antioxidant activities and total compound content of MC

Assays	MC*	Ascorbic acid	Trolox	Indomethacin
DPPH activity (IC_{50}, mg/mL)	3.132±0.004[b]	0.018±0.000[a]	-	-
ABTS activity (IC_{50}, mg/mL)	2.463±0.006[b]		0.080±0.001[a]	-
Anti-lipoxgenase activity (IC_{50}, mg/mL)	0.045±0.001[b]		-	0.022±0.001[a]
Total phenolic content** (mg GAE/g extract)	3.440±0.080		-	-

*MC: *Momordica charantia* extract; **Total phenolic content was expressed as 4 (GAE); ***Each value in the table is represented as mean ± standard deviation (n=3). Different letter superscripts in the same line indicate significant differences ($p<0.05$). DPPH: 2,2-diphenyl-1-picrylhydrazyl.

Caspase-3 Activity and 8-OHdG Levels

Although Caspase-3 activity and 8-OhdG levels were increased with MTX ($p<0.01$; $p<0.001$, respectively), MC treatment reduced both of these levels ($p<0.05$) (Figure 4a, b).

TGF-β Levels

While TGF-β levels increased with MTX ($p<0.05$), MC treatments reduced these levels ($p<0.01$) (Figure 5).

Histopathologic Evaluation

After examination of the stained liver sections, the control group was seen to have regular liver parenchyma (Figure 6a). The MTX-treated group had an increased number of Kupffer cells, dilated sinusoidal spaces, irregularly organized hepatocytes with cytoplasmic degeneration, and congestive central vein surrounded by inflammatory connective tissue (Figure 6b, c). These findings showed a prominent regeneration with MC treatment. Hepatocytes with normal cytoplasmic appearance, well-organized in regular liver parenchyma were observed in the MTX + MC group, however, in some regions, dilated sinusoids were seen (Figure 6d, e).

DISCUSSION

The results of the current study revealed that MTX leads to liver damage, as assessed by increased pro-inflammatory cytokines TNF-α and IL-1β, pro-apoptotic Caspase-3, fibrotic activity indicator TGF-β, oxidative DNA marker 8-OhdG levels, and decreased antioxidant enzyme SOD and CAT activities. Moreover, histopathologic alterations indicated prominent hepatic injury. However, MC extract showed significant beneficial effects in the MTX-induced hepatotoxicity model as was shown biochemically and histologically.

TNF-α and IL-1β pro-inflammatory cytokines are immediately released after tissue injury and both of them play essential roles in the inflammatory reaction.[23] It has been reported that there are increased hepatic TNF-α[24,25] and IL-1β levels[24] with MTX administration. In agreement with earlier studies, in our study, MTX caused a significant increase in the pro-inflammatory cytokines TNF-α and IL-1β. However, increased TNF-α levels in the liver tissue following MTX administration were reversed by MC treatment, and IL-1β levels also tended to decrease. In the neuropathic pain model, Jain et al.[26] demonstrated that MC reduced inflammation and pain in the sciatic nerve tissue by lowering TNF-α levels. Raish[27] also demonstrated that MC decreased TNF-α levels in cardiac tissue in a myocardial infarction model. Our results support these previous studies.

MTX application has previously been shown to cause oxidative DNA damage in liver cells.[28] Consistent with this report, our data showed that MTX increased 8-OHdG levels in liver tissue. However, in a previous study, it was reported that plasma 8-OHdG levels decreased with MC treatment.[29] The decreased 8-OHdG levels with the MC treatment which we found in our study supports this previous study. This decrease in 8-OHdG levels may be due to the moderate free radical scavenging activity of MC and an increase in SOD enzyme activity.

MTX administration leads to triggers of Caspase-3 mediated apoptosis.[17,24] Kim et al.[30] reported that MC reduces pro-apoptotic protein Caspase-3

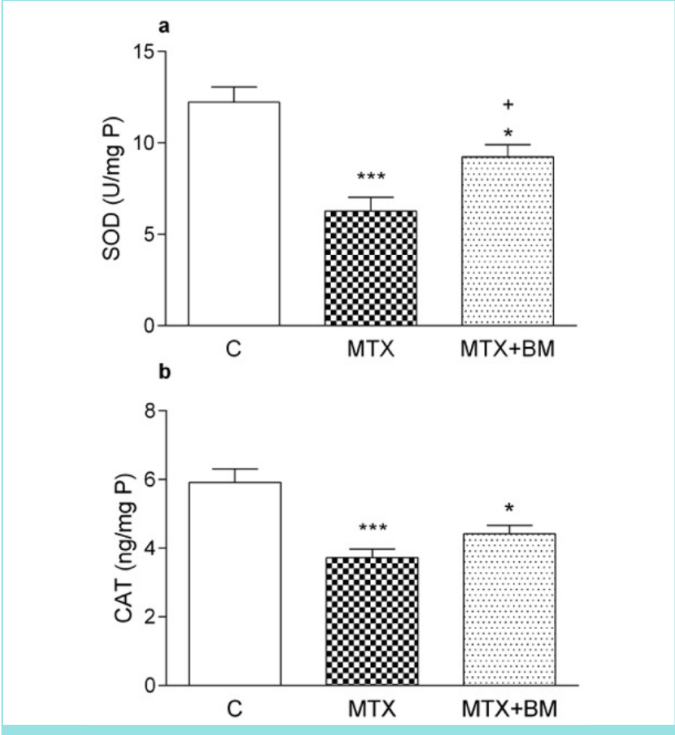

Figure 3. Superoxide dismutase (SOD), catalase (CAT) activities of the groups. Each group consisted of 8 animals. *$p<0.05$, ***$p<0.001$: versus the control group, +$p<0.05$: versus the MTX group. C: Control group, MTX: Methotrexate group, MC: *Momordica charantia* extract group.

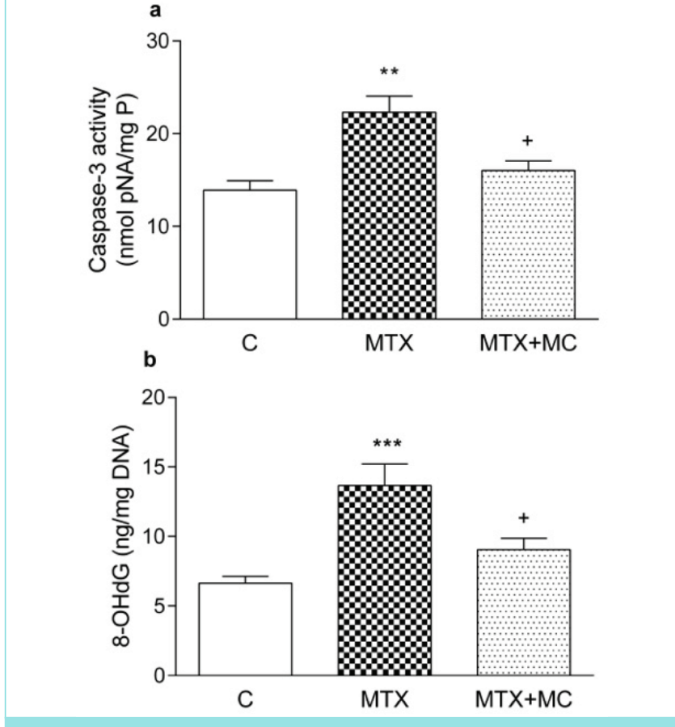

Figure 4. Caspase-3 and 8-hydroxy-2'-deoxy-guanosine (8-OhdG) activities of the groups. Each group consisted of 8 animals. **$p<0.01$, ***$p<0.001$: versus the control group, +$p<0.05$: versus the MTX group. C: Control group, MTX: Methotrexate group, MC: *Momordica charantia* extract group.

in human neuroblastoma SK-N-MC cells, liver cells,[5,31] and brain cells.[32] This decrease in Caspase-3 with MC therapy supports previous studies showing the anti-apoptotic effects of MC.

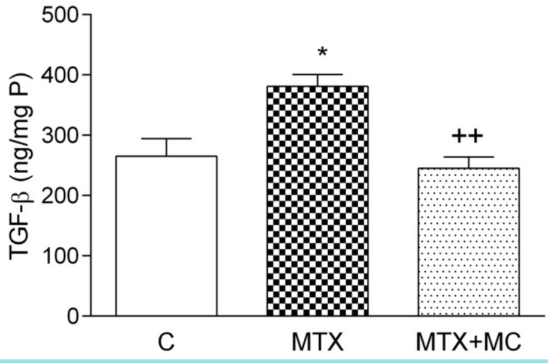

Figure 5. Transforming growth factor-β (TGF-β) levels of the groups. Each group consisted of 8 animals. *p<0.05: versus the control group, ++p<0.01: versus the MTX group C: Control group, MTX: Methotrexate group, MC: *Momordica charantia* extract group.

MTX is stored in the form of polyglutamate in the cell, however, in the long-term, MTX-polyglutamates accumulate and cause a decrease in folate levels. It has been understood that high levels of MTX polyglutamates are responsible for toxicities in the liver. In addition, by inhibiting dihydrofolate reductase, thymidylate synthesis and thus DNA synthesis is suppressed by MTX. Furthermore, MTX causes inhibition of nicotinamide adenosine diphosphate [NAD (P)]-dependent dehydrogenases and lowers NADPH levels in the cell. Since the maintenance of GSH in the cell in reduced form takes place via NADPH with the enzyme GSH-reductase, in the case of decreased NADPH, lower levels of reduced GSH increases susceptibility to oxidant damage.[33] It has been reported that MTX triggers oxidative stress both by raising free radicals and also by suppressing the antioxidant system.[24,34] Cetin et al.[34] demonstrated that MTX causes decreased SOD and CAT enzyme activities in the liver tissue. In the present study, MTX administration considerably decreased SOD and CAT activities in the liver tissues. SOD activity was partially reversed by MC treatment, and CAT enzyme activity tended to increase. According to the literature, it was shown that MC has an elevating effect on SOD and CAT activity in the alcoholic fatty liver in mice.[35] Additionally, aqueous and ethanol extracts of MC have been shown to decrease SOD activity in mice in a high-fat diet model.[36]

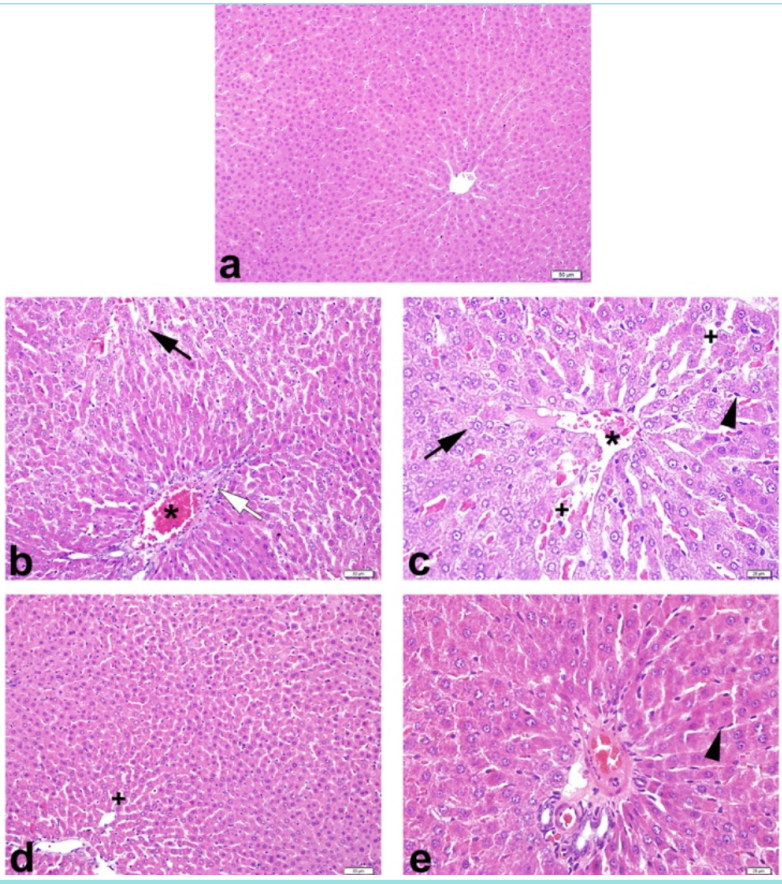

Figure 6. Demonstrative micrographs of liver tissues from the experimental groups. (a) The Control group: Regular hepatocyte organization, intact sinusoids, and Kupffer cells in normal numbers were seen. (b, c) The MTX group: Hepatocytes, which have cytoplasmic loss (arrow), irregularly organized in the liver parenchyma, dilated sinusoids (+), congestive central vein (*) surrounded by fibrotic connective tissue (white arrow) and an increased number of Kupffer cells (arrowhead) were observed. (d, e) The MTX + MC group: Hepatocytes showing regular cytoplasmic morphology in well-ordered liver parenchyma and reorganized normal sinusoidal arrays were noticed. Each group consisted of 8 animals. C: Control group, MTX: Methotrexate group, MC: *Momordica charantia* extract group.

MC has been shown to reduced inflammation and tissue fibrosis in a CCl4 induced liver injury.[14] Similarly, in our study, an MTX-induced increase in TGF-β was decreased with MC therapy, which demonstrated its antifibrotic activity. Furthermore, histopathological evaluations confirmed the hepatoprotective effect of MC against liver damage induced by MTX. Deng et al.[16] histopathologically determined that MC extract had a significant protective effect on the liver structure in restraint-stressed mice.

The results obtained from the *in vitro* activity studies conducted in our current study also confirm the antioxidant and anti-inflammatory activity of MC. In this study, MC was found to have moderate antioxidant and strong anti-lipoxygenase activity. Previous phytochemical studies have shown that MC contains triterpene compounds, especially cucurbitane-type triterpenes, as their main compounds.[37-39] In addition, some of these triterpene compounds have been reported to have significant antioxidant and anti-inflammatory activity.[37,39] Therefore, these cucurbitane-type triterpenes together with other ingredients in MC may be responsible for the antioxidant and anti-inflammatory activity of MC. Also, in our current study, the total phenolic ingredient of MC extract was found to be low. The fact that MC is rich in triterpene compounds overlaps with this result.

CONCLUSION

This study proved that MC has a protective role in MTX-induced inflammation, apoptosis, oxidative DNA damage, and fibrotic activity by reducing the levels of TNF-α, Caspase-3, 8-OHdG, and TGF-β respectively in rat liver. Thus, MC may reduce hepatic damage. Further experiments are required to understand the molecular mechanisms of the protective effects that MC has in MTX-induced liver injury.

MAIN POINTS

- *Momordica charantia* displays good anti-lipoxygenase activity.
- *Momordica charantia* ameliorates methotrexate-induced inflammation, apoptosis, and oxidative DNA damage.
- *Momordica charantia* may reduce hepatic fibrotic activity.

