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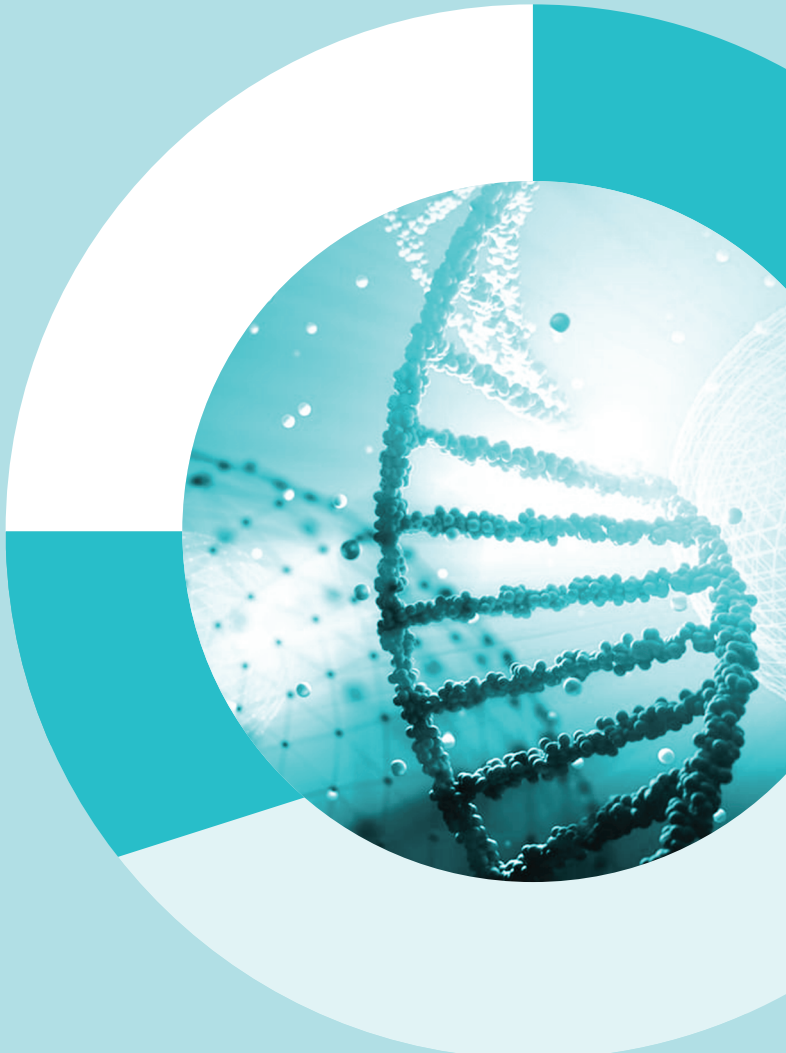

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REVIEW

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Optical Behavior of Zirconia Generations

Dilem Toksoy, Özay Önöral

Department of Prosthetic Dentistry, Near East University Faculty of Dentistry, Nicosia, North Cyprus

Abstract

The lack of a glassy matrix in the crystalline structure causes high opacity in 3 mol% yttria-doped tetragonal zirconia polycrystals (zirconia generation I). Physically, it has a high refractive index, which leads to high amounts of total reflection. The orientation of tetragonal crystals can cause birefringence, which alters the refractive index. This high reflection tends to produce a mirror-like surface, thereby leading to poor esthetics. To overcome this drawback, zirconia-generation I was veneered with feldspathic ceramics. However, the frequent occurrence of catastrophic failures in veneered ceramics has culminated in the emergence of monolithic zirconia. However, there has been a lack of study into the optical properties of contemporary zirconia generations; thus, the purpose of this review article is to examine light patterns in non-metallic materials, define zirconia generations based on their optical qualities, and explore the parameters that influence the optical properties of zirconia ceramics.

Keywords: Zirconia, translucency, contrast ratio, optical properties

INTRODUCTION

Zirconia, which is a bioinert polymorphic ceramic, has become a popular restorative material owing to its advantageous features, such as chemical inertness, superb biocompatibility, low tendency for bacterial adhesion, and a coefficient of thermal expansion comparable to enamel and dentine.[1] However, it is extremely hard (Vickers: ~12.7 GPa),[2] with a high melting point (~2690 °C),[3] modulus of elasticity (~210 GPa),[4] and high opacity.[5,6]

It displays 3 distinct crystallographic forms [monoclinic (M), tetragonal (T), and cubic (C)-phases], known as allotropism, in dependence on temperature and preserves its T-phase at room temperature owing to its stabilization with alloying metal oxides such as yttrium oxide. The transformations among these allotropes are martensitic and a-thermal.[5,7,8] When it is stressed, T→M (transformation from T- to M-phase) occurs, which is related to a volumetric increase (4.5%). This compresses the crack flaws and inhibits further propagation, thereby exhibiting superior mechanical service (transformation-toughening trait).[9,10] Although 3 mol% yttria-doped tetragonal zirconia polycrystal (3Y-TZP) remains a popular choice, numerous other polycrystalline zirconia materials have emerged for dental applications.

Studies on the optical characteristics of zirconia generations are scarce. This article aims to scrutinize light patterns in non-metallic materials, define zirconia generations and their optical properties, and discuss the parameters that influence the optical properties of zirconia ceramics.

Light Patterns in Non-Metallic Materials

When light hits a polycrystalline material, some of it passes through (transmission), some reflects off the surface because of its surface roughness, and some is either scattered or absorbed within the material.[11-13]

The light transmission qualities of non-metallic materials are affected by electronic polarization and electron transitions between the valence and conduction bands. These materials with varying bandgaps might appear opaque, opaque-colored, or transparent-colored.[12,14,15] Non-metallic materials with bandgaps greater than 3.1 eV are typically transparent to light. However, electrical polarization can cause minimal light absorption, resulting in a translucent appearance and diffuse light transmission.[12,15]

The transmittance of light is affected by three parameters: the absorption coefficient, scattering coefficient, and scattering anisotropy

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ORCID IDs of the authors: D.T. 0000-0002-2230-2822; Ö.Ö. 0000-0002-5264-9376.

Address for Correspondence: Dilem Toksoy
E-mail: dilem.toksoy@neu.edu.tr
ORCID ID: orcid.org/0000-0002-2230-2822

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factor of the material.[16] The scattering anisotropy factor is the average scattering angle value, which measures how much light is forward scattered (translucency) or backward scattered (opacity) during a single scattering event. The higher the number of scattering events, the more homogeneous the transition of light from anisotropic to isotropic.[12,15] The transport coefficient is calculated by adding the absorption and scattering coefficients, which attenuate the transmitted light. Non-ideal materials have a reduced scattering coefficient, which combines the three aforementioned parameters. The reduced scattering coefficient denotes the proportion of forward-scattered light without absorption. Longer wavelengths in zirconia lead to more forward-scattered light in the visible spectrum.[12,15,16] It can be highlighted that multiple internal and external parameters can influence the optical properties of zirconia ceramics.[11,15,17,18] Zirconia exhibits low translucency with elevated opacity. The contrast ratio of zirconia was estimated at 1.[19]