ETHICS

Ethics Committee Approval: The study procedures were approved by the Marmara University, Animal Experiments Local Ethics Commission, İstanbul-Turkey (approval number: 66. 2019.mar). This study was performed in Marmara University Experimental Animals Implementations and Researches Centre (DEHAMER, İstanbul-Turkey).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.Ö., G.Ş., Design: D.Ö., G.Ş., Supervision: G.Ş., Fundings: D.Ö., G.Ş., Materials: D.Ö., G.Ş., Data Collection and/or Processing: D.Ö., A.Ş., Ö.Ç., S.E., G.Ş., Analysis and/or Interpretation: A.Ş., Ö.Ç., Ö.T.Ç.K., G.Ş., Literature Search: D.Ö., A.Ş., Ö.E., Writing: D.Ö., A.Ş., Ö.Ç., Ö.T.Ç.K., G.Ş., Critical Review: G.Ş.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors

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REFERENCES

1. Malaviya AN. Landmark papers on the discovery of methotrexate for the treatment of rheumatoid arthritis and other systemic inflammatory rheumatic diseases: a fascinating story. Int J Rheum Dis. 2016; 19(9): 844-51.
2. Ali N, Rashid S, Nafees S, Hasan SK, Shahid A, Majed F, et al. Protective effect of Chlorogenic acid against methotrexate induced oxidative stress, inflammation and apoptosis in rat liver: An experimental approach. Chem Biol Interact. 2017; 25(272): 80-91.
3. Visser K, van der Heijde DM. Risk and management of liver toxicity during methotrexate treatment in rheumatoid and psoriatic arthritis: a systematic review of the literature. Clin Exp Rheumatol. 2009; 27(6): 1017-25.
4. Sener G, Kabasakal L, Yüksel M, Gedik N, Alican Y. Hepatic fibrosis in biliary-obstructed rats is prevented by Ginkgo biloba treatment. World J Gastroenterol. 2005; 11(35): 5444-9.
5. Lee HJ, Cui R, Choi SE, Jeon JY, Kim HJ, Kim TH, et al. Bitter melon extract ameliorates palmitate-induced apoptosis via inhibition of endoplasmic reticulum stress in HepG2 cells and high-fat/high-fructose-diet-induced fatty liver. Food Nutr Res. 2018; 62.
6. Ebrahimi R, Sepand MR, Seyednejad SA, Omidi A, Akbariani M, Gholami M, et al. Ellagic acid reduces methotrexate-induced apoptosis and mitochondrial dysfunction via up-regulating Nrf2 expression and inhibiting the IκBα/NFκB in rats. Daru. 2019; 27(2): 721-33.
7. Cao Y, Shi H, Sun Z, Wu J, Xia Y, Wang Y, et al. Protective effects of magnesium glycyrrhizinate on methotrexate-induced hepatotoxicity and intestinal toxicity may be by reducing COX-2. Front Pharmacol. 2019; 25 (10): 119.
8. Abdelaziz RM, Abdelazem AZ, Hashem KS, Attia YA. Protective effects of hesperidin against MTX-induced hepatotoxicity in male albino rats. Naunyn Schmiedebergs Arch Pharmacol. 2020; 393(8): 1405-17.
9. Çakır T, Baştürk A, Polat C, Aslaner A, Durgut H, Şehirli AÖ, et al. Does alfa lipoic acid prevent liver from methotrexate induced oxidative injury in rats? Acta Cir Bras. 2015; 30(4): 247-52.
10. Jia S, Shen M, Zhang F, Xie J. Recent advances in momordica charantia: functional components and biological activities. Int J Mol Sci. 2017; 18(12): 2555.
11. Liu JQ, Chen JC, Wang CF, Qiu MH. New cucurbitane triterpenoids and steroidal glycoside from Momordica charantia. Molecules. 2009; 14(12): 4804-13.
12. Baldemir A, Ekinci K, İlgün S, Dalda A, Yetişir H. Evaluation of total phenolic contents and antioxidant capacities of Momordica charantia L. (Bitter gourd) Fruits. Derim. 2018; 35(1): 45-50.
13. Qader SW, Abdulla MA, Chua LS, Najim N, Zain MM, Hamdan S. Antioxidant, total phenolic content and cytotoxicity evaluation of selected Malaysian plants. Molecules. 2011; 16(4): 3433-43.
14. Sagor AT, Chowdhury MR, Tabassum N, Hossain H, Rahman MM, Alam MA. Supplementation of fresh ucche (Momordica charantia L. var. muricata Willd) prevented oxidative stress, fibrosis and hepatic damage in CCl4 treated rats. BMC Complement Altern Med. 2015; 15: 115.
15. Xu X, Shan B, Liao CH, Xie JH, Wen PW, Shi JY. Anti-diabetic properties of Momordica charantia L. polysaccharide in alloxan-induced diabetic mice. Int J Biol Macromol. 2015; 81: 538-43.

16. Deng Y, Tang Q, Zhang Y, Zhang R, Wei Z, Tang X, et al. Protective effect of Momordica charantia water extract against liver injury in restraint-stressed mice and the underlying mechanism. Food Nutr Res. 2017; 61(1): 1348864.

17. Raish M, Ahmad A, Ansari MA, Alkharfy KM, Aljenoobi FI, Jan BL, et al. Momordica charantia polysaccharides ameliorate oxidative stress, inflammation, and apoptosis in ethanol-induced gastritis in mucosa through NF-kB signaling pathway inhibition. Int J Biol Macromol. 2018; 111: 193-9.

18. Zeng Y, Guan M, Li C, Xu L, Zheng Z, Li J, et al. Bitter melon (Momordica charantia) attenuates atherosclerosis in apo-E knock-out mice possibly through reducing triglyceride and anti-inflammation. Lipids Health Dis. 2018; 17(1): 251.

19. Gao X, Ohlander M, Jeppsson N, Björk L, Trajkovski V. Changes in antioxidant effects and their relationship to phytonutrients in fruits of sea buckthorn (Hippophae rhamnoides L.) during maturation. J Agric Food Chem. 2000; 48(5): 1485-90.

20. Yıldırım A, Şen A, Doğan A, Bitis L. Antioxidant and anti-inflammatory activity of capitula, leaf and stem extracts of Tanacetum cilicicum (Boiss.) Grierson. Int J Sec Metabolite. 2019; 6(2): 211-22.

21. Zou YH, Liu WT, Zhang JX, Xiang DC. Triterpenoids from the bark of Dysoxylum hainanense and their anti-inflammatory and radical scavenging activity. Fitoterapia. 2017; 121: 159-63.

22. Phosrithong N, Nuchtavorn N. Antioxidant and anti-inflammatory activites of Clerodendrum leaf extracts collected in Thailand. European Journal of Integrative Medicine. 2016; 8(3): 281-5.

23. Trunkey D. Current Therapy of Trauma and Surgical Critical Care 2nd Edition Imprint: Elsevier; 2015.

24. Al Kury LT, Dayyan F, Ali Shah F, Malik Z, Khalil AAK, Alattar A, et al. ginkgo biloba extract protects against methotrexate-induced hepatotoxicity: a computational and pharmacological approach. Molecules. 2020; 25(11): E2540.

25. Owumi SE, Ajijola IJ, Agbeti OM. Hepatorenal protective effects of protocatechuic acid in rats administered with anticancer drug methotrexate. Hum Exp Toxicol. 2019; 38(11): 1254-65.

26. Jain V, Pareek A, Paliwal N, Ratan Y, Jaggi AS, Singh N. Antinociceptive and antiallodynic effects of Momordica charantia L. in tibial and sural nerve transection-induced neuropathic pain in rats. Nutr Neurosci. 2014; 17(2): 88-96.

27. Raish M. Momordica charantia polysaccharides ameliorate oxidative stress, hyperlipidemia, inflammation, and apoptosis during myocardial infarction by inhibiting the NF-κB signaling pathway. Int J Biol Macromol. 2017; 97: 544-51.

28. Ekinci-Akdemir FN, Yildirim S, Kandemir FM, Gülçin İ, Küçükler S, Sağlam YS, et al. The effects of casticin and myricetin on liver damage induced by methotrexate in rats. Iran J Basic Med Sci. 2018; 21(12): 1281-8.

29. Cevik O, Akpinar H, Oba R, Cilingir OT, Ozdemir ZN, Cetinel S, Yoldemir T. The effect of Momordica charantia intake on the estrogen receptors ESRα/ESRβ gene levels and apoptosis on uterine tissue in ovariectomy rats. Mol Biol Rep. 2015; 42(1): 67-177.

30. Kim KB, Lee S, Kang I, Kim JH. Momordica charantia Ethanol Extract Attenuates H_2O_2-Induced Cell Death by Its Antioxidant and Anti-Apoptotic Properties in Human Neuroblastoma SK-N-MC Cells. Nutrients. 2018; 10(10): 1368.

31. Saad DY, Soliman MM, Baiomy AA, Yassin MH, El-Sawy HB. Effects of Karela (Bitter Melon; Momordica charantia) on genes of lipids and carbohydrates metabolism in experimental hypercholesterolemia: biochemical, molecular and histopathological study. BMC Complement Altern Med. 2017; 17(1): 319.

32. Duan ZZ, Zhou XL, Li YH, Zhang F, Li FY, Su-Hua Q. Protection of Momordica charantia polysaccharide against intracerebral hemorrhage-induced brain injury through JNK3 signaling pathway. J Recept Signal Transduct Res. 2015; 35(6): 523-9.

33. Friedman B, Cronstein B. Methotrexate mechanism in treatment of rheumatoid arthritis. Joint Bone Spine. 2019; 86(3): 301-7.

34. Cetin A, Kaynar L, Kocyigit I, Hacioglu SK, Saraymen R, Ozturk A, et al. Role of grape seed extract on methotrexate induced oxidative stress in rat liver. Am J Chin Med. 2008; 36(5): 861-72.

35. Lu KH, Tseng HC, Liu CT, Huang CJ, Chyuan JH, Sheen LY. Wild bitter gourd protects against alcoholic fatty liver in mice by attenuating oxidative stress and inflammatory responses. Food Funct. 2014; 5(5): 1027-37.

36. Wang J, Ryu HK. The effects of Momordica charantia on obesity and lipid profiles of mice fed a high-fat diet. Nutr Res Pract. 2015; 9(5): 489-95.

37. Lin KW, Yang SC, Lin CN. Antioxidant constituents from the stems and fruits of Momordica charantia. Food Chem. 2011; 127(2): 609-14.

38. Chiy-Rong C, Yun-Wen L, Yueh-Hsiung K, Jue-Liang H, Chi-I C. Cucurbitane-Type Triterpenoids from Momordica charantia, Natural Product Communications. 2017; 12(6): 889-92.

39. Shivanagoudra SR, Perera WH, Perez JL, Athrey G, Sun Y, Jayaprakasha GK, et al. Cucurbitane-type compounds from Momordica charantia: Isolation, in vitro antidiabetic, anti-inflammatory activities and in silico modeling approaches. Bioorg Chem. 2019; 87: 31-42.

RESEARCH ARTICLE

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Endodontic Practice in North Cyprus: A Questionnaire Survey Study

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Abstract

BACKGROUND/AIMS: Much equipment and many materials have been introduced to improve endodontic treatment outcomes and shorten its treatment time. This study aimed to gather information on the materials and methods employed in root canal treatment by dentists in North Cyprus.

MATERIAL AND METHODS: A questionnaire regarding endodontic practice was designed and distributed to dentists in North Cyprus. One hundred and seventeen dentists were asked face-to-face to complete this survey. The structured questionnaire comprised 25 questions about the materials and techniques used in endodontic treatments. Data were statistically analyzed using chi-square tests to find out the effect of the years of professional experience on the preference of irrigation solutions and obturation techniques. Statistical significance was set at $p<0.05$.

RESULTS: One hundred and seventeen respondents completed the questionnaire and 47% were female and 53% male. There was a wide range between the dentists' years of professional experience. 14.1% of them reported that they did not use periapical films in their clinics. The majority of dentists replied that they had never used a rubber dam (83%). There was an association between their years of professional experience and their preferred irrigation solutions ($p<0.05$). For root canal preparation, 54.7% stated using rotary Nickle-Titanium instruments. There was also an association between their years of professional experience and their preferred canal obturation technique ($p<0.05$).

CONCLUSION: The need for endodontic training after graduation seems to be a common opinion among practitioners. Hands-on courses may help practitioners to adopt advances in endodontics into their practice.

Keywords: Dentist, endodontics, materials, North Cyprus, techniques

INTRODUCTION

The ultimate objective of endodontic practice is for patients to retain their natural teeth for function and aesthetics.[1] The success of root canal treatment is related to many factors such as maintaining the original root canal anatomy during and after instrumentation, maintaining the apical constriction shape, achieving sufficient root canal irrigation for cleaning and disinfection, and creating an impermeable fluid-tight seal of the root canal.[2] A great variety of endodontic equipment, materials and treatment modalities have been proposed and used in endodontic treatment in order to achieve these goals.[3] However, endodontic treatment is one of the most technically challenging clinical procedures and considered an uninteresting procedure for general dentists.[4]

In recent decades, technological advancements in the field of endodontics have allowed dental practitioners to shorten the duration of treatment, to simplify the treatment procedures and to make the treatment outcome more predictable.[5] Some of these advancements include new-generation Nickel Titanium instruments with torque controlled endodontic motors with adjustable kinematics in different directions, improved apex-locators which are the most reliable tool for working length determination, negative pressure irrigation systems,

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new-generation cone-beam computed tomography devices, and surgical operating microscopes which greatly enhance the clinician's ability to view the tiniest details inside the tooth.[3] Also, several techniques and materials have been improved for better and condensed filling of the root canal with apical sealing. Regardless of the techniques and materials used, the European Society of Endodontology have proposed quality guidelines to clarify the standard care in endodontics and these guidelines should be followed by dentists when performing endodontic treatment.[4]

In essence, there are a great number of techniques, instruments, and materials used in endodontic treatment. Additionally, there are numerous dental schools and universities worldwide which give various teaching methods in dentistry.[6] For these reasons, this current study was carried out to gather information on the materials and methods employed in root canal treatment by dentists in North Cyprus and to find out the opinions of practitioners on their levels of practice and their training needs. In addition, within the scope of this study, it was also hoped to determine whether the years of professional experience of the dentists affected their choice of irrigation solution and canal obturation technique.

MATERIALS AND METHODS

After receiving ethics committee approval from Near East University Ethics Committe (approval number: YDU/45-378), a questionnaire dealing with current endodontic practice was designed to be suitable for our research with the help of previous studies.[7,8] This questionnaire was distributed to the dental practitioners in North Cyprus who were registered with the Chamber of Turkish Cypriot Dentists. One hundred and seventeen dental practitioners, who were general and specialist dentists, completed the questionnaire. After making appointments with the respondents, all of them were interviewed face-to-face and the questionnaire was filled out by two researchers (A.S., D.K.). The interview between the respondents and the two researchers took at least 20 minutes to fill out the questionnaire. The respondents' names were not recorded in the questionnaire to maintain privacy.

The structured questionnaire comprised 25 questions about the materials and techniques used in the dental clinics for root canal treatment. The first part of the questionnaire contained personal questions about the respondents including gender, years of experience, graduation year, whether they were a general practitioner or a specialist, the name of the university graduated from, and if they were performing root canal treatment or not. The second part included questions about the radiograph techniques used, methods of determining working length, and the use of rubber dams. In the next part, data were collected about the materials and instruments used while performing root canal treatment such as irrigation solutions, root canal medicaments, canal preparation instruments, and Nickle-Titanium (NiTi) systems. Questions regarding root canal obturation materials and techniques were also included in the last part of the questionnaire.