Zirconia Generation

Generation I

The first generation of polycrystalline zirconia (3Y-TZP) has been successfully used for years in the fabrication of all-ceramic restorations.[9,20] The components like yttrium oxide (4.5< x ≤6 wt%), hafnium oxide or hafnia (≤5.0 wt%), aluminum oxide or alumina (0.5-1.0 wt%), and other oxides (calcium oxide and magnesium oxide) (≤1.0 wt%) are incorporated into the zirconium oxide lattice (88-95.5 wt%).[21] The yttrium III ion has a radius of 104 pm, which is significantly larger than that of the zirconium cation (86 pm). Although this results in significant distortion, the yttrium III ion is related to C structure stabilization.[22,23] Hafnium oxide is isomorphic to zirconia, and the crystal ionic radius of hafnium ion (85 pm) is nearly identical to the radius of quadrivalent zirconium (86 pm), allowing for optimal solid solubility.[24] Alumina is often employed in formulations, although its solubility in zirconia is poor due to aluminum cation's short ionic radius of ~68 pm.[25] This inclusion increases densification during sintering, potentially by enhancing ion mobility, and it also has favorable effects on fracture toughness when the concentration is kept low. It is also helpful to reduce the detrimental low-temperature degradation (LTD).[11,26] The sintered 3Y-TZP material contains nearly 98% metastable T-phase.[27]

Because 3Y-TZP is partially stabilized although it is in the T-phase at room temperature, its internal structure contains energy to transform into the M-phase.[28] If 3Y-TZP is subjected to stress or any force, cracking occurs in its structure; T-crystals begin to shift to the M-phase and a 3-5% increase in volume occurs. This volume increase prevents crack progression by creating compressive stresses. This phenomenon, namely "transformation toughening", provides superior mechanical properties to 3Y-TZP.[15,29,30] The typical grain size is reported as 0.5 µm and the aforementioned martensitic transformation depends on the grain size.[15] The grain size determines the stability and mechanical properties of zirconia ceramic.[31] High sintering temperatures and long sintering times cause particle sizes to increase.[8] When the grain size is less than the critical size (<0.3 µm), zirconia loses its capacity to T→M during crack propagation, resulting in lower toughness.[15,32]

Zirconia ceramics are also susceptible to LTD, which can be accelerated by processing procedures, humidity, stress, and low temperatures (200-300 °C. Because yttrium is triatomic and contains oxygen vacancies, water can enter the zirconia lattice a hygroscopic medium.[33] Initially, this diffusion can produce lattice contraction, which concentrates tensile stresses on the surface of the zirconia grains, causing the T→M. This generates micro-fissures, which allow water molecules to penetrate further into the innermost grains, and therefore T→M of the superficial layer advances deeper into the bulk of the material, creating macro-cracks. This phenomenon may be influenced by grain size, the proportion of stabilizer, residual tension, and manufacturing flaws.[33-35]

3Y-TZP restorations also exhibit high opacity due to the lack of a glassy matrix in the crystallographic structure.[29,36] From a physical perspective, it has a high refractive index, resulting in high total reflection. The orientation of T-crystals can generate birefringence, which leads to changes in the refractive index (Figure 1).[8,9] This high reflection tends to produce a mirror-like surface that causes poor esthetics. This can be explained by the T grains, which are optically anisotropic.[11,26,37,38] Moreover, a high amount of small crystalline grains, possible pores, and precipitated aluminum oxide lead to a further deterioration in translucency by forming excessive interfaces that act as scattering zones.[11,18,39] To circumvent these poor esthetic characteristics, it has been suggested to be used only as a coping in fixed prosthetic restorations and to be veneered with low-fusing feldspathic porcelain (bilayer manner).[8,29,40] Although several catastrophic complications including cracking, chipping, and delamination have been reported; these restorations have been produced in this manner for decades, up until 2014.[29,41] The main reason for these complications is the difference in thermal expansion coefficient between zirconia and low-fusing feldspathic porcelain, followed by firing shrinkage, poor wetting, overloading, fatigue, and insufficient coping design.[8,41]

With the development of full-contour (monolithic) zirconia restorations that do not require veneering (monolayer manner), an important contribution has been made to eliminating catastrophic complications.[29,41] Moreover, these restorations save dental tissue, provide superior fracture resistance, and can be preferred in patients with limited inter-occlusal space, as only a 0.5 mm occlusal thickness is sufficient to withstand high masticatory forces.[41] Different ways for individualizing restoration, such as embedding in coloring liquids, the addition of metallic pigments to the preliminary zirconia powder, or painting zirconia with liners, are in use; however, the optical properties of these restorations were still unsatisfactory, and new generations were necessary.[8] In the past 10 years, serious progress has been made, and manifold zirconia materials offering different optical and mechanical characteristics, concerning differences in their chemistries and notably stabilizer content, have been developed (Table 1)[8,38].

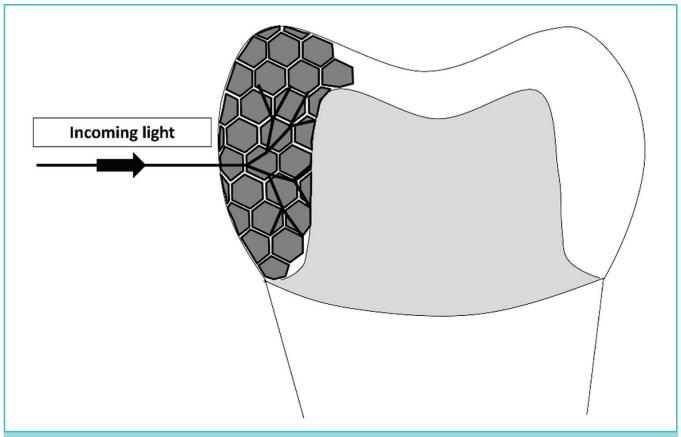

Figure 1. Light patterns of zirconia.

Generation II

The studies carried out on new-generation zirconia ceramics have been aimed at obtaining a more esthetic and translucent material without compromising superior mechanical properties as much as possible.[42] The 2nd generation (3Y-TZP with modified alumina content) has been introduced, which shows the same amount of yttria as the first generation 3Y-TZP. However, the 2nd generation 3Y-TZP exhibits some difference in the degree of light transmittance by reducing the aluminum oxide content from 0.25 to 0.05% by weight and also by reducing the aluminum oxide particle sizes and repositioning them at the zirconia grain boundaries.[20,43-46] With this modification, the aluminum oxide ratio fell below 0.05%. It has been observed that although this attempt slightly weakens the mechanical properties by making the T-phase of the material less stable, causing it to be more sensitive to LTD; it also contributes to a slight increase in translucency.[42,43,47]

Another approach to improve zirconia translucency involves the addition of 0.2 mol% lanthanum (III) oxide to the material.[5,47] The addition of lanthanum (III) oxide to 3Y-TZP improved translucency but weakened the mechanical properties.[7] In studies investigating approaches in which the aluminum oxide or lanthanum (III) oxide contents in zirconia are modified while the amount of yttrium oxide (3 mol%) remains constant, it has been observed that translucency is still insufficient for anterior restorations.[5,7]

Generation III

5Y-TZP subgeneration

The increasing demand for esthetics has led to the development of 3rd generation zirconia-based ceramics, in which the C-phase content of the material is increased by adding a greater amount of stabilizing oxide.[9] Third-generation zirconia was introduced in 2015 and thus fulfilled the esthetic desire expected from the material with its high yttria content of 5 mol%.[8,38,43]

4Y-TZP subgeneration

Since the 5Y-TZP sub-generation could not meet the desired mechanical requirements in long-span restorations, a 4 mol% yttria-stabilized (4Y-TZP) material with an approximately 30% C-phase content proportional to T-phase content was developed as a middle point between the second generation and 5Y-TZP sub-generation.[43,48] Translucent zirconia containing 4 or 5 mol% yttria has a flexural strength of 600-900 MPa and a fracture strength of 2.2-4.0 MPa(m).[49]

>5Y-TZP subgeneration

They have a larger yttrium oxide concentration and hence more C-phase in proportion to the T-phase, which renders the structure more stable and resistant to hydrothermal aging, making it less vulnerable to LTD.[8,11,43,50] The key explanation for the increased translucency is the isotropic feature of the C-phase, which reduces the optical scattering coefficient and inhibits the birefringence of the current T-phase.[43,51] This characteristic means that the incoming light is spread more evenly in all spatial directions.[8] The translucency is also affected by the microstructure. The fact that C-crystals have a larger volume than T-crystals results in a decrease in the number of grain boundaries, which improves the translucency properties of the material.[48] The higher the sintering temperature and yttria content, the higher the C-crystal phase ratio in zirconium dioxide.[43] In addition to improved optical properties, the fact that the material contains C-crystals in a stable structure results in a lower or no transformation toughening ability, which occurs with the T→M as a result of tension, resulting in disadvantages such as a decrease in the flexural and fracture strength of the material.[43,45,52] Carrabba et al.[50] Observed an inverse relationship between resistance and translucency in zirconia ceramics.

Generation IV

As a solution to improving the esthetic properties of monolithic zirconia restorations with a monochromatic structure, 4th generation multi-layer/multi-chromatic zirconia blanks consisting of layers with different tones and translucency gradients have been developed.[9,18] While translucency/color transition creates a masking effect in the cervical region, it imitates the optical properties of dentin tissue in the middle region and enamel tissue in the incisal region. Multi-layer/multi-chromatic zirconia blanks can have three or four different tone layers (enamel, first transition, second transition, and dentin or body).[18,53] From the cervical to the incisal regions, tones can have up to seven layers and a visible light transmittance percentage of 44% to 49%.[18]

Parameters Influencing the Optical Characterization of Zirconia

The optical characteristics of zirconia restorations are influenced by both intrinsic (fabrication process) and extrinsic (laboratory procedures and clinical variables) factors.[15,17,18] While fabrication processes dictate the basic optical properties of zirconia ceramics, diverse laboratory operations performed on zirconia ceramics may result in optical alterations in the material (Figure 2).[18,54]

Intrinsic Parameter 1: Blank Fabrication

During the fabrication, some parameters, such as the chemical purity of the powder, type of pressing applied, particle properties, additives added to the structure, and pre-sintering process applied, have a very important effect on determining the final optical properties of the material.[39]

Intrinsic Parameter 2: Microstructure

Y-TZP optical performance can be improved through a variety of microstructural modifications, including increasing the yttria content, lowering or eliminating aluminum oxide doping, improving the sintering conditions, minimizing residual porosities, and producing a nanometric microstructure.[29]

Intrinsic Parameter 3: Particle Size and Grain Boundary Effect

In the light spectrum, the wavelength of visible light is between 300 and 700 nm, and in daylight it is approximately 555 nm. The largest scattering is recorded when the particle size is similar to the wavelength of visible light.[39] When the particle size and light wavelength are in close range; as the particle size increases, light scattering will increase and the translucency of the material will decrease. However, if the particle size is much larger than the wavelength of light, scattering decreases as the particle size rises, independent of wavelength.[18,39,54] Materials containing particles smaller than approximately 0.1 μm appear more translucent due to less reflection and absorption when exposed to visible light wavelengths than materials containing larger particles.[32,39] On the other hand, in materials with particle sizes larger than 10 μm, light encounters fewer grain boundaries because of the low number of particles in unit volumes, and less light reflection occurs, thus reducing opacity.[39] While translucency is provided by high diffusion transmission

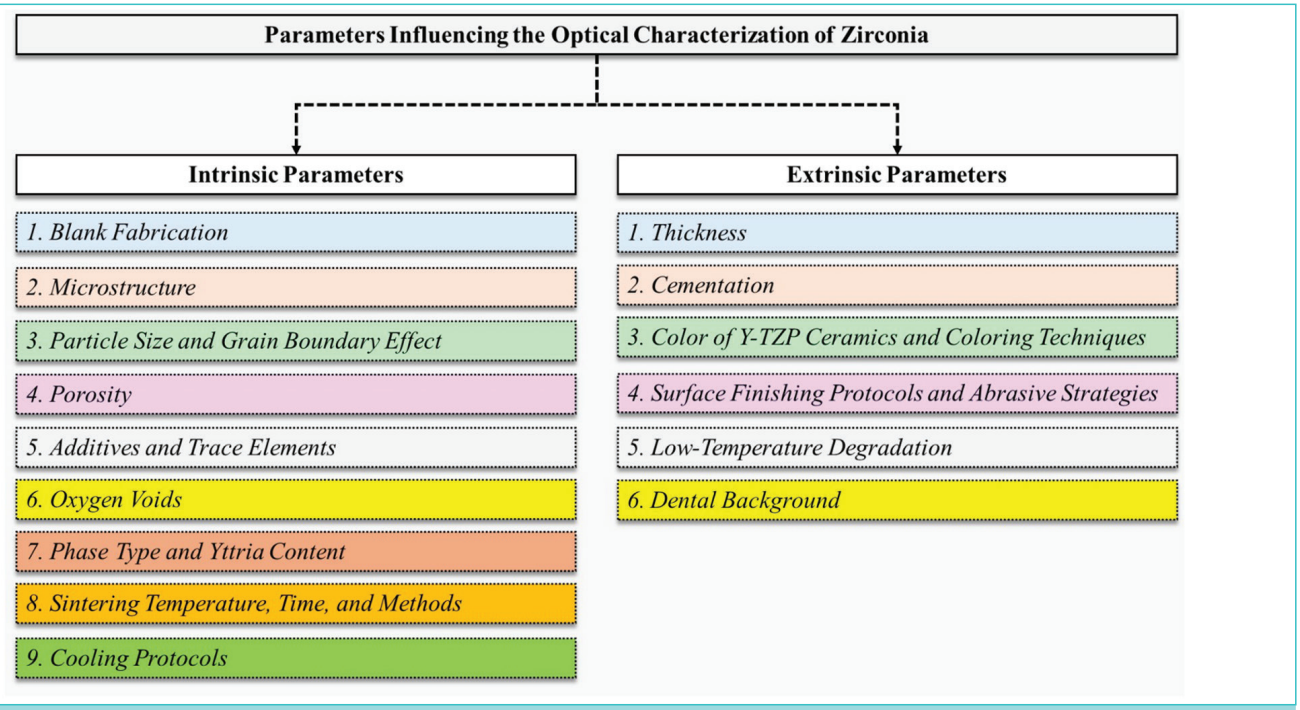

Figure 2. Parameters influencing the optical characterization of zirconia.

in materials with large particle sizes; in materials with small particle sizes, high in-line transmission is achieved.[55] When particle diameters are between 0.01 and 0.1 µm, translucency is provided by in-line transmission, and the material exhibits a translucent to transparent appearance. While grain boundary scattering is observed at particle diameters of 0.1-1.0 µm, diffuse transmission is observed at particle diameters of 1-10 µm and the material is largely translucent.[39,56]

Intrinsic Parameter 4: Porosity

Porosities can be intergranular or intragranular and exhibit different optical properties from each other.[12,15] Intergranular porosities are the porosities between particles with different orientations and are typically considered as amorphous defect regions in the form of voids located in different directions on the grain boundaries between two or three crystalline particles. Intragranular porosities are porosities found within the particles and represent separate interfaces between two effective isotropic phases.[11,12,15] Reducing the particle size tends to reduce the porosity size proportionally. In addition, with smaller particle sizes, it becomes easier to remove the gas trapped in the intragranular porosities, thereby preventing the removal of the porosities.[12] Partial or complete elimination of porosity occurs during condensation, which is driven by ionic diffusion at high temperatures.[15]