Statistical Analysis

The data was entered into Excel software (Microsoft Corporation, Redmont, WA, USA) and processed with the statistical software IBM SPSS Statistics (version 22.0; IBM Corp., Armonk, NY, USA) using the chi-square test to find out the effect of the years of professional experience (≤30 and >30 years) on the selection of materials and techniques. The significance level was set at $p<0.05$.

RESULTS

All the 117 respondents completed the questionnaire since the questions were asked face-to-face by the two researchers with a response rate of 100%. Table 1 summarizes the respondents' answers in this survey. Of the respondents, 47% were female and 53% male. Most of the respondents (81.2%) were general dentists whereas the remainder were specialists. A total of 106 of the participants reported performing root canal treatment, representing a rate of 90.6%. Eleven respondents reported that they did not perform root canal treatments in their clinic and they directed their patients to a specialist. These respondents (9.4%) were excluded from the next questions of this survey. Thus, only those participants who reported performing root canal treatment (90.6%) were included when evaluating the responses to questions regarding root canal treatment. However, there was a wide range between the dentists' years of professional experience. Five dentists (4.7%) stated that they had <5 years of professional experience. The highest percentage of dentists had worked for more than 30 years (53.8%). 9.4% of the dentists had 5-10 professional years, 17% of the dentists had worked for 11-20 years, and 15.1% had 21-30 years in dental practice. However, the years of professional experience were divided into two groups, namely, ≤30 years (49 dentists) and >30 years (57 dentists).

Of the 106 dentists who performed root canal treatment, 88 dentists (83%) stated that they did not use any magnification tools, and 18 dentists (17%) stated that they used a dental loupe while performing root canal treatment. None of the respondents reported using a dental microscope in their practice.

The dentists were asked about the type of periapical radiographs used in their clinics. Of the 106 participants, 45.3% used the RadioVisioGraphy imaging system, 32.1% used conventional periapical radiography, 8.5% stated that they used the phosphor plate imaging system, 1.9% used cone beam computed tomography, while 14.1% reported that they did not use periapical films in their clinics. Of the 106 respondents, 64 dentists (60.3%) stated that they used periapical radiographs for diagnostic proposes before treatment, 42 respondents (39.6%) used them for working length determination, 25 respondents (23.5%) for examining the master cone, and 67 respondents (63.2%) used periapical radiographs after root canal obturation. Fifteen dentists (15.9%) reported that they did not use periapical radiographs while performing root canal treatment. On the other hand, 25 dentists (23.5%) stated that they used periapical radiographs for all root canal treatment steps (diagnosis, working length, master cone, and canal obturation). The respondents were asked about their canal working length determination methods which they used in their practice and 36.8% of them used a digital tactile sense to determine the working length, 18.9% used periapical radiographs, 10.35% used an apex locator, 20.75% used radiograph with apex locator, 9.4% combined radiographs with tactile sense, 2.8% used an apex locator with tactile sense, and 0.9% stated that they combined radiographs with an apex locator and tactile sense.

The responses to the isolation technique questions were as follows; the majority of the dentists replied that they never used rubber dams for isolation and they only used cotton rolls (83%), 14.15% used rubber dams occasionally, while 2.83% always used rubber dams in addition to cotton rolls. All of the dentists used saliva suction during all of their root canal treatments.

Table 1. Summary of the respondents' answers in the survey	
Variable	**Number (percent)**
1. Gender	
Female	55 (47.01%)
Male	62 (52.99%)
2. Specialty	
General practitioner	95 (81.2%)
Specialist	22 (18.8%)
3. Years of professional experience	
<5	5 (4.7%)
5-10	10 (9.4%)
11-20	18 (17%)
21-30	16 (15.1%)
>30	57 (53.8%)
4. Magnification tools	
Dental loupe	18 (17%)
Not used	88 (83%)
5. The type of periapical radiographs	
RVG	47 (45.3%)
Conventional film	33 (32.1%)
Phosphor plate films	9 (8.5%)
Cone beam computed tomography	2 (1.9%)
Not used	15 (14.1%)
6. The purpose of radiograph	
Diagnosis	64 (60.3%)
Working length determination	42 (39.6%)
Master cone	25 (23.5%)
Root canal obturation	67 (63.2%)
All root canal treatment steps	25 (23.5%)
7. Working length determination methods	
Digital tactile sense	39 (36.8%)
Periapical radiographs	20 (18.9%)
Apex locator	11 (10.35%)
Radiograph with apex locator	22 (20.75%)
Radiograph with tactile sense	10 (9.4%)
Apex locator with tactile sense	3 (2.8%)
Radiographs with apex locator and tactile sense	1 (0.9%)
8. Irrigation solution	
Sodium hypochlorite	44 (41.5%)
Chlorhexidine	23 (21.7%)
Sodium chloride	10 (9.4%)
Combination solutions	29 (27.4%)
9. The reasons for not using NiTi rotary instruments	
Lack of experience	27 (56.4%)
No extra benefits	8 (16.8%)
Fear of complication	7 (14.5%)
The cost	4 (8.5%)
Harmful	2 (4.2%)
10. The frequency of using NiTi instruments	
Until distortion occurred	27 (46.5%)
At most 3 times	18 (31.1%)
4-6 times	11 (18.9%)
Once	2 (3.4%)
11. Root canal sealer	
AH plus	46 (43.4%)
Endomethasone	33 (31.2%)
AH 26 sealer	21 (20.2%)
Calcium hydroxide	6 (5.6%)
12. Obturation technique	
Cold lateral compaction	55 (51.9%)
Single cone	41 (38.7%)
Warm gutta-percha	10 (9.4%)

RVG: RadioVisioGraphy, NiTi: Nickle-Titanium.

After dividing the experience years into two groups (≤30 and >30 years), the chi-square test was applied and it showed that there was a significant association between the years of professional experience and the preferred irrigation solution ($p<0.05$). In the <5 years group, 40% used a combination of sodium hypochlorite (NaOCl), chlorhexidine (CHX), and ethylenediaminetetraacetic acid (EDTA) for root canal irrigation. Most of the dentists in the 5-10 and the 11-20 professional years' groups used combination solutions for irrigation. The majority of respondents in the 21-30 and the >30 years' groups preferred to use NaOCl alone in endodontic treatment. In general, regardless of the years of professional experience, 41.5% of the participants stated that they used NaOCl alone for root canal irrigation, 21.7%, 27.4%, and 9.4% used CHX alone, combination solutions, and sodium chloride alone, respectively (Table 2).

The majority of respondents (68%) reported using calcium hydroxide as a root canal medicament between sessions, 24.84% placed Cresophene (Cresophene, Septodont Ltd., UK) in the canal as an inter-appointment medicament, 5% of the dentists left the canal empty while 4 practitioners performed the root canal treatment in one session in all cases.

Of all the total 106 participants, 54.7% (58 dentists) used rotary NiTi instruments for root canal preparation. Those dentists who did not use rotary NiTi were asked to indicate their reasons from a list of five options. The most commonly chosen reason was "*lack of experience*" (56.4%) followed by these reasons respectively; "*no extra benefits*" (16.8%), "*fear of complication*" (14.5%), "*the cost*" (8.5%), and "*harmful*" (4.2%). The majority of respondents (65%) used the ProTaper Universal NiTi system (Dentsply Maillefer, Ballaigues, Switzerland) when they were asked about the type of NiTi system. The second most common type was the ProTaper Next system (Dentsply Maillefer, Ballaigues, Switzerland) (17%) followed by the Hero Shaper system (Micro Mega, Becacon, France).

The frequency of using NiTi instruments was also investigated in the questionnaire. Twenty-seven dentists stated that they used instruments or the files until distortion occurred, 18 used them at most 3 times, 11 dentists used instruments 4-6 times, and 2 dentists reported using them only once.

The type of endodontic motor was investigated and 51.72% used the electric endomotor with cable in rotation motion, 22.41% used a contra-angle hand-piece attached to the micro-motor, 13.8% used an electric Endomotor with cable in rotation and reciprocal motions, and 8.6% used an electric Endomotor without cable in a rotation motion.

The type of temporary filling used between the sessions was investigated and the majority of the respondents (about 60%) stated that they used Cavit (ESPE America, INC., Norristown, PA, USA) temporary filling. 12.6% used glass ionomer, 9.1% used zinc phosphate, 8.4% filled with zinc oxide eugenol, and 7% used Coltosol F (Coltosol group, Coltène Whaledent, Cuyahoga Falls, OH, USA) as a temporary filling.

Over 43.4% of the respondents used gutta-percha with AH plus sealer (Dentsply DeTrey, Konstanz, Germany) for root canal obturation. Additionally, 31.2% used gutta-percha with Endomethasone (Septodont, Saint-Maur-des-Fossés, France) and about 20.2% replied that they used gutta-percha with AH 26 sealer (Dentsply Maillefer, Ballaigues, Switzerland). 6 dentists reported that they filled the root canal with gutta-percha and calcium hydroxide sealer (Sealapex, Sybron Kerr, Romulus, MI).

According to the chi-square statistical analysis test, there was an association between the years of professional experience (≤30 and >30 years) and the preferred canal obturation technique (Cold lateral compaction, Single cone and Warm gutta-percha) ($p<0.05$). However, in the 11-20 experience years group, 72.2% of the dentists obturated the root canal via the single cone technique. Those practitioners with 21-30 professional years of experience stated that they filled the canals via cold lateral compaction or single cone techniques with rates of 56.3% and 43.8%, respectively. The majority of respondents (66.7%) in the >30 years group filled the canals by the cold lateral compaction technique. In general, regardless of their professional years, the dentists in this survey stated that they performed obturation of the root canals by cold lateral compaction, single cone, and warm gutta-percha techniques with rates of 51.9%, 38.7%, and 9.4%, respectively (Table 3). Most of the practitioners who used warm techniques stated that they used the Thermafil system. The Obtura, MicroSeal, vertical compaction, and lateral compaction techniques were rarely used.

DISCUSSION

The purpose of this study was to evaluate the selection and preference of the instruments, materials, and methods used during root canal treatment by dentists in North Cyprus and to determine whether the years of professional experience affected the choice of canal irrigation solution and obturation techniques. One of the factors which enhances the validity of this survey is that all or most of the respondents answered the questionnaire. In this study, all the respondents completed the questionnaire since they were asked face-to-face. This is in contrast to previous studies in which the questionnaires were sent by mail to the respondents and low response rates were reported.[7,9] In one recent study, it was reported that a long questionnaire could decrease the response rate by the respondents.[10] Therefore, we tried to make our questionnaire about the endodontic treatment as short and comprehensive as possible.

The results of the first part of our questionnaire showed that 47% of the respondents were female and 53% male, which are close to each other. In 2012, Unal et al.[11] reported that the percentage of male and female dentists were close to each other in Turkey. The majority of the respondents (90.6%) stated that they performed endodontic treatment in their practice, which was considered to be a high percentage. The questions about root canal treatment were asked only to those dentists who performed this procedure and the response rates are according to their replies.

In the literature, a comparison between the outcomes of root canal treatment with or without magnification was made, however, it was challenging due to many confounding factors.[12] Several studies supported that using magnification during endodontic treatment

Table 2. The preferred irrigation solution with respect to years of experience

Years in the profession	Irrigation solution			
	Sodium hypochlorite	Chlorhexidine	Combination (NaOCl + CHX + EDTA)	Sodium chloride
<5 years	1 (20%)	2 (40%)	2 (40%)	0 (0%)
5-10 years	0 (0%)	3 (30%)	7 (70%)	0 (0%)
11-20 years	3 (16.7%)	5 (27.8%)	10 (55.6%)	0 (0%)
21-30 years	7 (43.8%)	3 (18.8%)	2 (12.5%)	4 (25%)
>30 years	33 (57.9%)	10 (17.5%)	8 (14%)	6 (10.5%)
Total	**44 (41.5%)**	**23 (21.7%)**	**29 (27.4%)**	**10 (9.4%)**

NaOCl: sodium hypochlorite, CHX: chlorhexidine, EDTA: ethylenediaminetetraacetic acid.

Table 3. The preferred obturation technique with respect to years of experience

Years in the profession	Obturation technique		
	Cold lateral compaction	Single cone	Warm gutta-percha
<5 years	0 (0%)	3 (60%)	2 (40%)
5-10 years	3 (30%)	2 (20%)	5 (50%)
11-20 years	5 (27.8%)	13 (72.2%)	0 (0%)
21-30 years	9 (56.3%)	7 (43.8%)	0 (0%)
>30 years	38 (66.7%)	16 (28.1%)	3 (5.3%)
Total	**55 (51.9%)**	**41 (38.7%)**	**10 (9.4%)**

enhanced treatment outcomes.[13-15] However, in this study, only 18 respondents (17%) stated that they used a dental loupe while performing root canal treatment. Eighty-eight dentists (83%) did not use any magnification tool during endodontic treatment.

In addition to factors such as knowledge and skills, the ability to obtain accurate radiographs is critical for successful root canal treatment. Good radiographs serve the dentists during diagnosis, treatment, and follow-up.[16] In endodontics, the periapical radiograph is important before, during, and after root canal treatment. The results of this study showed that 15 respondents (14.1%) did not use any type of periapical radiographs in their practice. The remainder stated that they used periapical radiographs in different stages of the treatment. Only 25 dentists (23.5%) stated that they used periapical radiographs in all stages of the treatment, namely, for diagnosis, working length determination, master cone examination, and root canal filling.

Accurately determining working length is the key factor in the success of root canal treatment. Accurately observing the working length determines the end point of the canal preparation and filling.[17] Among the most common methods of determining the working length are the radial methods and electronic methods. There are other methods such as paper point measurements, apical periodontal sensitivity and digital tactile sense, but they are imprecise and liable to significant intra-subject differences.[18] According to our data, 0.9% stated that they used a combination of radiographs with apex locator and digital tactile sense to determine the working length, which is considered a low percentage when compared to previous studies.[8,19]

Especially during endodontic treatment, the rubber dam is an ideal instrument for the isolation of teeth and a standard of care in dentistry.[4] In addition to isolation from oral and salivary contamination, the rubber dam has many advantages such as patient protection by preventing inhalation or ingestion of endodontic instruments, preventing the soft tissues from retracting, and cross-infection prevention between the dentist and patient. Although the rubber dam has many advantages, using it for isolation during endodontic treatment in dental practice is still not accepted in many countries.[20] The drawbacks of using the rubber dam include it being a time-consuming process, challenges in placement techniques, insufficient experience and training of the practitioner, and the cost of the rubber dam's equipment and materials.[21] In addition, patient discomfort and rejection have been considered as other drawbacks of using the rubber dam.[22] Unfortunately, 83% of the dentists replied that they never used rubber dams for isolation during root canal treatment. Previously, a survey carried out in Turkey showed that >70% of the participants had never used rubber dams during root canal treatment while 1.5% of dentists stated that they used it always in their dental practice.[7] However, only 14.1% of the respondents in our study reported that they used the rubber dam occasionally.