Intrinsic Parameter 5: Additives and Trace Elements

Additives in Y-TZP ceramics, such as aluminum oxide, scandium oxide, neodymium oxide, lanthanum (III) oxide, magnesium oxide, hafnium oxide, sodium oxide, silicon dioxide, iron oxide, calcium oxide, yttrium oxide, and germanium oxide, that can be used as oxides can cause segregation on the grain boundaries of zirconium dioxide and can affect the translucency of the material.[7,15,39] It is known that aluminum oxide added to the structure of zirconia helps the chemical stability of zirconia, minimizes the LTD potential that may occur in the oral environment, reduces the required sintering temperature and time, and increases the densification of Y-TZP ceramics by creating fine-particle and homogeneous microstructures.[11,26] On the other hand, aluminum oxide and zirconium dioxide have different refractive indices and the presence of aluminum oxide inclusions, which are accepted as important scattering centers by increasing light scattering between the two materials; it causes the zirconia material to show low translucency. Therefore, it has been suggested to eliminate aluminum oxide or reduce its concentration to increase translucency.[11,18] The refractive indices of aluminum oxide and zirconium dioxide at 600 nm wavelength are 1.77 and 2.22, respectively.[11,18,57] Developers focused on increasing translucency by reducing the aluminum oxide content from 0.25% to less than 0.05% and minimizing light refraction.[5,11,26] Although it was observed that reducing aluminum oxide below 0.25% by weight prevented the formation of particles acting as light scattering centers; it has been suggested that, due to the advantageous properties of aluminum oxide in its material structure, completely removing it from the structure is not a good option. In addition, studies have shown that zirconia without aluminum oxide does not show any difference in translucency compared to zirconia with reduced aluminum oxide content and that only reducing the amount of aluminum oxide rather than completely removing it from the structure is sufficient to produce a more translucent material.[9]

Zhang et al.[58] Devised a different method for creating zirconia that is highly translucent, strong, and resistant to aging. Compared with quadrivalent zirconium, trivalent ions with larger radii were considered to be additives. Researchers reported that trivalent additives such as lanthanum cations from lanthanum (III) oxide added to quadrivalent zirconium exhibited significant segregation at the zirconium dioxide grain boundary. The use of lanthanum (III) oxide as an auxiliary doping oxide increases the possibility of obtaining a microstructure with smaller particles and improves optical properties due to the

small particle size, narrow grain boundary width, and reduction in birefringence.[39,58] The incorporation of lanthanum (III) oxide (0.2 mol%) into standard aluminum oxide (0.1-0.25 wt%) doped 3Y-TZP yielded an average translucency, better hydrothermal stability, and excellent mechanical characteristics.[11,39] On the other hand, the addition of 0.2 mol% lanthanum (III) oxide to 0.1 wt% aluminum oxide-doped Y-TZP significantly improved the translucency.[12] Researchers observed that adding 0.2 mol% lanthanum (III) oxide to 0.1 wt% aluminum oxide-doped 3Y-TZP resulted in 42% higher translucency compared to conventional 0.25 wt% aluminum oxide-doped 3Y-TZP. [39]

Transition and rare-earth metals can be used in the composition of additives because they give color tones to colorless oxides. The study on zirconia color improvement has focused on the influence of incorporating ferric oxide or employing 3Y-TZP nanopowders on the microstructure and mechanical characteristics.[12,15] A study examining the mechanochemical processing of praseodymium-doped 3Y-TZP nanopowders showed that this additive is promising, exhibiting good esthetic results and biocompatibility. Since zirconium ions are tetravalent, divalent, or trivalent (e.g. trivalent yttrium, divalent iron, trivalent iron (added to the structure to prevent the T→M), divalent nickel, trivalent chromium); positively charged stabilizing additives must be charge-balanced. The value, concentration, ionic radius, and applied sintering temperature of the additives added to the zirconia structure can affect the defect distribution, defect stability, and therefore optical properties.[12]

Intrinsic Parameter 6: Oxygen Voids

Since the value of quadrivalent zirconium is smaller than that of yttrium (III) ions added to the structure for stabilization, oxygen voids are formed within the structure, and when the amount of these

Table 1. Commercial examples of zirconia from different generations

Material	Generation					Brand
	3Y-TZP	4Y-TZP	5Y-TZP	>5Y-TZP	ML/MC	
Ceramill zolid FX	-	-	-	5.3-5.5%	5-5.5%	Amann Girrbach
Prettau 4 Anterior	-	-	-	7%	-	Zirkonzahn GmbH
Prettau 4 Anterior Dispersive	-	-	-	-	7%	Zirkonzahn GmbH
Lava Plus	3%	-	-	-	-	3M ESPE
Lava Esthetic Zirconia	-	-	5%	-	-	3M ESPE
IPS Emax ZirCAD Multi	-	4%	-	-	4-5%	Ivoclar Vivadent Inc.
VITA YZ HT	3%	-	-	-	-	VITA Zahnfabrik
VITA YZ ST	-	4%	-	-	4%	VITA Zahnfabrik
VITA YZ XT	-	-	5%	-	5%	VITA Zahnfabrik
CopraSupreme	-	4%	-	-	4%	Whitepeaks
CopraSmile	-	-	-	5.4%	5.4%	Whitepeaks
CopraSmile Symphony	-	-	4.8-5.3%	-	4.8-5.3%	Whitepeaks
CopraSupreme Symphony	-	4%	-	-	4%	Whitepeaks
Zenostar T	3%	-	-	-	-	Wieland Dental
Zenostar MT	-	4%	-	-	-	Wieland Dental
DD Bio ZX² - HT	3%	-	-	-	-	Dental Direkt GmbH
DD cube ONE- HT⁺	-	4%	-	-	-	Dental Direkt GmbH
DD cubeX² SHT	-	-	5%	-	5%	Dental Direkt GmbH
Cercon HT	3%	-	-	-	3-5%	Dentsply Sirona
Cercon XT	-	-	5%	-	5%	Dentsply Sirona
inCoris TZI	3%	-	-	-	-	Dentsply Sirona
BruxZir Full Strength	3%	-	-	-	-	Glidewell Direct
BruxZir Esthetic	-	4%		-	-	Glidewell Direct
BruxZir Anterior	-	-	5%	-	-	Glidewell Direct
KATANA Zirconia HT & ML	3%	-	-	-	3%	Kuraray Noritake Dental Inc.
KATANA Zirconia HTML Plus	-	-	5%	-	5%	Kuraray Noritake Dental Inc.
KATANA Zirconia STML	-	4%	-	-	4%	Kuraray Noritake Dental Inc.
KATANA Zirconia UTML	-	-	5%	-	5%	Kuraray Noritake Dental Inc.
KATANA Zirconia YML	-	-	-	-	3-5%	Kuraray Noritake Dental Inc.
Shofu Disk ZR Lucent	-	-	5%	-	-	Shofu Inc.
Shofu Disk ZR Lucent Supra	-	-	-	-	3-5%	Shofu Inc.