Regardless of the concentrations, EDTA and NaOCl are considered the most important irrigation solutions in endodontic treatment because of their effects on lubrication, debridement, microbe destruction, and the dissolution of tissues as well as smear layer removal.[23] CHX digluconate is widely used in disinfection due to its high antibacterial activity against *Enterococcus faecalis*.[24] The results of this study showed that there was an association between years of professional experience and the preferred irrigation solution. 41.5% of the participants stated that they used NaOCl alone for root canal irrigation, 21.7%, 27.4%, and 9.4% used CHX alone, combination solutions, or NaOCl alone, respectively. The most frequently used irrigation solution in this survey was NaOCl which is in agreement with other reports in the literature.[9,19,25]

In the present study, the majority of respondents reported using calcium hydroxide as a root canal medicament between sessions, and 24.8% placed cresophene in the canal as an inter-appointment medicament. Raoof et al.[8] stated that the most used intra-canal medicament was calcium hydroxide, which is in agreement with the results of this survey. Using an inter-appointment medicament after root canal preparation and irrigation has been shown to improve disinfection significantly.[26] One of the most commonly used intra-canal medicaments is calcium hydroxide. Calcium hydroxide had many advantages such as its antibacterial properties and its ability to dissolve tissue.[27,28] However, about 5% of the dentists stated that they did not use any medicament in the canal between sessions.

Rotary NiTi instruments have been developed in the field of endodontic treatment due to the super-elasticity of this alloy, which is superior to other traditional stainless-steel instruments. This attribute made them the preferred materials for preparing and shaping curved root canals.[29] The manufacture of rotary NiTi endodontic instruments has been developed with different chemical compositions and geometrical designs.[30] However, one of the main disadvantages of NiTi rotary instruments is their sudden breakage during endodontic treatment. Therefore, in order to optimize their flexibility and microstructure, NiTi endodontic tools were improved via several mechanical and thermal treatment technologies.[30] In the present survey, root canal preparation was performed using rotary NiTi instruments by 54.7% of the respondents. Elham and Sedigheh[31] reported that 50.1% of their respondents used NiTi rotary system, which is similar to our result, while Parashos and Messer[32] stated that 26% used rotary NiTi files. In the present survey, the reasons for not using these files given by the other dentists were "*lack of experience*" (56.4%), "*no extra benefits*" (16.8%), "*fear of complication*" (14.5%), "*the cost*" (8.5%), and "*harmful*" (4.2%). The most commonly used NiTi system was the ProTaper Universal NiTi system, followed by the ProTaper Next system. 46.5% of the respondents stated that they used the NiTi instrument until distortion occurred. 31.1% used the files at most 3 times and 3.4% stated that they used them only once.

In multiple-visit root canal treatment, using an effective temporary filling between sessions is considered essential. This temporary filling material in the time between sessions should seal the tooth, prevent leakage of bacteria, microorganism, and fluids to the canal from the oral cavity, and prevent the escape of medicaments from the canal to the oral cavity.[33] The type of temporary filling used between sessions was investigated and Cavit was the top choice for temporary restorative materials (60% of respondents), which is in agreement with a previous study.[34]

Various core materials and sealers have been introduced as root canal fillings. The materials used should be biocompatible, prevent leakage, prevent re-infection, be easily adaptable to the canal wall, be easy-to-use, and also be radiopaque.[35] Several obturation techniques, including cold lateral compaction, single cone, and thermoplasticized injectable techniques have been introduced in an attempt to improve the hermetic filling of the root canal with the apical seal.[35] Over 43% of the respondents in this study used gutta-percha with AH plus sealer for root canal obturation. 31.2% used gutta-percha with endomethasone

and 18.9% replied that they used gutta-percha with AH 26 sealer. Thus, the most preferred sealer was a resin-based sealer, which is consistent with a study carried out in 2014 in Iran,[8] and with another study in 2008 in the United States.[34] In this study, according to a chi-square statistical analysis test, there was an association between the years of professional experience and the preferred canal obturation technique. The dentists in this survey stated that they performed obturation of the root canal by cold lateral compaction, single cone, and warm gutta-percha techniques with rates of 51.9%, 38.7%, and 9.4%, respectively. This is in agreement with the results of another recent study.[11] Most of the practitioners who used warm techniques stated that they used the Thermafil system for root canal obturation.

MAIN POINTS

• The results of this study demonstrate that the majority of respondents did not use any magnification tools or rubber-dam during endodontic practice.

• About half of respondents reported using NiTi rotary files for root canal preparation. In addition, half of them used NaOCl solution alone for canal irrigation.

• It seems that the need for endodontic training after graduation is agreed upon among the participants. Hands-on courses may allow dentists to adopt advances in endodontics into their practice.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Near East University (approval number: 2018-07).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.S., D.K., U.A., Design: M.A., U.A., Supervision: M.A., U.A., Fundings: U.A., Materials: U.A., Data Collection and/or Processing: A.S., D.K., U.A., Analysis and/or Interpretation: A.S., D.K., U.A., Literature Search: A.S., D.K., U.A., Writing: M.A., U.A., Critical Review: M.A., U.A.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Ravanshad S, Sahraei S, Khayat A. Survey of endodontic practice amongst Iranian dentists participating restorative dentistry congress in Shiraz, November 2007. Iran Endod J. 2008; 2(4): 135-42.
2. Kim S, Kratchman S. Modern endodontic surgery concepts and practice: a review. J Endod. 2006; 32: 601-23.
3. Shahravan A, Rahimi H, Eghbal M, Movahedian A, Moradi S. A comprehensive reference of root canal preparation instruments and techniques. 1st ed. Tehran: Moalefi Publications 2005; pp. 121-58, 222-45, 256-66.
4. European Society of Endodontology. Quality guidelines for endodontic treatment: consensus report of the European Society of Endodontology. Int Endod J. 2006; 39: 921-30.
5. Pinkham J, Casamassimo P, McTigue D, Fields H, Nowak A. Pediatric dentistry infancy through adolescence. 4th ed. USA: Saunders Co 2005; pp. 577-88.
6. Tomson PL, Simon SR. Contemporary Cleaning and Shaping of the Root Canal System. Prim Dent J. 2016; 5(2): 46-53.
7. Küçükkaya S, Görduysus M, Görduysus MO, Anıl D. A Questionnaire survey on current endodontic practice of dental practitioners in Turkey. Clinical Dentistry and Research. 2015; 39(3): 101-9.
8. Raoof M, Zeini N, Haghani J, Sadr S, Mohammadalizadeh S. Preferred materials and methods employed for endodontic treatment by Iranian general practitioners. Iran Endod J. 2015; 10(2): 112-6.
9. Willershausen I, Wolf TG, Schmidtmann I, Berger C, Ehlers V, Willershausen B, et al. Survey of root canal irrigating solutions used in dental practices within Germany. Int Endod J. 2015; 48(7): 654-60.
10. Sahlqvist S, Song Y, Bull F, Adams E, Preston J, Ogilvie D; iConnect consortium. Effect of questionnaire length, personalisation and reminder type on response rate to a complex postal survey: randomised controlled trial. BMC Med Res Methodol. 2011; 11: 62.
11. Unal GC, Kaya BU, Tac AG, Kececi AD. Survey of attitudes, materials and methods preferred in root canal therapy by general dental practice in Turkey: Part 1. Eur J Dent. 2012; 6(4): 376-84.
12. Del Fabbro M, Taschieri S, Lodi G, Banfi G, Weinstein RL. Magnification devices for endodontic therapy. Cochrane Database Syst Rev. 2015; 12: CD005969.
13. Taschieri S, Del Fabbro M, Testori T, Francetti L, Weinstein R. Endodontic surgery using 2 different magnification devices: Preliminary results of a randomized controlled study. J Oral Maxillofac Surg. 2006; 64: 235-42.
14. Monea M, Hantoiu T, Stoica A, Sita D, Sitaru A. The impact of operating microscope on the outcome of endodontic treatment performed by postgraduate students. Eur Sci J. 2015; 11: 305-11.
15. Khalighinejad N, Aminoshariae A, Kulild JC, Williams KA, Wang J, Mickel A, et al. The effect of the dental operating microscope on the outcome of nonsurgical root canal treatment: A retrospective case-control study. J Endod. 2017; 43: 728-32.
16. Yusof ZYM, Nambiar P. Radiographic considerations in endodontics. Malaysian Dent J 2007; 1: 51-8.
17. Ricucci D. Apical limit of root canal instrumentation and obturation, Part 1. Literature review. Int Endod J. 1998; 31: 384-93.
18. Plotino G, Grande NM, Brigante L, Lesti B, Somma F. Ex vivo accuracy of three electronic apex locators: Root ZX, Elements Diagnostic Unit and Apex Locator and Propex. Int Endod J. 2006; 39: 408-14.
19. Palmer NO, Ahmed M, Grieveson B. An investigation of current endodontic practice and training needs in primary care in the north west of England. Br Dent J. 2009; 206(11): E22.
20. Madarati AA, Younes HAB. Survey on the modalities of rubber dam usage for root canal treatment. Taibah Univ Med Sci. 2016; 11: 152-8.
21. Mala S, Lynch CD, Burke F, Dummer PMH. Attitudes of final year dental students to the use of rubber dam. Int Endod J. 2009; 42: 632-8.
22. Ahmad I. Rubber dam usage for endodontic treatment: A review. Int Endod J. 2009; 42: 963-72.
23. Darcey J, Jawad S, Taylor C, Roudsari RV, Hunter M. Modern endodontic principles part 4: irrigation. Dent Update. 2016; 43(1): 20-2.
24. Schäfer E, Bössmann K. Antimicrobial efficacy of chlorhexidine and two calcium hydroxide formulations against Enterococcus faecalis. J Endod. 2005; 31: 53-6.
25. Mohammadi Z. Sodium hypochlorite in endodontics: an update review. Int Dent J. 2008; 58(6): 329-41.
26. Siqueira JF, Magalhaes KM, Rocas IN. Bacterial reduction in infected root canals treated with 2.5% NaOCl as an irrigant and calcium hydroxide/

camphorated paramonochlorophenol paste as an intracanal dressing. J Endod. 2007; 33: 667-72.

27. Hasselgren G, Olsson B, Cvek M. Effects of calcium hydroxide and sodium hypochlorite on the dissolution of necrotic porcine muscle tissue. J Endod. 1988; 14: 125-7.

28. Siqueira JF, Lopes HP. Mechanisms of antimicrobial activity of calcium hydroxide: a critical review. Int Endod J. 1999; 32: 361-9.

29. Aun DP, Peixoto IFDC, Houmard M, Buono VTL. Enhancement of NiTi superelastic endodontic instruments by TiO2 coating. Materials Science and Engineering C. 2016; 68: 675-80.

30. Aoun CM, Nehme WB, Naaman AS, Khalil IT. Review and Classification of Heat Treatment Procedures and Their Impact on Impact on Mechanical Behavior of Endodontic Files. International Journal of Current Research. 2017; 9(5): 51300-6.

31. Elham FG, Sedigheh Z. The use of instruments by Iranian endodontics and general practioners. Open Dent J. 2012; 6: 105.

32. Parashos P, Messer HH. Questionnaire survey on the use of rotary nickel-titanium endodontic instruments by Australian dentists. Int Endod J. 2004; 37(4): 249-59.

33. Sivakumar JS, Suresh Kumar BN, Shyamala PV. Role of provisional restorations in endodontic therapy. J Pharm Bioall Sci. 2013; 5: 120-4.

34. Lee M, Winkler J, Hartwell G, Stewart J, Caine R. Current trends in endodontic practice: emergency treatment and technological armamentarium. J Endod. 2009; 35(1): 35-9.

35. Johnson W, Kulild JC, Tay F. Obturation of the cleaned and shaped root canal system. In: Hargreaves KM, Berman LH, eds. Cohen's Pathways of the Pulp. 11th ed. St. Louis: Elsevier; 2016; p. 280-315.

RESEARCH ARTICLE

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The Effect of Deferasirox Dose and Treatment Duration on Frequency of Proteinuria and Renal Functions in Patients with Thalassemia Major

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Abstract

BACKGROUND/AIMS: Nephrotoxicity may develop in thalassemia major (TM) because of the disease and deferasirox (DFX) treatment. The aim of this study was to investigate the effect of deferasirox dose and treatment duration on the frequency of proteinuria and renal functions.

MATERIALS AND METHODS: Patients with TM who were undergoing regular transfusion and were using DFX as an iron chelator were included in this study. According to the international follow-up protocols, screening tests (urea, creatinine, electrolytes, ferritin, complete urine analysis, and spot urine protein-creatinine ratio) which are examined every 3 months, were recorded once for each patient (March 2018-June 2018).

RESULTS: Sixty-six patients were included in this study (35 boys and 31 girls). Their mean age was 9.89±4.67 years and the mean age of starting transfusion was 7.86±7.89 months. The mean duration of treatment with DFX was 7.12±3.94 years. A significant difference was found in the incidence of proteinuria when the DFX dose was higher than 40 mg/kg/day. When DFX treatment duration was evaluated, creatinine values were significantly lower in those patients with a treatment durations longer than 5 years (p=0.001).

CONCLUSION: Instead of increasing the dose of DFX, switching to combined therapy may be more effective and safer in terms of side effects.

Keywords: Deferasirox, proteinuria, thalassemia major, nephrotoxicity

INTRODUCTION

Beta-thalassemia syndromes are genetic hematologic disorders characterized by chronic hemolytic anemia. The main pathophysiological disorder is ineffective erythropoiesis due to a relatively increased alpha-globin chain imbalance versus decreased and completely stopped B-globin synthesis.[1] The clinical spectrum of the disease varies from transfusion-dependent anemia to thalassemia minor. Thalassemia is common in the Mediterranean Region and is an important public health problem. After the development of thalassemia screening programs in recent years, the number of patients with thalassemia has been determined. Screening programs in combination with prenatal genetic testing and genetic counselling has decreased the number of thalassemia major (TM) births. Regular transfusions, chelation therapy, and experience with this disease have led to a significant increase in the life expectancy of those patients with thalassemia.[1-3]

In TM, with increased life expectancy, cardiopulmonary system, endocrine, hepatic and renal complications can be seen more commonly. Tubular and glomerular disorders are the most common pathologies in renal complications. Chronic anemia, oxidative stress and iron chelators are thought to be the most common etiologic causes of nephrotoxicity.

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Deferasirox (DFX) is the most commonly used agent in iron chelators.[4] One of its most important side effects is nephrotoxicity. It is known that high doses of DFX cause renal tubular damage in animal experiments.[5,6] The aim of this study was to investigate the effect of DFX dosage and treatment duration on the frequency of proteinuria and renal functions by using primer screening tests.

MATERIALS AND METHODS

Patients with TM who underwent regular transfusion (15 mL/kg, every 3 weeks) and who were using DFX as an iron chelator were included in this study. Their age, gender, diagnosis time, transfusion starting time, duration of treatment, DFX dose, genetic mutation analysis, blood counts, liver-renal function tests (urea, creatinine, electrolytes, ferritin, complete urine analysis, and spot urine protein-creatinine ratio) were evaluated retrospectively. According to the international TM follow-up protocols, the check-up laboratory values which are examined every 3 months, were recorded for each patient (March-June 2018). Average and standard deviation values were calculated. The abdominal ultrasonography results of the patients were checked for anatomic and morphologic renal pathologies. Routine pediatric cardiology and pediatric endocrinology consultations were performed.

The upper limits of the creatinine are considered to be 0.9 mg/dL for the ages 3 to 18 years, and 0.7 mg/dL for under the age of 3 years. The urine protein/creatinine ratio limit in the morning is 0.5 mg/gram creatinine below 2 years of age and 0.2 mg/gram creatinine for children over 2 years of age.[7] For the urine protein method, benzethonium chloride was used via the turbimetric procedure. The creatinine value was studied biochemically with the Architect c1600 device. Normal glomerular filtration rate (GFR) values were considered to be 140±30 for 2-12 years of age, 133±27 for 13-21 years of age in boys and 126±22 for 13-21 years of age in girls.[8] Renal function test results and the frequency of proteinuria were compared according to the dose of DFX and its duration of treatment.

In general, the starting dose of DFX is 20 mg/kg/day, the starting time is 2 years of age and the serum level of ferritin should be >1,000 ng/mL (Exjade; Novartis). The dosage can increase up to 40 mg/kg/day depending on ferritin levels if there are no complications.[2] The FDA and European Medicines Agency have recommended doses up to 40 mg/kg/day in patients who inadequately chelate with lower doses. Doses above 40 mg/kg/day are not approved.[9] Therefore, we set the DFX dose limit at 40 mg/kg/day in our study.

Those patients who did not receive DFX treatment regularly and those who received combined chelator treatment were excluded from this study. We did not have the possible utility of other biomarkers to detect kidney injury or renal functions for a more detailed investigation. For this reason, only the screening tests of the TM protocols were used in this study.

This retrospective study was approved by the Diyarbakır University of Health Sciences Gazi Yaşargil Training and Research Hospital Local Ethics Committee in 2019 (approval number: 2019-235). An approval statement for participation was received from the parents or legal guardians of the participants.

Statistical Analysis

The normality of distribution of continuous variables was tested by the Shaphiro-Wilk's test. Student's t-test (for normal data) and Mann-Whitney U test (for non-normal data) was used for comparisons of two independent groups and the chi-square test was used to evaluate between categorical variables. The SPSS for Windows version 22.0 was used and a p-value <0.05 was accepted as significant. All analyses were conducted with the use of Statistical Product and Service Solutions (SPSS 22.0) software.

RESULTS

A total number of 66 patients were included in this study (35 boys and 31 girls). Their mean age was 9.89±4.67 years and their mean age at diagnosis and starting transfusion was 7.86±7.89 months. The mean duration of treatment with DFX was 7.12±3.94 years. The general characteristics and laboratory mean values of the patients are given in Table 1. A significant difference was found in terms of the incidence of proteinuria when the DFX dose was higher than 40 mg/kg/day (Table 2). When treatment duration was evaluated (Table 3), creatinine values were significantly lower in those patients with a treatment duration longer than 5 years (p=0.001). There were no findings suggestive of renal tubular nephropathy such as hypophosphatemia, low bicarbonate level and acidosis in routine blood biochemistry controls. No anatomic or morphological findings were detected on urinary system ultrasound.

Genetic mutation analysis was studied in 37 out of the 66 patients, and the most common mutation (67.6%) was the homozygous mutation of IVS I-110. In our study, no comparison or interpretation could be made between the genetic results and renal function tests.

DISCUSSION

In patients with TM, renal involvement can occur due to chronic anemia and iron overload.[5] DFX is the most commonly used oral chelator in

Table 1. Descriptive statistics

	(n=66)
Gender	n (%)
Boys	35 (53.0)
Girls	31 (47.0)
	Mean ± SD
Age	9.89±4.67
Diagnosis and starting transfusions (months)	7.86±7.89
Treatment time (years)	7.12±3.94
Body mass (kg)	30.12±13.33
Deferasirox (mg/kg)	30.3±4.57
Ferritin (ng/mL)	2,839.82±1,907.74
Leucocyte (/mm^3)	11,238.68±7,112.87
Hemoglobin (gr/dL)	9.27±1.31
Thrombocyte count (/mm^3)	405,984.85±212,351.99
AST (U/L)	37.33±28.02
ALT (U/L)	31.71±34.44
Urea (mg/dL)	28.09±9.08
Creatinine (mg/dL)	0.48±0.07
Urine density	1,012.2±5.85
Spot urine protein/creatinine	0.33±0.3
GFR (mL/min/1.73 m^2)	156.36±29.15

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate, SD: standard deviation.

the world. A slight increase in serum creatinine levels is the most often seen toxic impact of DFX. Nevertheless, DFX rarely cause renal insufficiency requiring dialysis.[3] Generally, nephrotoxicity is reversible and normalization of renal function is observed after the cessation of treatment. The most affected area is the proximal tubules but the pathophysiology is not fully known.[10] Although DFX is generally well tolerated, a moderate, dose-dependent and non-progressive increase in creatinine has been reported in 36% of patients in clinical trials.[11] In a retrospective study, treatment was terminated due to creatinine elevation in 7 out of 72 patients.[12] DFX-induced nephrotoxicity is thought to be more frequent in adults with accompanying diabetes.[10,13] Diabetes mellitus (DM) was not detected in the endocrinological examinations of our patients. We thought that the reason why creatinine values did not increase, in contrast to adult studies, might be related to the absence of DM in our patients.

Use of nephrotoxic drugs in combination with high doses of DFX increases renal involvement. After DFX initiation, serum creatinine levels must be checked regularly. However, patients with B TM should be followed up with spot urine protein/creatinine ratio measurements monthly for proteinuria. It is known that urinary protein excretion increases in beta TM compared to normal patients. Proteinuria should be considered if the urine protein/creatinine ratio is ≥0.6.[3] Aldudak et al.[14] determined this limit to be 0.7. In a study conducted in our country, proteinuria due to DFX was observed in 7 out of 37 patients (19%). It was noted that as the DFX dose increased, the probability of proteinuria increased.[15] In our study, the frequency of proteinuria was found to be significantly higher in the group with a DFX dose above 40 mg/kg/day. In one patient whose dose of DFX was increased to 40 mg/kg/day, proteinuria was detected in the urine analysis and their spot urine protein/creatinine ratio increased to 2.5. High creatinine levels, low C3-C4 levels and hypoalbuminemia were not detected in laboratory tests and no clinical findings were observed on physical examination. Dubourg et al.[16] showed that tubular damage could be stopped by decreasing the drug dosage. In our patient, proteinuria was not detected in the urine analysis at the 2nd week after the discontinuation of the drug.

Although renal failure was not reported during DFX therapy in previous studies, the development of renal dysfunction was observed. Renal dysfunction is mostly in the form of tubulopathy and resolved after the discontinuation of DFX treatment.[17-21] In addition to this, although tubulopathy is mostly reversible, the possibility of chronic tubular damage, interstitial fibrosis and chronic renal disease should be kept in mind. Glomerular and tubular damage develops over time due to the chronic toxic effects of the disease and chelators. It is thought that a

Table 2. Comparison of renal function tests of the patients according to deferasirox dose

	Deferasirox dose mg/kg/day		
	<40 (n=61)	≥40 (n=5)	
Variables	**Mean ± SD**	**Mean ± SD**	**p**
Urea (mg/dL)	27.8±7.82	31.6±20.11	0.689§
Creatinine	0.49±0.07	0.46±0.08	0.448‡
Urine density	1,012.2±5.92	1,012.2±5.63	0.999‡
Spot urine protein/creatinine	0.3±0.12	0.69±1.01	0.907§
GFR mL/min/1.73 m^2	157.33±29.91	144.6±14.08	0.479§
	n (%)	**n (%)**	
Proteinuria			
Negative	60 (98.4)	4 (80.0)	**0.021¶**
Positive	1 (1.6)	1 (20.0)	

SD: standard deviation, §: Mann-Whitney U test, ‡: Student's t-test, ¶: chi-square test.
*Significant at 0.05 level, GFR: glomerular filtration rate.

Table 3. Comparison of renal function tests according to deferasirox treatment duration

	Treatment time		
	≤5 years (n=25)	>5 years (n=41)	
Variables	**Mean ± SD**	**Mean ± SD**	**p**
Urea (mg/dL)	27.8±7.82	31.6±20.11	0.169§
Creatinine (mg/dL)	0.49±0.07	0.46±0.08	**0.001*‡**
Urine density	1,012.2±5.92	1,012.2±5.63	0.828‡
Spot urine protein/creatinine	0.3±0.12	0.69±1.01	0.173§
GFR (mL/min/1.73 m^2)	157.33±29.91	144.6±14.08	**0.001*§**
	n (%)	**n (%)**	
Proteinuria			
Positive	24 (96.0)	40 (97.6)	0.720¶
Negative	1 (4)	1 (2.4)	

GFR: glomerular filtration rate, SD: standard deviation, §: Mann-Whitney U test, ‡: Student's t-test, ¶: chi-square test, *significant at 0.05 level.

decrease in the GFR would cause an increase in serum creatinine levels.[16] In contrast to previous clinical trials, in our study, creatinine values were found to be significantly lower in those patients with a treatment duration longer than 5 years. We think that a decrease in creatinine may also be a sign of hyper filtration as a result of thalassemia and inadequate transfusions, rather than due to the DFX treatment.

In recent years, some studies have suggested that combined oral chelation with deferiprone (DFP) (Ferriprox-Chiesi) and DFX has better efficacy than either drug used alone. In these studies, there were no problems with adverse effects and drug tolerance in combined therapy as a safe dose range is maintained.[22,23] It is a fact that DFX, with its daily single dose use and its tablet form, which has been used in recent years, is the iron chelator most frequently preferred by patients and their relatives as well as physicians. However, its renal toxicity is well-known today and its use in high doses is one of the biggest risk factors for this.[24] Desferrioxamine is a non-feasible option for iron-chelation in a large majority of patients in developing countries because of its high cost, coupled with the need for continuous infusion. Monotherapy with DFP or DFX may cause inadequate control, especially in severe iron-loaded patients. The combination of DFP with DFX is a potential alternative especially so as to avoid high dose toxicities.[25]

Study Limitations

The main limitation of our study was the low number of patients, especially those who received a dose above 40 mg/kg/day. The fact that it was a single center study was the main reason for the limited number of patients.

CONCLUSION

DFX is an appropriate drug in terms of its use and efficacy, but proteinuria and other renal complications may be seen in higher doses. In patients with high ferritin levels and iron overload, we think that, instead of increasing the dose of DFX, switching to combined therapy may be more effective and safer in terms of side effects.

MAIN POINTS

• Nephrotoxicity may develop in thalassemia major because of the disease and deferasirox treatment.

• The frequency of proteinuria is significantly higher when the deferasirox dose is increased above 40 mg/kg/day.

• In patients with high ferritin levels and iron overload, instead of increasing the dose of DFX, switching to combined therapy may be more effective and safer in terms of side effects.

ETHICS

Ethics Committee Approval: This retrospective study was approved by the Diyarbakır University of Health Sciences Gazi Yaşargil Training and Research Hospital Local Ethics Committee in 2019 (approval number: 2019-235).

Informed Consent: An approval statement for participation was received from the parents or legal guardians of the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.S., Design: H.S., Supervision: H.S., M.A.K., Materials: H.S., Data Collection and/or Processing: H.S., Analysis and/or Interpretation: H.S., M.A.K., Literature Search: H.S., Writing: H.S., Critical Review: H.S.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med. 2005; 353(11): 1135-46.
2. Hoffbrand AV, Taher A, Cappellini MD. How I treat transfusional iron overload. Blood. 2012; 120(18): 3657-69.
3. Diaz-Garcia JD, Gallegos-Villalobos A, Gonzalez-Espinoza L, Sanchez-Niño MD, Villarrubia J, Ortiz A. Deferasirox nephrotoxicity-the knowns and unknowns. Nat Rev Nephrol. 2014; 10(10): 574-86.
4. Cappellini MD, Bejaoui M, Agaoglu L, Canatan D, Capra M, Cohen A, et al. Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. Blood. 2011; 118(4): 884-93.
5. Quinn CT, Johnson VL, Kim HY, Trachtenberg F, Vogiatzi MG, Kwiatkowski JL, et al. Renal dysfunction in patients with thalassaemia. Br J Haematol. 2011; 153(1): 111-7.
6. Taher A, El-Beshlawy A, Elalfy MS, Al Zir K, Daar S, Habr D, et al. Efficacy and safety of deferasirox, an oral iron chelator, in heavily iron-overloaded patients with beta-thalassaemia: the ESCALATOR study. Eur J Haematol. 2009; 82(6): 458-65.
7. Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J. Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). Pediatrics. 2005; 105(6): 1242-9.
8. Hogg RJ, Furth S, Lemley KV, Portman R, Schwartz GJ, Coresh J, et al. National Kidney Foundation's Kidney Disease Outcomes Quality Initiative clinical practice guidelines for chronic kidney disease in children and adolescents: evaluation, classification, and stratification. Pediatrics. 2003; 111(6 Pt 1): 1416-21.
9. Nisbet-Brown E, Olivieri NF, Giardina PJ, Grady RW, Neufeld EJ, Séchaud R, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet. 2003; 361(9369): 1597-602.
10. Mula-Abed WA, Al-Hashmi HS, Al-Muslahi MN. Indicators of Renal Glomerular and Tubular Functions in Patients with Beta-Thalassaemia Major: A cross sectional study at the Royal Hospital, Oman. Sultan Qaboos Univ Med J. 2011; 11(1): 69-76.
11. Cappellini MD, Cohen A, Piga A, Bejaoui M, Perrotta S, Agaoglu L, et al. A phase 3 study of deferasirox (ICL670), a once-daily oral iron chelator, in patients with beta-thalassemia. Blood. 2006; 107(9): 3455-62.
12. Murtadha Al-Khabori, Bhandari S, Al-Huneini M, Al-Farsi K, Panjwani V, Daar S. Side effects of Deferasirox iron chelation in patients with beta thalassemia major or intermedia. Oman Med J. 2013; 28(2): 121-4.

13. Mula-Abed WA, Al-Hashmi HS, AlMuslahi MN, Al Muslahi H, Al Lamki M. Prevalence of endocrinopathies in patients with beta-thalassaemia major: A cross-sectional study in Oman. Oman Med J. 2008; 23(4): 257-62.

14. Aldudak B, Karabay Bayazit A, Noyan A, Ozel A, Anarat A, Sasmaz I, et al. Renal function in pediatric patients with beta-thalassemia major. Pediatr Nephrol. 2000; 15(1-2): 109-12.

15. Bayhan T, Ünal Ş, Ünlü O, Küçüker H, Tutal AD, Karabulut E, et al. The questioning for routine monthly monitoring of proteinuria in patients with β-thalassemia on deferasirox chelation. Hematology. 2017; 22(4): 248-51.

16. Dubourg L, Laurain C, Ranchin B, Pondarré C, Hadj-Aïssa A, Sigaudo-Roussel D, et al. Deferasirox induced renal impairment in children: an increasing concern for pediatricians. Pediatr Nephrol. 2012; 27(11): 2115-22.