Data was collected from the manufacturers' websites and brochures. HT: High translucent, ST: Super translucent, XT: Extra translucent, T: Translucent, MT: Medium translucent, HT⁺: High translucent plus, SHT: Super high translucent, ML: Multi-layer, HTML: High translucent multilayered, STML: Super translucent multilayered, UTML: Ultra translucent multilayered, YML: Yttria multilayered, ZR: Zirconia.

voids increases, defect clusters that damage optical performance may occur.[12,47] Moreover, uncontrolled heating or sintering processes performed in an environment in which reactions are reduced have a significant effect on the formation of oxygen voids. They serve as light-scattering centers within the structure and reduce the translucency of the material. Therefore, it is important to control the heat treatment to reduce the number of oxygen voids in the material.[18,39]

Intrinsic Parameter 7: Phase Type and Yttria Content

Unstable zirconia crystal structures change with temperature.[7] The M-phase can act as a defect in the zirconium dioxide microstructure, and these defects can reduce translucency by increasing the scattering of incoming light.[39] The addition of stabilizing oxides to unstable zirconia can limit phase transitions and help stabilize the material in the C- or T-form at room temperature.[7] Conventional 3Y-TZP consists of 5.18% yttria (3 mol%) by weight and 90% or more of the T-phase.[18,47] The birefringence of T zirconia, as well as its anisotropic refractive index in distinct crystallographic directions, limit the material's light transmittance by causing reflection and refraction at grain boundaries.[26] A new approach to increasing the translucency of zirconia has been determined to develop a new generation of zirconia materials with an isotropic C-phase, which reduces light scattering from birefringent grain boundaries.[5,32] Higher yttrium oxide content tends to increase the amount of the optically isotropic C-phase in the zirconium dioxide structure, which makes light scattering at grain boundaries less critical, regardless of particle size, and improves optical properties by increasing translucency.[7,11,58] Cho et al.[10] reported that the increase in yttria (mol%) in the zirconia material significantly increased the TP value, and 5Y-TZP exhibited approximately 80% translucency at a thickness of 0.8 mm and approximately 89% translucency at a thickness of 1.5 mm, compared to lithium disilicate. An average particle size of less than 0.08 µm, 75% T - 25% C-phase content, and a porosity amount of less than 0.01% enable the fabrication of zirconia ceramics with translucent character. Increasing the C-phase content up to 50% increased the translucency to ultrahigh levels. However, both the decrease in particle size and the increase in the C-phase ratio reduce the flexural and fracture strength of zirconia.[9,18] From a general theoretical approach, 8 mol% yttria content provides complete stabilization of C-phase zirconia; 4-5 mol% yttria content (4Y-PSZ, 5Y-PSZ) provides partial stabilization (50%) of C-phase zirconia.[26,47] The combination of a small particle size with isotropic C zirconium dioxide provides translucency comparable to that of lithium disilicate.[7,39] Although it is a common finding in many studies that zirconia ceramics containing high amounts of yttria exhibit enhanced translucency properties; the effect of varying yttrium oxide content on the translucency of new-generation zirconia ceramics was reported by Inokoshi et al.[59] In a recent study. In the results obtained, the increase in the yttrium oxide content was associated with an increase in the C-phase and, consequently, an increase in translucency.

Intrinsic Parameter 8: Sintering Temperature, Time, and Method

Studies examining the effect of sintering temperature on the optical properties of zirconia have reported an increase in translucency and a decrease in contrast ratio due to the increase in density in the material as a result of the increased particle size and reduced porosity caused by high sintering temperatures. The optimum sintering temperature for monolithic zirconia is generally between 1400-1550 °C; At temperatures exceeding 1600-1700 °C or after long-term sintering procedures, grain boundary cracks that increase light scattering may occur in the material.[11] Kim et al.[60] reported that an increase in the sintering temperature (from 1350 °C to 1550 °C) reduced the porosity, making the polycrystalline structure of zirconia more compact, and reducing the sintering duration resulted in materials with smaller particle sizes and higher translucency. Ebeid et al.[61] Observed that higher temperatures (1600 °C) and longer waiting times (4 hours) led to higher translucency. Additionally, compared to its conventionally sintered equivalents, the rapid-sintered monolithic Y-TZP exhibits greater volume loss, which could impact the material's translucency over time. When the outer surface of Y-TZP is subjected to heat and the heat moves into the core, strong temperature gradients and internal tensions are produced, resulting in particle growth. Microwave sintering guarantees that the material is heated quickly and evenly both internally and externally, and particle coarsening is avoided by operating at a reduced temperature range during the operation. Thus, a final product with higher density, uniformity, and smaller particle sizes is obtained. As a result, Y-TZP ceramics sintered by the microwave sintering method exhibit higher translucency than ceramics sintered by the conventional method.[12,39,62] Additionally, it has been observed that Y-TZP ceramics sintered by field-assisted spark plasma sintering technology exhibit less porosity and smaller particle sizes.[39] Yang et al.[63] concluded that after rapid sintering, the optical properties of zirconia ceramics, including their translucency and color, changed so little that they were almost imperceptible to the naked eye.

Intrinsic Parameter 9: Cooling Protocols

Y-PSZ systems with a yttria content of 3-7 mol% consist of a T-phase formed by controlled diffusion and a metastable T-phase formed by a diffusion-free transformation from the C-phase by rapid cooling of the material from temperatures above 1425 °C. They have two types of T-phases. The T-phase is triggered by the displacement of oxygen ions in the crystallographic structure utilizing a diffusion-free mechanism; the fact that the crystal structure formed by this phase exhibits a character close to the isotropic structure can decrease the light scattering caused by birefringence, resulting in a boost in the translucency of zirconia.[7] Kim[7] found that the rapid cooling strategy increased translucency, although the translucency of 5Y-PSZ did not match that of glass ceramics.

Extrinsic Parameter 1: Thickness

The overall thickness of monolithic Y-TZP ceramics is significant for the amount of light that penetrates the restoration and thus plays a vital role in the translucency, color, and camouflage capability of the restoration.[5,17,18] In all investigations examining the influence of restoration thickness on the optical characteristics of monolithic Y-TZP ceramics, the thickness reduced the zirconia translucency.[17] When the thickness is reduced, the restoration becomes more translucent and natural, but it is less resistant to fracture. In contrast, increasing the thickness reduces esthetics and translucency while increasing the durability and stress resistance. In clinical settings, the thickness of conventional monolithic zirconia restorations can be appropriate between 0.5 and 0.75 mm; new generation translucent zirconia restorations can display satisfactory mechanical qualities and esthetic performance at 0.5-1.0 mm.[5] However, to obtain more translucent restorations, care should be taken to make the restorations thinner. Additionally, in the restorations of discolored teeth, a specific thickness balance should be achieved according to the case, taking into account the masking ability of zirconia.[17] Shen et al.[64] the translucency of the 5Y-TZP and 3Y-TZP decreased significantly with increasing ceramic

thickness, and the superior translucency of the 5Y-TZP disappeared when the material thickness reached 1.5 mm. Zirconia thickness can be minimized in the presence of a suitable dental background color and when a cement color suitable for restoration is applied. However, in the presence of a discolored/metal background and when opaque cements are used, the zirconia thickness should be increased.[18]

Extrinsic Parameter 2: Cementation

Resin cements, which exhibit good esthetics, low solubility, high durability, and high mechanical resistance, are the preferred cement type for all-ceramic restorations. The best choice for cementing zirconia restorations is dual-cure resin cement, which has both chemical and light-curing properties.[5,12] The cement layer, which acts as an intermediate layer in restorations, can optically affect both the restoration and the existing dental background.[5,18] Cements are classified as colored, bleached, opaque, or transparent according to their optical properties. The background effect becomes critical as cement transparency increases. As the translucency of the ceramic restoration increases, cement shade becomes critical.[17,18,65] Opaque cement can be a good choice for masking dark/metallic/discolored dental backgrounds; however, the ceramic thickness must be increased to compensate for the cement color. Choosing an appropriate cement color largely eliminates the need to increase the ceramic thickness.[17,18] The use of appropriately colored cement can help the masking effect of zirconia and contribute to color harmony for more esthetic results.[65]