17. Dee CM, Cheuk DK, Ha SY, Chiang AK, Chan GC. Incidence of deferasirox associated renal tubular dysfunction in children and young adults with beta-thalassaemia. Br J Haematol. 2014; 167(3): 434-6.

18. Even-Or E, Becker-Cohen R, Miskin H. Deferasirox treatment may be associated with reversible renal Fanconi syndrome. Am J Hematol. 2010; 85(2): 132-4.

19. Yacobovich J, Stark P, Barzilai-Birenbaum S, Krause I, Pazgal I, Yaniv I, et al. Acquired proximal renal tubular dysfunction in beta-thalassemia patients treated with deferasirox. J Pediatr Hematol Oncol. 2010; 32(7): 564-7.

20. Wei HY, Yang CP, Cheng CH, Lo FS. Fanconi syndrome in a patient with beta-thalassemia major after using deferasirox for 27 months. Transfusion. 2011; 51(5): 949-54.

21. Rheault MN, Bechtel H, Neglia JP, Kashtan CE. ReversibleFanconi syndrome in a pediatric patient on deferasirox. Pediatr Blood Cancer. 2010; 56(4): 674-6.

22. Parakh N, Chandra J, Sharma S, Dhingra B, Jain R, Mahto D. Efficacy and Safety of Combined Oral Chelation with Deferiprone and Deferasirox in Children With β-Thalassemia Major: An Experience from North India. J Pediatr Hematol Oncol. 2017; 39(3): 209-13.

23. Karami H, Kosaryan M, Amree AH, Darvishi-Khezri H, Mousavi M. Combination Iron Chelation Therapy with Deferiprone and Deferasirox in Iron-Overloaded Patients with Transfusion-Dependent β-Thalassemia Major. Clin Pract. 2017; 7(1): 912.

24. Nafea OE, Zakaria M, Hassan T, El Gebaly SM, Salah HE. Subclinical nephrotoxicity in patients with beta-thalassemia: role of urinary kidney injury molecule. Drug Chem Toxicol. 2019; 45(1): 93-102.

25. Totadri S, Bansal D, Bhatia P, Attri SV, Trehan A, Marwaha RK. The deferiprone and deferasirox combination is efficacious in iron overloaded patients with β-thalassemia major: A prospective, single center, open-label study. Pediatr Blood Cancer. 2015; 62(9): 1592-6.

RESEARCH ARTICLE

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A Comparison of the Effects of Early and Late Ovarian Stimulation on Reproductive Outcomes in Patients with Polycystic Ovary Syndrome

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Abstract

BACKGROUND/AIMS: Data on the effect of onset time of gonadotropins for ovarian stimulation on in vitro fertilization (IVF) outcomes are limited. This study was planned to compare the effects of early and late-onset ovarian stimulation on gonadotropin dose, ongoing pregnancy and live birth rates in women with polycystic ovary syndrome (PCOS).

MATERIALS AND METHODS: The data of 432 patients who underwent IVF/intracytoplasmic sperm injection for PCOS-induced infertility/subfertility were reviewed retrospectively. Among them, 304 were included in this study. They were divided into two groups according to the timing of their ovarian stimulation (2nd & 5th days of the menstrual cycle).

RESULTS: The total oocyte count, the number of fertilized oocytes, and the number of grade 1 or 2 embryos were significantly higher in those subjects receiving ovarian stimulation on the 2nd day of the menstrual cycle. Those patients who received ovarian stimulation on day 2 had a higher total gonadotropin dose and a longer gonadotropin administration time. Although the number of total oocytes was higher in those patients starting treatment on the 2nd day, treatment started on day 5 (shorter treatment) provided better fertilization.

CONCLUSION: In women with infertile PCOS, ovarian stimulation started on the 2nd day of the cycle provided more favorable IVF results in terms of total oocytes and fertilized oocytes, while the total gonadotropin dose was found to be higher. Fertilization and oocyte quality were better in the stimulations started on the 5th day.

Keywords: Polycystic ovary syndrome, infertility, in vitro fertilization, early or late stimulation

INTRODUCTION

Polycystic ovary syndrome (PCOS), which is characterized by polycystic ovary morphology, ovulatory dysfunction and hyperandrogenism, has been reported to affect up to 10% of reproductive-age women.[1] It is also one of the leading causes of anovulatory infertility.[2] In vitro fertilization (IVF) protocols have been reported to be successful in achieving clinical pregnancy in women with PCOS.[3] In this protocol, one or more mature egg cells are taken from the woman's ovaries and fertilized in a special environment outside the body with sperm taken from the male. After the procedure, this fertilized egg is placed in the uterus or frozen and stored for future use. IVF is a repeatable procedure with satisfactory results, applied in many infertility cases caused by men or women.[4]

Controlled ovarian hyper-stimulation is used to prevent the development of multiple follicles and the associated risk of premature luteinization,

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as well as ovarian hyper-stimulation syndrome (OHSS).[5] The purpose of controlled ovarian hyper-stimulation is to support the production of oocytes of good quality, and it is frequently initiated in the early stages of the menstrual cycle.[6] Recombinant follicle-stimulating hormone (rFSH) is also usually administered on the 2nd or 3rd day of the menstrual cycle. However, such early administration may not only lead to OHSS but could also cause the development of multiple low-quality oocytes.[7] On the other hand, late administration of rFSH may limit the number of oocytes which are required for fertilization.

Data concerning the impact of the timing of ovarian stimulation on IVF outcomes are very limited. This study aimed to compare early (2nd day of the menstrual cycle) and later (5th day of the menstrual cycle) ovarian stimulation in terms of oocyte quality, total gonadotropin dose and also the rates of pregnancy, ongoing pregnancy and live birth.

MATERIALS AND METHODS

The data of 432 patients with PCOS (aged between 18-37 years) who had undergone IVF due to infertility at the gynecology department of a tertiary healthcare institute, between January 2012 and January 2020, were obtained from institutional digital records. The diagnosis of PCOS was based on the diagnostic criteria revised by the Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group.[8]

Among the 432 patients, 128 were excluded (pregnant women, smokers, women in early menopause, breastfeeding women, women with diagnosed hypertension, diabetes mellitus, and adrenal gland disorder). The final group of 304 women with PCOS was divided into two groups, according to the timing of ovarian stimulation, as follows: Ovarian stimulation on the 2nd day of the menstrual cycle (group 1) and ovarian stimulation on the 5th day of the menstrual cycle (group 2). All procedures performed in this study involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and within the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Clinical Research Ethic Committee of Erciyes University (approval number: 2011-KAEK-80). Informed consent was obtained from all individual participants included in this study.

The patients' FSH, estradiol and baseline ultrasonography analyses were performed on the 2nd and 3rd days of menstruation. Initial gonadotropin dose was determined according to their body mass index, antral follicle counts and serum anti-mullerian hormone (AMH) levels. Before initiating gonadotropins, we confirmed the absence of >20 mm follicles and evaluated baseline estradiol and progesterone levels (confirming, E2 <40 pg/mL, progesterone <1 ng/mL). All patients were treated with flexible daily gonadotropin releasing hormone (GnRH) protocols for controlled ovarian stimulation. The initiation of GnRH antagonists (Cetrotide, Merck-Serono) was performed after the determination of ≥14 mm follicle size and/or ≥400 pg/mL serum E_2 levels on the fifth day of treatment. Ovulation was triggered with choriogonadotropin alfa 250 mch (Ovitrelle, Merck-Serono) when at least two leading follicles were ≥18 mm. Oocytes were collected 35 or 36 hours after triggering. Oocytes were fertilized by the microinjection method and embryo transfer was performed 5 days later. One or two blastocyst embryo transfer was performed at the stage of top quality or good quality embryos according to Gardner and Schoolcraft blastocyst grading system. Luteal phase support with progesterone gel was continued until a pregnancy test was performed. The patients underwent pregnancy testing via blood samples (beta-hCG) 12 days after transfer and were scheduled for USG evaluation 15 days later for the identification of the fetal heart-beat.

Biochemical pregnancy was established when the pregnancy test result was positive with >20 mIU/mL HCG levels on the 12th day after embryo transfer. Clinical pregnancy was defined as the presence of fetal cardiac activity on vaginal ultrasonography.

The differences between the two groups with respect to total oocyte count, MII oocyte count, fertilization, biochemical and clinical pregnancy rates were the primary outcome measures of this study. The total dose of gonadotropin used was the secondary outcome measure.

Statistical Analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Q-Q and histogram plots were used to assess normal distribution. According to the distribution characteristics, continuous data are given as mean ± standard deviation or median (minimum-maximum). Categorical variables are described with frequency (and percentage). The comparison of normally distributed variables was performed with the independent samples t-test; whereas non-normally distributed variables were analyzed with the Mann-Whitney U test. The comparison of groups in terms of categorical variables was carried out with chi-square tests. Multiple logistic regression analysis (forward conditional method) was performed to determine significant factors effective on pregnancy and live birth. Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

A total of 304 women with PCOS who underwent IVF at our institute were analyzed (mean age: 28.60±4.80 years). Among these, 161 received ovarian stimulation on the 2nd day of the menstrual cycle and

Table 1. Summary of the patients' characteristics with regard to starting day

	Starting day			
	2nd day (n=161)	5th day (n=143)	Total (n=304)	p
Age, years	28.88±4.82	28.28±4.77	28.60±4.80	0.276
Duration of infertility, years	6 (1-22)	5 (1-24)	6 (1-24)	0.094
BMI, kg/m^2	27.02±2.21	26.77±1.94	26.90 ±2.09	0.242
E_2 (day 2), pg/mL	35 (8-97)	36 (6-93)	36 (6-97)	0.458
Progesterone (day 2), ng/mL	0.2 (0.01-0.8)	0.1 (0.01-0.7)	0.17 (0.01-0.8)	0.009
AMH, ng/mL	5.9 (4.6-8.2)	5.1 (4.0-7.1)	5.4 (4.0-8.2)	<0.001

AMH: anti-müllerian hormone, BMI: body mass index, E_2: estradiol. Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables according to normality of distribution.

143 received ovarian stimulation on the 5th day of the menstrual cycle. The progesterone concentration measured on the second menstrual day was significantly higher in those subjects receiving ovarian stimulation on the 2nd day of the menstrual cycle compared to those receiving ovarian stimulation on the 5th day of the cycle [0.2 (0.01-0.8) vs. 0.1 (0.01-0.7), p=0.009]. Recipients of ovarian stimulation on the 2nd day of the menstrual cycle had higher E_2 and progesterone concentrations on the day of ovulation compared to those receiving ovarian stimulation on the 5th day of the menstrual cycle (p<0.001, for each). Additionally, anti-mullerian hormone (AMH) values were significantly higher in the recipients of ovarian stimulation on the 2nd day (p<0.001) (Table 1).

As shown in Table 2, those patients who received ovarian stimulation on day 2 had a higher total gonadotropin dose and a longer gonadotropin administration time compared to those receiving ovarian stimulation on the 5th day of the cycle. When the two groups were compared, we found that the total oocyte count [28 (12-66) vs. 21 (11-37), p<0.001], the number of fertilized oocytes [14 (4-45) vs. 13 (6-26), p=0.041], and the number of grade 1-2 embryos [21 (7-55) vs. 17 (10-35), p=0.001] were significantly higher in those subjects receiving ovarian stimulation on the 2nd day of the menstrual cycle (longer treatment). It was also noted that those subjects starting ovarian stimulation on the 2nd day of the menstrual cycle were more likely to undergo thaw cycles; whereas those starting ovarian stimulation on the 5th day of the menstrual cycle were more likely to undergo fresh cycles. Both groups were similar in terms of clinical pregnancy, ongoing pregnancy and live birth rates (Figure 1).

During multiple logistic regression analysis, we found that early hCG administration was associated with a higher frequency of clinical pregnancy rates (p=0.004). Other variables included in the model, such as 2nd day E_2 (p=0.053), 2nd day progesterone (p=0.230), total gonadotropin dose (p=0.642), stimulation day (p=0.785), days with gonadotropin (p=0.785), hCG day E_2 (p=0.388), total oocyte number (p=0.822), M_2 (p=0.179), PN (p=0.109), type of procedure (p=0.870) and embryo day (p=0.113) were found to be non-significant (Table 3).

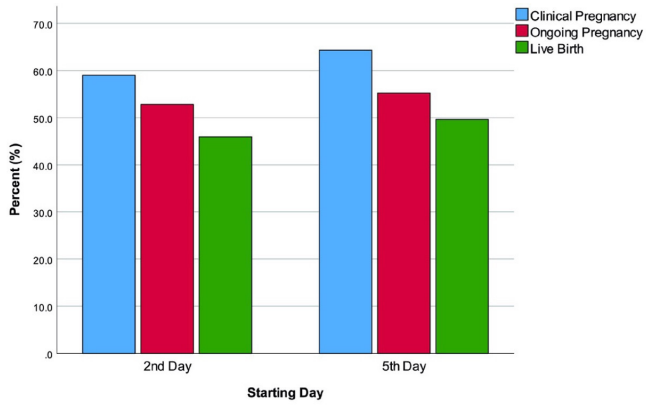

Figure 1. Pregnancy and live birth rates with regard to starting day.

Table 2. Comparison of the characteristics of the groups according to the onset day of ovarian stimulation.

	Starting day			
	2nd day (n=161)	5th day (n=143)	Total (n=304)	p
Total GND dose	2,700 (1,000-4,500)	1,600 (800-3,375)	2,000 (800-4,500)	<0.001
Days with GND	10 (8-13)	8 (8-10)	9 (8-13)	<0.001
E_2 (hCG day), pg/mL	3,300 (1,000-12,470)	2,890 (1,016-7,577)	3,000 (1,000-12,470)	<0.001
Progesterone (hCG day), ng/mL	1.2 (0.09-4)	0.9 (0.1-2.5)	1.09 (0.09-4)	<0.001
Total oocyte count, (n)	28 (12-66)	21 (11-37)	24 (11-66)	<0.001
M^2 embryos, (n)	21 (7-55)	17 (10-35)	18 (7-55)	0.001
PN, (n)	14 (4-45)	13 (6-26)	13 (4-45)	0.041
Embryo day				
2 & 3	70 (43.48%)	51 (35.66%)	121 (39.80%)	0.165
5 & 6	91 (56.52%)	92 (64.34%)	183 (60.20%)	
Procedure				
Thaw cycle, (n)	118 (73.29%)	55 (38.46%)	173 (56.91%)	<0.001
Fresh cycle, (n)	43 (26.71%)	88 (61.54%)	131 (43.09%)	
Clinical pregnancy, (n)	95 (59.01%)	92 (64.34%)	187 (61.51%)	0.340
Ongoing pregnancy, (n)	85 (52.80%)	79 (55.24%)	164 (53.95%)	0.669
Live birth, (n)	74 (45.96%)	71 (49.65%)	145 (47.70%)	0.521

E_2: estradiol, GND: gonadotropin, hCG: human chorionic gonadotropin. Data are given as median (minimum-maximum) for continuous variables, and as frequency (percentage) for categorical variables.

Table 3. Factors affecting clinical pregnancy rates during logistic regression analysis

	β coefficient	Standard error	Wald	p	Exp (β)	95% confidence interval for β	
hCG day	-0.606	0.211	8.240	0.004	0.546	0.361	0.825
(Constant)	1.168	0.273	18.301	<0.001	3.215	-	-

Dependent variable: Clinical pregnancy; Nagelkerke R^2=0.038. hCG: human chorionic gonadotropin.

DISCUSSION

This study compared IVF outcomes in subjects receiving ovarian stimulation on the 2nd day or the 5th day of the menstrual cycle. Our findings showed that the total oocyte count, the number of grade 1-2 embryos, and the number of fertilized oocytes were higher in those subjects receiving earlier ovarian stimulation than in those receiving ovarian stimulation later in the cycle; however, this advantage of earlier ovarian stimulation did not translate into an increased frequency of clinical pregnancies or live births. We also determined that the number of days with gonadotropin and total gonadotropin dose were lower in those subjects receiving earlier ovarian stimulation compared to those receiving later ovarian stimulation. These results show that shorter treatment has similar pregnancy results compared to longer treatment, with advantages of less drug exposure and lower cost. The logistic regression model revealed that earlier hCG administration was independently associated with higher clinical pregnancy rates.

IVF has been reported to be successful in about 50% of cases, with significant success particularly in those younger than 35 years of age.[9] It is also well-known that IVF is frequently utilized in the treatment of PCOS-related infertility, which is one of the most common causes of female infertility.[10,11] Although earlier practice with IVF was based on the spontaneous cycle of women, later studies showed that it was possible to obtain a higher number of oocytes by inducing ovulation through the administration of gonadotropins during the menstrual cycle.[12,13] To date, several protocols for achieving controlled ovarian hyper-stimulation in patients undergoing IVF have been introduced.[7,14] Although some of these protocols may provide more favorable pregnancy outcomes depending on the underlying cause of infertility and the hormonal status of the subject, none of the various protocols have demonstrated universal superiority.[15-17]

Recombinant FSH (rFSH) is a commonly utilized agent in controlled ovarian hyper-stimulation of patients undergoing IVF.[7,18,19] Current practice is based on administering rFSH earlier in the cycle, on the 2nd or 3rd day.[17,18] However, earlier administration of rFSH may be associated with OHSS development and may increase healthcare costs. However, data concerning IVF outcomes in subjects receiving ovarian hyper-stimulation later in the menstrual cycle are limited. To the best of our knowledge, there are no directly comparable studies in the literature. Only a few studies have evaluated the role of ovarian stimulation timing on IVF-related characteristics. For instance, in a recent study including patients who were to receive gonadotoxic therapy, Von Wolff et al.[20] reported that ovarian stimulation after day 5 of the menstrual cycle was associated with an increased number of oocytes compared to ovarian stimulation between the 1st and 5th days of the menstrual cycle. Studies conducted on patients requiring urgent cancer treatment have also shown that "random start" ovarian stimulation is comparable to conventional stimulation protocols with regard to the yield of mature oocytes and their developmental potential into embryos.[21,22] Taking into account the data derived from studies investigating random ovarian stimulation, we hypothesize that ovarian stimulation in the later stages of the menstrual cycle would perform similar to ovarian stimulation in the early stages of the menstrual cycle in terms of IVF outcomes in women with PCOS. This is a critical result as shorter treatment would result in lower exposure to gonadotropins and would lower the cost of treatment.

We must also mention the fact that women with PCOS are often considered to have a higher propensity for OHSS.[23] Fischer et al.[24] reported that when FSH dosage was calculated sparingly (low-dose stimulation), women with PCOS had no significant increase in the frequency of OHSS. Other studies have also identified a reduced risk of OHSS in PCOS with the use of various treatments; including metformin,[25] lower GnRH dose,[26] GnRH antagonists,[27] and the "*coasting*" method.[28] Therefore, the higher total gonadotropin dose and longer treatment with earlier stimulation may represent a risk for OHSS. However, there is no unanimous opinion on this topic and considering the deviations between studies, it seems apparent that there is a yet-to-be-elucidated dynamic hormonal balance/imbalance which is at play during the development of OHSS, especially considering its unquestionable relationship with the hCG trigger.[26] It has been reported that AMH-based ovarian stimulation protocols significantly reduce the risk of OHSS, the dose of rFSH used, and the duration of stimulation.[29] Therefore, in determining the initial rFSH dose, we use patient age, previous starting doses as well as a serum AMH measurement. We prefer AMH mostly to assess ovarian reserve in poor responders, premature ovarian aging or in cases of endometrioma/endometriosis. However, we use AMH values to determine the starting dose of rFSH to minimize the risk of OHSS due to PCOS.

In this study, clinical pregnancy rates were similar between the groups, and overall, 61.5% of the cases had clinical pregnancy and 47.7% of them had live birth. When the previous studies were examined, it was seen that the reported frequencies are heterogeneous. Although there were studies in which similar results were published with our study,[30-32] lower frequencies were also reported.[33-35] In particular, the results of studies in which the cumulatively pregnancy and live birth rates of several IVF trials were published were higher than our study, while single IVF trial results were lower. The difference in participant characteristics between the studies may have affected these results. The relatively younger ages of the subjects in our study may be one of the reasons for this situation. Additionally, in a meta-analysis, it was reported that the frequency of live births after IVF in PCOS cases was higher than in infertility cases caused by other reasons (odds ratio: 1.29, 95% confidence interval: 1.24-1.34).[36] The fact that all of the participants in our study were PCOS cases may be one of the reasons for better results compared to infertility cases caused by other reasons.

This is the first study investigating the timing of ovarian stimulation on IVF and pregnancy outcomes in women with PCOS. Our findings show that early ovarian stimulation provides higher total oocyte and fertilized oocytes compared to late ovarian stimulation in PCOS women. We also found that the later start of ovarian stimulation was associated with a shorter length of ovarian stimulation and lower total gonadotropin dose. Although a detailed cost-effect analysis was not performed, given the lower amount of gonadotropins used in subjects receiving fifth day ovarian stimulation (shorter treatment), we speculate that later ovarian stimulation may reduce treatment costs for infertility in women with PCOS. Another critical finding of this study was that the day of hCG administration was independently associated with clinical pregnancy rates. Nevertheless, there were no significant differences between those subjects receiving earlier or later ovarian stimulation with respect to clinical pregnancy rates and live birth rates.

Another controversial issue regarding IVF outcomes in PCOS or non-PCOS patients undergoing FET or fresh cycle is basal or pre-transfer

serum progesterone levels. We found a significant difference in serum progesterone levels between the second and fifth day groups (1.2 ng/mL vs 0.9 ng/mL). However, changes in progesterone levels did not cause a difference between the groups in terms of clinical pregnancy and live birth rates. The results of other studies on the relationship between serum progesterone levels and reproductive outcome in FET cycles are heterogeneous. While there are some studies showing that pre-transfer serum progesterone concentration affects live birth rates,[37] there are other studies reporting that progesterone levels do not affect IVF outcome.[38] As we showed in the logistic regression analysis, the difference in progesterone levels on the 2nd day and ovulation day did not cause any significant changes in the reproductive outcome parameters. Consistent with our results, it has been reported that hCG day progesterone values measured in fresh cycles do not have a significant effect on subsequent FET results in PCOS patients.[38]

Study Limitations

The important limitations of our study are that it was conducted in a single center and it had a retrospective design. Due to this study design, some variables which may have affected the results could not be evaluated retrospectively. An important limitation of our study was the inhomogeneous distribution of fresh and FET cycles among the groups. The high thaw cycle rates in the early stimulation group with the high fresh cycle rate in the late stimulation group may be due to the heterogeneity of the groups and the freeze all criteria. In both groups, OHSS risk, preimplantation genetic screening, fluid accumulation in the endometrium, weak endometrium and social indications were accepted as criteria for freeze-all. The fact that the groups could not be determined randomly may explain the difference in fresh and thaw cycle rates to some extent.

CONCLUSION

In conclusion, ovarian stimulation on the 2nd day of the menstrual cycle appears to provide more favorable IVF outcomes in terms of the total oocyte count, the number of grade 1-2 embryos and the number of fertilized oocytes when compared to ovarian stimulation on the 5th day of the cycle. However, the total gonadotropin dose was lower in those patients receiving ovarian stimulation on the 5th day of the menstrual cycle. In terms of the ultimate goals of IVF, the results of the two groups were similar.

MAIN POINTS

- In PCOS women with infertility, ovarian stimulation starting on the 2nd day of the menstrual cycle appears to provide more favorable IVF outcomes in terms of the total oocyte count and the number of fertilized oocytes.
- In PCOS women with infertility, the total gonadotropin dose is lower in those recipients of ovarian stimulation on the 5th day of the menstrual cycle.
- In PCOS women with infertility, fertilization and oocyte quality were better in those starting treatment on the 5th day.

ETHICS

Ethics Committee Approval: This study was approved by the Clinical Research Ethic Committee of Erciyes University (approval number: 2011-KAEK-80).

Informed Consent: Informed consent was obtained from all individual participants included in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.T., R.Ö., A.Y., Design: N.T., R.Ö., A.Y., Supervision: N.T., R.Ö., Resource: A.Y., Materials: A.Y., Data Collection and/or Processing: R.Ö., A.Y., Analysis and/or Interpretation: R.Ö., A.Y., Literature Search: A.Y., Writing: N.T., R.Ö., A.Y., Critical Review: N.T., R.Ö., A.Y.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016; 106(1): 6-15.
2. Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female infertility, infertility-associated diagnoses, and comorbidities: a review. J Assist Reprod Genet. 2017; 34(2): 167-77.
3. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016; 22(6): 687-708.
4. Choe J, Archer JS, Shanks AL. In vitro fertilization. [Internet]. StatPearls; 2020.
5. Kurzawa R, Ciepiela P, Baczkowski T, Safranow K, Brelik P. Comparison of embryological and clinical outcome in GnRH antagonist vs. GnRH agonist protocols for in vitro fertilization in PCOS non-obese patients. A prospective randomized study. J Assist Reprod Genet. 2008; 25(8): 365-74.
6. Grisendi V, La Marca A. Individualization of controlled ovarian stimulation in vitro fertilization using ovarian reserve markers. Minerva Ginecol. 2017; 69(3): 250-8.
7. Maher JY, Christianson MS. Controlled ovarian stimulation and triggers in in vitro fertilization: protocol personalization key to optimize outcomes. Minerva Endocrinol. 2018; 43(1): 37-49.
8. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004; 19(1): 41-7.
9. Eskew AM, Jungheim ES. A History of Developments to Improve in vitro Fertilization. Mo Med. 2017; 114(3): 156-9.
10. Yang W, Yang R, Yang S, Li J, Tu B, Gao C, et al. Infertile polycystic ovary syndrome patients undergoing in vitro fertilization with the gonadotropin-releasing hormone-antagonist protocol: role of hyperandrogenism. Gynecol Endocrinol 2018; 34(8): 715-8.
11. Spritzer PM, Motta AB, Sir-Petermann T, Diamanti-Kandarakis E. Novel strategies in the management of polycystic ovary syndrome. Minerva Endocrinol. 2015; 40(3): 195-212.
12. Legro RS. Practices in in vitro fertilization. Semin Reprod Med. 2015; 33(2): 61-2.
13. Reichman D, Rosenwaks Z. The difficult in vitro fertilization patient: an individualized approach. Semin Reprod Med. 2015; 33(2): 153-8.
14. Alper MM, Fauser BC. Ovarian stimulation protocols for IVF: is more better than less? Reprod Biomed Online. 2017; 34(4): 345-53.

15. Romar R, Funahashi H, Coy P. In vitro fertilization in pigs: New molecules and protocols to consider in the forthcoming years. Theriogenology. 2016; 85(1): 125-34.

16. Wang P, Zhao J, Jin C, Yu R, Lin J, Zhu R, et al. Comparision of in vitro maturation applied in PCOS and non-PCOS patients undergo stimulated and unstimulated protocols. Zhonghua Fu Chan Ke Za Zhi. 2014; 49(12): 903-8.

17. Paulson RJ. Introduction: Contemporary approaches to alternative ovarian stimulation strategies for in vitro fertilization. Fertil Steril. 2017; 108(4): 555-7.

18. Howie R, Kay V. Controlled ovarian stimulation for in-vitro fertilization. Br J Hosp Med (Lond). 2018; 79(4): 194-9.

19. Zech NH, Zech M, Baldauf S, Comploj G, Murtinger M, Spitzer D, et al. Ovarian stimulation in ART - Unwinding pressing issues. Minerva Ginecol. 2015; 67(2): 127-47.

20. Von Wolff M, Capp E, Jauckus J, Strowitzki T, Germeyer A; FertiPROTEKT study group. Timing of ovarian stimulation in patients prior to gonadotoxic therapy: an analysis of 684 stimulations. Eur J Obstet Gynecol Reprod Biol. 2016; 199: 146-9.

21. Danis RB, Pereira N, Elias RT. Random Start Ovarian Stimulation for Oocyte or Embryo Cryopreservation in Women Desiring Fertility Preservation Prior to Gonadotoxic Cancer Therapy. Curr Pharm Biotechnol. 2017; 18(8): 609-13.

22. Cakmak H, Rosen MP. Random-start ovarian stimulation in patients with cancer. Curr Opin Obstet Gynecol. 2015; 27(3): 215-21.

23. Thakre N, Homburg R. A review of IVF in PCOS patients at risk of ovarian hyperstimulation syndrome. Expert Rev Endocrinol Metab. 2019; 14(5): 315-9.

24. Fischer D, Reisenbüchler C, Rösner S, Haussmann J, Wimberger P, Goeckenjan M. Avoiding OHSS: Controlled Ovarian Low-Dose Stimulation in Women with PCOS. Geburtshilfe Frauenheilkd. 2016; 76(6): 718-26.

25. Palomba S, Falbo A, Carrillo L, Villani MT, Orio F, Russo T, et al. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertil Steril. 2011; 96(6): 1384-90 e4.

26. El Tokhy O, Kopeika J, El-Toukhy T. An update on the prevention of ovarian hyperstimulation syndrome. Womens Health (Lond). 2016; 12(5): 496-503.

27. Lin H, Li Y, Li L, Wang W, Yang D, Zhang Q. Is a GnRH antagonist protocol better in PCOS patients? A meta-analysis of RCTs. PLoS One. 2014; 9(3): e91796.

28. Ohata Y, Harada T, Ito M, Yoshida S, Iwabe T, Terakawa N. Coasting may reduce the severity of the ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome. Gynecol Obstet Invest. 2000; 50(3): 186-8.

29. Cui L, Lin Y, Lin J, Wang F. AMH-based ovarian stimulation versus conventional ovarian stimulation for IVF/ICSI: a systematic review and meta-analysis. Arch Gynecol Obstet. 2020; 301: 913-22.

30. Chen R, Chen S, Liu M, He H, Xu H, Liu H, et al. Pregnancy outcomes of PCOS overweight/obese patients after controlled ovarian stimulation with the GnRH antagonist protocol and frozen embryo transfer. Reprod Biol Endocrinol. 2018; 16(1): 36.

31. Bezirganoglu N, Seckin K, Baser E, Karsli M, Yeral M, Cicek M. Isolated polycystic morphology: Does it affect the IVF treatment outcomes? J Obstet Gynaecol. 2015; 35(3): 272-4.