Extrinsic Parameter 3: Colors of Y-TZP Ceramics and their Coloring Techniques

Achieving color harmony in monolithic Y-TZP restorations with existing adjacent teeth or restorations present in the mouth is the critical step.[17] In an attempt to enhance the color of zirconia, manufacturers have launched zirconia ceramics with multiple translucency levels (high, super, and ultra), pre-colored zirconia ceramics, multi-layer/multi-chromatic zirconia ceramics, and zirconia ceramics externally dyed by immersion in coloring solutions.[17,18] Pre-colored zirconia ceramics are produced by adding coloring metal oxides to their structures during the fabrication process.[18] Pre-colored translucent zirconia discs offer optimum translucency and color properties matching the "VITA Classical Shade Guide" shades, minimizing the need for external surface coloring.[5,17,18] On the other hand, the fabrication of highly translucent multi-layer/multi-chromatic zirconia discs that can mimic the different color and translucency gradient between the dentin and enamel layers from incisal to cervical along the tooth crown has greatly improved the optical properties.[5,17] There are two different techniques in external coloring procedures: dipping un-sintered or pre-sintered zirconia into solutions containing coloring ions or applying colored primers with a brush on sintered zirconia. These solutions have different shades that match the VITA Classical Shade Guide or the VITA 3D Master shades.[17,18] Since zirconia has a more porous structure before sintering, coloring solutions can be absorbed more easily at this stage; thus, the material can be easily colored, and color stability is achieved with the sintering process. Metal oxides added to the structure of pre-colored zirconia ceramics and the metal oxide concentration, type, application technique, and time in the colored solutions significantly affect the CIE Lab values and translucency of zirconia ceramics.[18,66] For this reason, the instructions recommended by the manufacturers should be followed carefully and accurately when coloring zirconia. Although some studies have reported that zirconia ceramics are not easily affected by coloring processes; there are also studies showing that external coloring procedures reduce translucency when colored and uncolored zirconia ceramics with similar particle sizes are compared. To ensure that the coloring process does not affect the translucency and fracture strength of the material, it is recommended that the coloring content of the solution be adjusted, and the dipping time should not exceed 2 minutes.[54]

Extrinsic Parameter 4: Surface Finishing Protocols and Abrasive Strategies

The effects of procedures such as polishing or glazing recommended for final surface treatments before cementation, such as abrasion with rotary tools, by laser irradiation and sandblasting applied to the intaglio surface of the restoration on translucency, are important issues that should be taken into consideration.[17,18] Although the color difference between polished and glazed zirconia restorations is lower than the perceptibility limit, the restorations show similar surface brightness due to the decrease in the lightness value in both processes.[18,54] Various studies reported no difference in translucency between polished and unpolished monolithic zirconia surfaces.[67,68] However, Kim et al.[67] observed no difference in translucency parameter values between polished and glazed zirconia. McLaren et al.[26] highlighted that polished restorations are more effective than glazed restorations because they exhibit a more natural and realistic appearance and that glaze application alone is not sufficient to provide a natural appearance. Lee et al.[69] Showed that glazing in zirconia restorations resulted in a higher color difference (ΔE=3.27) than polishing (ΔE=2.85). Manziuc et al.[6] suggested that both the color and translucency of zirconia ceramics changed after the glazing process, but only the color changes were statistically and clinically significant. Another essential consideration when polishing zirconia is the color stability of the restorations over time. Long-term aging in the oral cavity may induce color shifts in zirconia restorations. Glazing treatments applied to the restoration surface might limit aging by protecting the surface integrity of zirconia.[18,54]

Extrinsic Parameter 5: Low-Temperature Degradation

LTD causes a decrease in the elastic modulus, flexural strength, and fracture strength of the material as a result of saliva/water exposure and low temperatures to which zirconia ceramics are exposed in the oral environment over time. This causes T→M on the zirconia surface and affects the clinical effectiveness of restorations.[12,17,39] Aging or mechanical stress can cause a T→M in monolithic Y-TZP ceramics.[70] The change in translucency after aging, as M-crystals cause more light scattering than T- and C-crystals, is associated with the T→M of zirconia.[17] Smaller particle sizes and higher yttrium oxide concentrations have been suggested to delay the onset of LTD. While the small particle size effectively prevents the T→M. Similarly, yttrium (III) ions provide phase stabilization and therefore slow down LTD.[12] Jerman et al.[43] Revealed that the translucency of extra translucent and highly translucent zirconia ceramics increased with thermomechanical aging. Shen et al.[64] Concluded that 5Y-TZP offers higher LTD resistance than 3Y-TZP. Kim and Kim[71] realized that the translucency of Y-TZP and lithium disilicate glass ceramics increased slightly with increasing aging time, as did the phase transformations and surface changes on the surfaces of pre-colored monolithic zirconia ceramics.

Extrinsic Parameter 6: Dental Background

The dental tissues and basic dental materials present in the patient's mouth serve as the dental background and constitute the deepest layer through which light can pass in a restoration. Dental materials must have the ability to imitate the optical behaviors of enamel and dentin tissue in order to optimize esthetics. Otherwise, background color incompatibilities may occur in the restorations, as well as a background effect on the color and translucency of monolithic zirconia restorations.[18] Zirconia ceramics fabricated by increasing yttria content offer improved translucency; however, in the presence of clinical conditions, such as a colored dental background, they can harm esthetic results due to the reflection of the underlying color.[10] It is important to consider the color of the tooth to be restored during the fabrication of full ceramic restorations. In this context, teeth without discoloration can be better restored with zirconia with high translucency; in the presence of dyschromic teeth, more opaque zirconia restorations are needed to mask the dark background.[5] The fact that the ceramic thickness in implant-supported restorations is significantly higher than that in tooth-supported restorations may influence the material's translucency. The choice of abutment (titanium or zirconia) can also alter the restoration's translucency.[17] For this reason, some researchers advocate zirconia abutments over titanium abutments, especially for implant-supported fixed all-ceramic restorations in the esthetic area.[18] To compensate for the existing background surface; solutions such as using backgrounds close to the targeted restoration color, masking the background with suitable cements, and increasing the zirconia thickness have been suggested.[18,72,73] However, it is stated that zirconia with high opacity can mask backgrounds such as colored teeth, metal posts, or metal abutments.[5] On the other hand, monolithic zirconia restorations are generally produced thicker than zirconia frameworks; this reduces the translucency and background effect of monolithic zirconia restorations. Many manufacturers have created zirconia ceramic materials with various degrees of camouflage capabilities on colored backgrounds (light, medium, dark, metal).[18]

CONCLUSION

Based on the findings of this review, the following conclusions were drawn: 1) Zirconia provides better mechanical service than other full ceramic restorations because of its transformation-toughening trait; 2) first-generation zirconia has an opaque appearance because of the lack of a glassy matrix. Therefore, it was used as a coping in fixed partial restorations and veneered with feldspathic ceramics (bi-layered manner); 3) The monolithic manner emerged as an alternative to the bi-layered manner. Therefore, a number of monolithic zirconia materials having varied optical and mechanical qualities, as well as changes in their chemistries, particularly stabilizer content, have been developed; 4) Fourth generation offering multilayer/multi-chromatic zirconia blanks is the ultimate option in the dental market; 5) The optical properties of zirconia restorations are influenced by both intrinsic and extrinsic factors; 6) When choosing materials, clinicians should carefully consider both monolithic zirconia options with different chemical contents and factors that affect the optical properties of the restorations.

MAIN POINTS

- Zirconia, a bioinert polymorphic ceramic, has become a popular restorative material owing to its advantageous features.

- 3Y-TZP restorations also exhibit high opacity owing to the lack of a glassy matrix in the crystallographic structure. Therefore, 3Y-TZP was used as a coping material and veneered with feldspathic ceramics (bilayer manner).

- Several catastrophic complications, including cracking, chipping, and delamination, have been reported in the bilayer manner; to circumvent this, monolithic zirconia restorations with a plethora of different generations have been introduced.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.T., Ö.Ö., Concept: D.T., Ö.Ö., Design: D.T., Ö.Ö., Data Collection and/or Processing: D.T., Ö.Ö., Analysis and/or Interpretation: D.T., Ö.Ö., Literature Search: D.T., Ö.Ö., Writing: D.T., Ö.Ö.

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RESEARCH ARTICLE

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Overview of Vital Teeth Bleaching Methods and Utilized Materials by Dentists

Mine Başan Tosun, Batu Can Yaman, Hatice Tepe, Özge Çeliksöz

Department of Restorative Dentistry, Eskişehir Osmangazi University Faculty of Dentistry, Eskişehir, Türkiye

Abstract

BACKGROUND/AIMS: This study aimed to determine the perspectives of dentists practicing in Türkiye on vital bleaching treatments, their preferences regarding application methods and materials, and to evaluate the obtained data with a cause-and-effect relationship.

MATERIALS AND METHODS: A survey designed to collect data on the perspectives and preferences of dentists and administered online using Google Forms. Voluntary dentists reached the form after filling out the consent form. All analyses were performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). The pearson's chi-square test was used to compare categorical variables. A p value <0.05 was considered statistically significant.

RESULTS: Among the participating dentists, 58.5% practiced vital bleaching and office bleaching, the most preferred method (84.5%) in all groups. There was a correlation between the sector and the "single session" preference (p<0.001). There was a relationship between specialization status and "light activation" preference (p=0.001). General dentists preferred it more than specialist dentists. Dentists working in the private sector reported more experience about pain, sensitivity, and irritation of soft tissues after bleaching than those working in the public.

CONCLUSION: Vital office bleaching is the most effective method. Dentists generally prefer to apply 2 sessions and light device activation. Additionally, they generally wait 14 days for restoration after bleaching. Dentists in the private sector are more likely to experience side effects than those in the public sector.

Keywords: Dental health survey, dentisty, teeth bleaching

INTRODUCTION

A beautiful smile is recognized as one of the most effective tools in one's social life. Dentistry has evolved from the past to the present to provide patients with healthier, more functional, and esthetically satisfying teeth. The impact of social media and digital photography has increased the desire to have snow-white teeth and an attractive smile among patients who seek esthetic dentistry in addition to healthy teeth.

Metabolic disorders, hereditary diseases, iatrogenic causes, such as tetracycline and fluorosis, trauma, and aging, can cause tooth discoloration. It also occurs when external staining factors adhere to the surfaces of the teeth.[1] Vital tooth bleaching is the process of lightening the color of the teeth in the clinic or at home by oxidation of the organic chromophores that settle in the dental hard tissues by free radical molecules as a content of various chemicals applied to the discolored teeth.[2]

The mechanisms involved in the decolorization of chromophores, which are the structures primarily responsible for tooth discoloration, are the opening of their double carbon bonds, the breaking of the conjugated chain to form shorter chains, and the oxidation of other chemical moieties in the chain.[2] The bleaching mechanism involves the formation of free oxygen (O_2^-) and peroxide (HO_2^-) from active hydrogen peroxide. These unstable free radicals diffuse into the interprismatic

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ORCID IDs of the authors: M.B.T. 0009-0009-9181-6980; B.C.Y. 0000-0003-4295-0760; H.T. 0000-0003-4744-5691; Ö.Ç. 0000-0002-4879-3631.

Address for Correspondence: Mine Başan Tosun
E-mail: minebtosun@gmail.com
ORCID ID: orcid.org/0009-0009-9181-6980

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spaces in the enamel and are transported to the outer surface of the tooth by the foaming up of the pigmented molecules into small fragments. As the pigmented molecules are removed, the color of the tooth appears lighter.[3]

The most reliable and professional method of vital tooth bleaching treatment is office bleaching, which is performed by a dentist in a clinic. Since the concentration of hydrogen peroxide applied is high, the bleaching result can be visible quickly depending on the rate of free radical formation.[4] The home bleaching method is a method that patients can apply at home with carbamide peroxide or lower concentrations of hydrogen peroxide placed in plaques specially prepared by the dentists.[5] Continuation of the bleaching treatment by the patient at home, which was initiated by the dentist in the clinic, is a combined office and home bleaching method.[6] The microabrasion technique is the controlled removal of material from the colored superficial enamel layer with the help of an acidic and abrasive paste containing 6-6.6% hydrochloric acid and silicon carbide microparticles.[7]

In the in-office bleaching method, high levels of hydrogen peroxide are applied with or without additional activation by heat, light, or laser. Today, halogen and plasma arc light devices are not preferred due to their impracticality and potential to emit infrared light.[8] Light emitting diode (LED) devices developed in parallel with technological developments can effectively perform bleaching with bleaching mode as well as resin polymerization.[9] There are also studies showing that led lights don't have any effect on bleaching efficacy check that literature.[10] With the violet LED devices produced with the latest technology, bleaching can be done safely with only light activation without the need for chemical agents.[9]

Among the complications of vital tooth bleaching treatments, sensitivity is the most common. One of the main reasons is that the end products of the peroxide diffuse into the dentinal tubules and reach the pulp, and the other is that the glycerin in the agents dehydrates the teeth due to its hydrophilic structure.[8] Burns may occur as a result of contact of the caustic agents used in vital bleaching with surrounding soft tissues.[11] If the bleaching agent is highly concentrated or in contact with the tooth for a long time, the organic matrix is destroyed as a result of calcium and phosphate loss. In addition, the physical properties of enamel, such as its microhardness and wear resistance, are weakened. Due to its hydrophilic nature, the bleaching agent absorbs water from the resin composite components, resulting in changes in the form of increased surface roughness and porous areas.[12] In the home-type vital teeth bleaching method, temporomandibular joint (TMJ) damage may occur as a result of using the plaque for a long time or not being prepared in accordance with the patient's dentition. The toxicity of properly applied bleaching treatment is limited to the oral cavity and rendered harmless by the body's defense systems.[11]

After vital bleaching treatment, it is necessary to wait from 24 hours to 3 weeks for adhesive procedures due to the weakened bond strength of enamel to adhesive systems and reduced resin tags.[12] Since free oxygen reagents also act as polymerization inhibitors, they negatively affect the polymerization and bonding of resin adhesives in the early post-bleaching period. According to the results of recent studies, the application of antioxidants at the end of bleaching treatment allows restoration to be performed in the same session. After bleaching, antioxidant agents such as ascorbic acid, catalase, alpha-tocopherol, or sodium ascorbate are used to increase the enamel adhesive bond strength.[13,14]

Clinical and *in vitro* studies on vital tooth bleaching have been conducted for many years. In addition to advances in methods and materials, it is critical for dentists to keep pace with these developments. For this reason, surveys among dentists are becoming increasingly important. In the survey studies on bleaching treatment conducted so far, a limited number of studies have provided limited information, including questions about the rate of patients' visits to dentists with bleaching requests, chemical bleaching agent preferences, and vital bleaching method preferences. Thus, the aim of this study was to investigate the approaches and material method preferences of different categories of dentists for bleaching vital teeth for various reasons. This study also aimed to compare the data obtained from dentists who were grouped according to specialty status, duration of experience, and sector in which they work.

MATERIALS AND METHODS

The study protocol was approved by Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (approval number: 49, date: 15.02.2022).

This web-based questionnaire was developed by the researchers after a comprehensive literature review of previous studies. The model was tested for content and face validity. The survey was created using Google Forms. The data were sent to dentists via e-mail and social media using the databases of the Association of Restorative Dentistry and the Turkish Dental Association. The survey was displayed on the screen after the dentists acknowledged that they had given their consent to participate in the study. The survey consisted of 15 questions. The first part of the survey was including 7 sociodemographic questions about the dentists' gender, title, age, year of graduation, specialization, professional experience, length of time working as a dentist, and where they work. The second part consisted of 8 questions about vital bleaching. Because these questions included multiple-choice options, more results were obtained than the number of participants. The data were analyzed in this way. Information such as identity information and e-mail addresses were not asked of the dentists. A total of 518 dentists completed the survey.

Statistical Analysis

All analyses were performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). The pearson's chi-square test was used to compare categorical variables. The categorical variables are expressed as frequencies and percentages. A p value <0.05 was considered statistically significant.