32. Li HW, Lee VC, Lau EY, Yeung WS, Ho PC, Ng EH. Cumulative live-birth rate in women with polycystic ovary syndrome or isolated polycystic ovaries undergoing in-vitro fertilisation treatment. J Assist Reprod Genet. 2014; 31(2): 205-11.

33. Chen ZJ, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med. 2016; 375: 523-33.

34. Swanton A, Storey L, Mcveigh E, Child T. IVF outcome in women with PCOS, PCO and normal ovarian morphology. Eur J Obstet Gynecol Reprod Biol. 2010; 149(1): 68-71.

35. Kuivasaari-Pirinen P, Hippeläinen M, Hakkarainen H, Randell K, Heinonen S. Cumulative baby take-home rate among women with PCOS treated by IVF. Gynecol Endocrinol. 2010; 26(8): 582-9.

36. Sha T, Wang X, Cheng W, Yan Y. A meta-analysis of pregnancy-related outcomes and complications in women with polycystic ovary syndrome undergoing IVF. Reprod Biomed Online. 2019; 39(2): 281-93.

37. González-Foruria I, Gaggiotti-Marre S, Álvarez M, Martínez F, García S, Rodríguez I, et al. Factors associated with serum progesterone concentrations the day before cryopreserved embryo transfer in artificial cycles. Reprod Biomed Online. 2020; 40(6): 797-80.

38. Pouya K, Şükür YE, İsrafilova G, Özmen B, Sönmezer M, Berker B, et al. hCG day progesterone level has no impact on the frozen thawed embryo transfer cycle outcome. J Gynecol Obstet Hum Reprod. 2021; 50(6): 102120.

CASE REPORT

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The Use of Plasma-Derived Factor VIII in Two Patients Diagnosed with TTP

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Abstract

Thrombotic thrombocytopenic purpura (TTP) develops due to increased von Willebrand factor multimers as a result of a deficiency of the a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 enzyme. It has two forms; acquired or congenital (hereditary and familial). The initial clinical manifestations of this disease have been defined as a pentad consisting of thrombocytopenia, microangiopathic hemolytic anemia, neurological findings, acute renal failure, and fever. The basis of TTP therapy consists of fresh frozen plasma (FFP) and therapeutic plasma exchange (TPE). Our cases were two patients diagnosed with congenital TTP. Plasma-derived factor 8, which is a Factor VIII concentrate, was administered to these patients at a dose of 30 U/kg/week due to the allergic reactions the patients developed during their FFP and TPE treatments, prevention of exposure to the viral agent and ineffective treatment. After this treatment, laboratory parameters improved in case 1 and clinical improvement was achieved. In case 2, however, the desired level of laboratory parameters could not be reached and no clinical improvement was achieved.

Keywords: TTP, plasma-derived factor VIII, ADAMTS-13

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare disease and its annual incidence in the United State of America is less than 4 million.[1] There are 2 forms of TTP; acquired and congenital (hereditary and familial). Acquired TTP occurs almost exclusively in adults and is an autoimmune disorder. The congenital form usually occurs in infancy or early childhood and is known as Upshaw-Schulman syndrome.[2] The initial clinical manifestations of this disease have been defined as a pentad consisting of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurological findings, acute renal failure, and fever. The symptoms of MAHA and the presence of thrombocytopenia are considered as indications of possible TTP. The deficiency of the a disintegrin and metalloproteinase with thrombospondin type 1 motif, member-13 (ADAMTS-13) enzyme, which is the von Willebrand factor (vWF)-cleaving protease, for the pathogenesis of TTP, or an inhibition developed against the ADAMTS-13 enzyme, was first described by Furlan et al.[3] in 1997-1998. TTP can be diagnosed via a diagnostic test which indicates the deficiency of ADAMTS-13. The acute condition of TTP is a life-threatening condition which requires urgent treatment. This treatment is usually initiated without waiting for therapeutic plasma exchange (TPE). TTP treatment is a long-term treatment which often progresses but then relapses.[4] This disease was initially treated with plasma infusions. However, subsequently, daily TPE was found to be more effective, and it has thus become the standard treatment. In this way, the overall mortality rate had decreased to less than 10%.[5] Corticosteroids are often used in addition to TPE and help control the antibodies which act as inhibitors. Cyclosporine, azathioprine, and vincristine have been included in other adjunctive treatments aimed

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at reducing inhibitors.[6] After the relationship between ADAMTS-13 deficiency and TTP became clear, the use of recombinant ADAMTS-13, which increases ADAMTS-13 activity and reduces the level of inhibitors, was brought to the agenda. In one study carried out along these lines, ADAMTS-13 activity was found to be high in the medication called plasma-derived factor 8, which is a plasma-derived factor VIII concentrate used in hemophilia A patients.[7] In our study, we aimed to present two cases where we employed plasma-derived factor 8 treatment as an alternative treatment in congenital TTP.

CASE PRESENTATION

Case-1

A 13-year-old female was suspected of having TTP disease at the center where she presented with schistocytes in peripheral smear, and epileptic seizures [hemoglobin (Hgb): 9 g/dL (13.5-17.5 g/dL), platelet: 92,000/mcL (150,000-450,000/mcL), and lactate dehydrogenase (LDH): 567 IU/L (0-248 IU/L)]. The patient's ADAMTS-13 activity was found to be less than 10%, and the patient was diagnosed with TTP as a result. Clinical improvement was achieved in this patient who had no family history of TTP after treatment with fresh frozen plasma (FFP) and broad-spectrum antibiotics. Afterward, she was treated with FFP transfusions every 28 days for 12 years to maintain her platelet count at a level of >100,000/mcL. The patient presented to the emergency department of our hospital at the age of 25 with the complaint of speech difficulty, drowsiness, and jaundice (serum creatinine: 1.9 mg/dL (0.6-1.2 mg/dL), Hgb: 8.1 g/dL, platelet: 56,000/mcL, and LDH: 352 IU/L). Upon the detection of schistocytes in the peripheral smear, it was accepted that she had an acute exacerbation of TTP. TPE transfusions were then increased to maintain the >100,000/mcL platelet count. In this patient, who developed urticarial rash and pruritus with FFP, premedication was started. However, the patients continued to have similar complaints despite this premedication, and thus it was decided to administer plasma-derived factor 8 to the patient after obtaining off-label consent. Plasma-derived factor 8 was administered under service conditions with a dose of 30 U/kg/week. The patient tolerated the infusions without presenting with any allergic reactions. Platelet reached 151,000/mcL from 115,000/mcL 24 hours after infusion. During the first 4 weeks of this treatment, platelet counts were closely monitored and dose titration was performed to maintain the >100,000/mcL platelet count. Each week, the patient tolerated plasma-derived factor eight 1x1,500 unit infusions without any complications. The patient was able to self-administer the medication on her own at home. No thrombotic and renal complications were observed in this patient during the period of the use of this medication.

Case-2

A 31-year-old female patient presented to the hospital with a complaint of headache, weakness, and jaundice. TTP was suspected after her test results revealed Hgb: 7.8 g/dL, platelet: 64,000/mcL, LDH: 427 IU/L, serum creatinine: 1.7 mg/dL, and schistocytes in peripheral smear. The patient's ADAMTS-13 activity was found to be less than 10%, and the patient was diagnosed with TTP as a result. Plasmapheresis was performed 8 times in total on this patient, who had no family history of TTP. The patient was then followed up every 28 days by administering 3 units of FFP. The need for FFP was increased due to her low Hgb levels and the continuing thrombocytopenia, which were determined during check-ups. However, plasma-derived factor 8 was initiated instead at a dose of 30 U/kg/week due to the dose-dependent allergic effects of FFP and the necessity to treat the patient in the hospital. The plasma-derived factor 8 dose was increased to 40 U/kg/week since her platelet count could not reach >100,000/mcL, yet still the desired platelet and Hgb response could not be obtained. For this reason, plasma-derived factor 8 treatment was discontinued and 3 units of FFP treatment were continued instead once every 2 weeks.

DISCUSSION

TTP develops as a result of vWF multimers accumulating due to a deficiency of the ADAMTS-13 enzyme, which is congenitally included in the metalloproteinase family, or as a result of acquired inhibition.[8] vWF multimers have a highly prothrombotic structure and lead to platelet aggregation and multi-organ microthrombus. Symptoms may appear during infancy.[9] Recurrent hemolytic anemia can progress with attacks of thrombocytopenia or life-threatening thrombosis afterwards.[10] FFP infusions (10 to 15 mL/kg) may partially remedy the ADAMTS-13 deficiency or enable remission. However, prophylactic FFP infusions frequently require treatment under hospital conditions and also increase the risks associated with transfusion reactions and pathogens.[11] Associated allergic reactions and exposure to viral agents suggest that other treatment modalities can be applied instead of FFP transfusions, which are the standard treatment in congenital TTP. Concentrated treatments which are virally inactivated may be more appropriate, especially in a smaller volume. In the study conducted by Aledort et al.[12], 8 congenital TTP patients were administered plasma-derived factor 8 treatment without any problems. They did not present with any allergic reactions and did not require the use of a central venous catheter. It has been stated that the plasma-derived factor 8 treatment is to be titrated prophylactically to be administered in the range of 2 times per week up to once every 3 weeks.[12] Allford et al.[13], studied the ADAMTS-13 levels in plasma-derived factor VIII products and recombinant factor VIII. Plasma-derived factor 8, a product of factor VIII, was determined to yield 100% activity for ADAMTS-13 efficacy. Plasma-derived factor 8, which is used in hemophilia A patients, is a medium purity plasma-derived recombinant factor VIII concentrate. The amount of ADAMTS-13 is 900% higher in plasma-derived factor 8 compared to FFP.[13] Lester et al.[14] successfully treated a 14-year-old girl who had been diagnosed with congenital TTP and was, therefore, being treated with FFP every 2 weeks for 10 years with BPL8Y, which is another preparation with a high amount of ADAMTS-13. In another patient who was administered plasma-derived factor 8 due to TTP, the ADAMTS-13 activity level increased from 2% to 8% after a single infusion and the number of continuous platelets increased. Even a small increase in protease activity provides clinical benefits. More importantly, in fever-related attacks, a good amount of control was achieved with the administration of additional doses.[15] In case 1, effective treatment was provided with plasma-derived factor 8 as was the case in the other studies available in the literature. However, in case 2, plasma-derived factor 8 was initiated at a dose of 30 U/kg/week, then this dose was increased to 40 U/kg/week since the desired platelet count of >100,000/mcL could not be reached, and yet the desired platelet and Hgb response was still not obtained. Contrary to other cases reported in other studies available in the literature, administering even increased doses of plasma-derived factor 8 did not yield an effective treatment in case 2. Therefore, her treatment was continued with FFP and TPE. The main limitation of our study was not checking the post-treatment ADAMTS-13 levels of our cases.

We report an alternative treatment approach for a patient with TTP who was intolerant of FFP infusions. The potential advantages over the current standard use of FFP are a much smaller volume infused to the patients and a lower risk of transmission of blood-borne infections. In addition, due to the reduction of complications with, the hospitalization process is decreased and so this treatment option may be more cost-effective. However, plasma-derived factor 8 treatment did not produce any results in our second case, and this case is, in fact, the only case to date in the literature where effective treatment was not achieved with plasma-derived factor 8. Thus, the use of plasma-derived factor 8 in TTP patients should be evaluated taking into consideration these cases as well as other similar cases.

ETHICS

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.N.K., G.İ., H.K., Design: M.N.K., G.İ., H.K., Supervision: M.N.K., G.İ., H.K., Materials: M.N.K., G.İ., H.K., Data Collection and/or Processing: M.N.K., G.İ., H.K., Analysis and/or Interpretation: M.N.K., G.İ., H.K., Literature Search: M.N.K., G.İ., H.K., Writing: M.N.K., G.İ., H.K., Critical Review: M.N.K., G.İ., H.K.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. J Clin Apher. 2013; 28(3): 145-284.
2. Rennard S, Abe S. Decreased cold-insoluble globulin in congenital thrombocytopenia (Upshaw-Schulman syndrome). N Engl J Med. 1979; 300(7): 368.
3. Furlan M, Robles R, Solenthaler M, Wassmer M, Sandoz P, Lämmle B. Deficient activity of von Willebrand factor-cleaving protease in chronic relapsing thrombotic thrombocytopenic purpura. Blood. 1997; 89(9): 3097-103.
4. Bandarenko N, Brecher ME. United States Thrombotic Thrombocytopenic Purpura Apheresis Study Group (US TTP ASG): multicenter survey and retrospective analysis of current efficacy of therapeutic plasma exchange. J Clin Apher. 1998; 13(3): 133-41.
5. Henon P. Treatment of thrombotic thrombogenic purpura. Results of a multicenter randomized clinical study. Presse Med. 1991; 20(36): 1761-7.
6. Cataland SR, Jin M, Lin S, Kennedy MS, Kraut EH, George JN, et al. Cyclosporin and plasma exchange in thrombotic thrombocytopenic purpura: long-term follow-up with serial analysis of ADAMTS13 activity. Br J Haematol. 2007; 139(3): 486-93.
7. Plaimauer B, Kremer Hovinga JA, Juno C, Wolfsegger MJ, Skalicky S, Schmidt M, et al. Recombinant ADAMTS13 normalizes von Willebrand factor-cleaving activity in plasma of acquired TTP patients by overriding inhibitory antibodies. J Thrombosis Hemostasis. 2011; 9(5): 936-44.
8. Rieger M, Mannucci PM, Kremer Hovinga JA, Herzog A, Gerstenbauer G, Konetschny C, et al. ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. Blood. 2005; 106(4): 1262-7.
9. Tsai HM. Thrombotic thrombocytopenic purpura: a thrombotic disorder caused by ADAMTS13 deficiency. Hematol Oncol Clin North Am. 2007; 21(4): 609-23.
10. Veyradier A, Obert B, Houllier A, Meyer D, Girma JP. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. Blood. 2001; 98(6): 1765-72.
11. Peyvandi F, Ferrari S, Lavoretano S, Canciani MT, Mannucci PM. von Willebrand factor cleaving protease (ADAMTS-13) and ADAMTS-13 neutralizing autoantibodies in 100 patients with thrombotic thrombocytopenic purpura. Br J Haematol. 2004; 127(4): 433-9.
12. Aledort LM, Singleton TC, Ulsh PJ. Treatment of Congenital Thrombotic Thrombocytopenia Purpura: A New Paradigm. J Pediatr Hematol Oncol. 2017; 39(7): 524-7.
13. Allford SL, Harrison P, Lawrie AS, Liesner R, Mackie IJ, Machin SJ. Von Willebrand factor--cleaving protease activity in congenital thrombotic thrombocytopenic purpura. Br J Haematol. 2000; 111(4): 1215-22.
14. Lester WA, Williams MD, Allford SL, Enayat MS, Machin SJ. Successful treatment of congenital thrombotic thrombocytopenic purpura using the intermediate purity factor VIII concentrates BPL 8Y. Br J Hematol. 2002; 119(1): 176-9.
15. Naik S, Mahoney DH. Successful treatment of congenital TTP with a novel approach using plasma-derived factor VIII. J Pediatr Hematol Oncol. 2013; 35(7): 551-3.

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