RESULTS

The responses of 518 participants were analyzed. The general sociodemographic information about the participants is presented in Figure 1. When asked, "Do you perform vital bleaching?" 41.5% of dentists answered "yes" and 58.5% answered "no" (Figure 1). The most preferred method was found to be "Office bleaching method" with a preference rate of 84.5%. The data for this question are presented in Figure 2.

The answers to the question "Which type of vital teeth bleaching method do you prefer?" were compared according to the professional experience, sector, and specialization status of the dentists. The obtained data are presented in Table 1. There was a relationship between

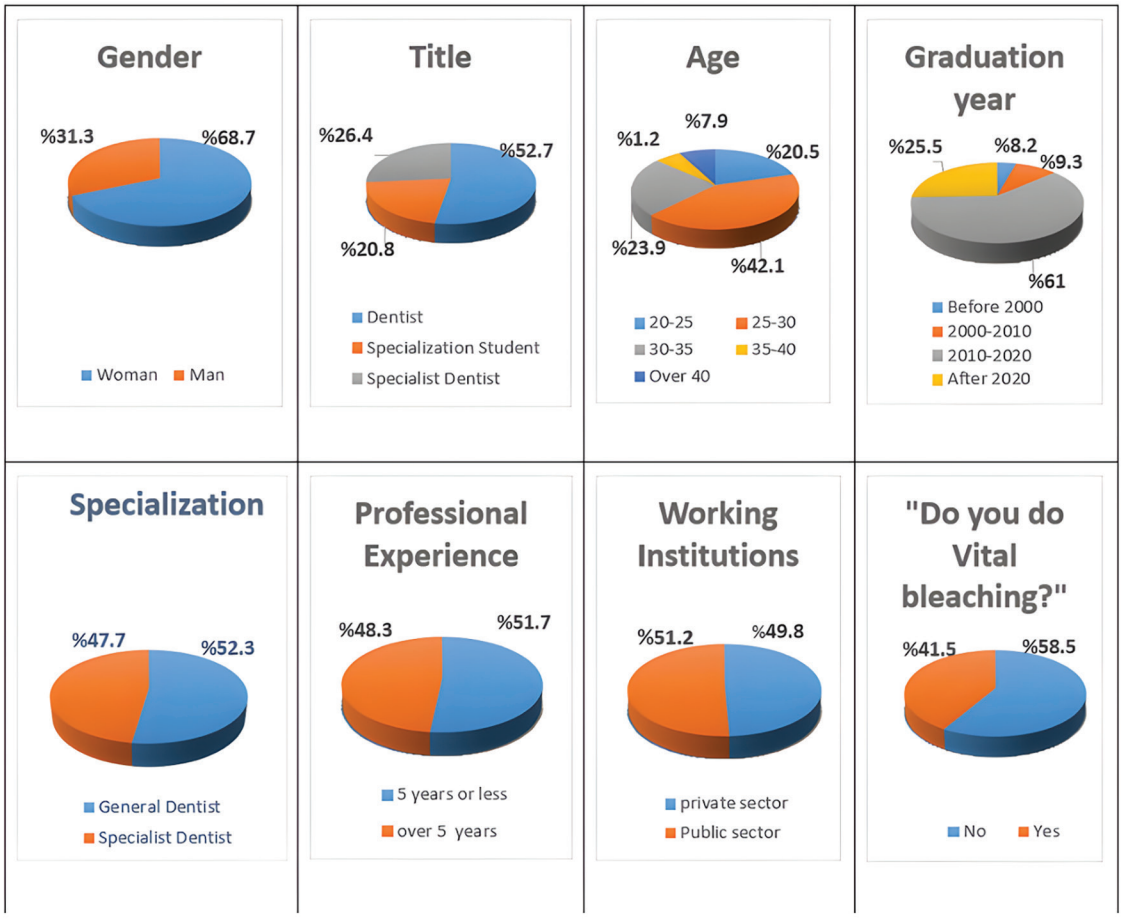

Figure 1. Basic descriptive information about the dentists and the distribution of dentists who perform vital tooth bleaching.

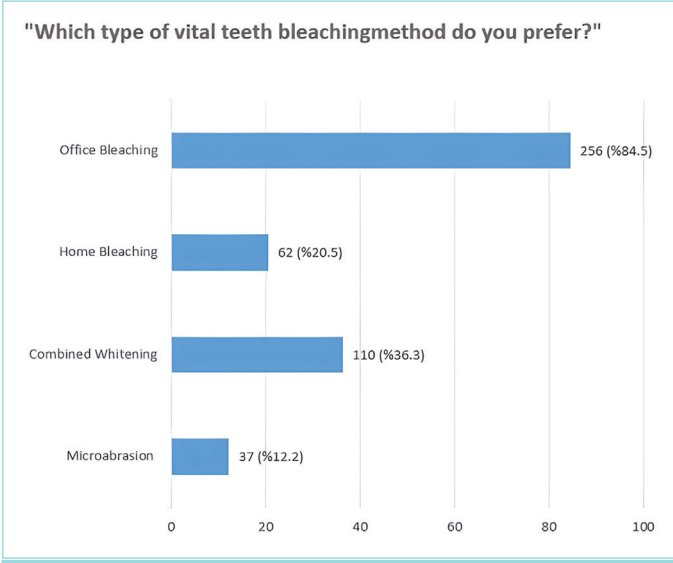

Figure 2. Distribution of the vital bleaching methods used by the surveyed dentists.

professional experience and home bleaching (p=0.010). There was a relationship between professional experience and combined office and home bleaching (p=0.032). There was a relationship between the sector in which dentists work and combined office and home bleaching (p=0.015). There was a correlation between the specialty status of dentists and home bleaching (p=0.010). Specialized dentists performed home bleaching and combined office and home bleaching at a higher rate than general dentists (p=0.010) (Table 1).

The most preferred bleaching brand by dentists was "Ultradent Opalescence Boost PF 40% Hp Office Whitening" (Ultradent Inc, South Jordan, USA) with a rate of 59.4%. The second most preferred bleaching brand was "FGM Whiteness HP 35% Hp Office Whitening" (Joinville, SC, Brazil), with a rate of 38.3% (Figure 3).

The answers to the question "How many sessions of office bleaching do you perform?" were compared according to the professional experience, specialization status, and sector in which the dentists work. The obtained data are presented in Table 2. There was a relationship between the sector in which dentists worked and single-session teeth bleaching treatment (p<0.001). There was a correlation between the sector in which dentists worked and 2-session teeth bleaching treatment (p<0.001). General dentists preferred single-session bleaching treatment more than specialist dentists (p<0.001) (Table 2).

The answers to the question "What do you use as activator during the bleaching process?" were compared according to their professional experience, specialization status, and sector in which they worked. The obtained data are presented in Table 3. There was a relationship

Table 1. Comparison of the answers to the question "Which type of vital teeth bleaching method do you prefer?" according to the interaction groups of specialty, place of work, and working time

Variables	Office bleaching		p	Home bleaching		p	Combined office and home bleaching		p	Microabrasion		p
	Yes, (n %)	No, (n %)		Yes, (n %)	No, (n %)		Yes, (n %)	No, (n %)		Yes, (n %)	No (n %)	
Professional experience												
≤5	58 (21.6%)	210 (78.4%)	0.289	19 (7.1%)	249 (92.9%)	0.010*	45 (16.8%)	223 (83.2%)	0.032*	36 (13.4%)	232 (86.6%)	0.625
>5	64 (25.6%)	186 (74.4%)		35 (14%)	215 (86%)		61 (24.4%)	189 (75.6%)		30 (12.0%)	220 (88.0%)	
Working institutions												
Public sector	53 (20.4%)	207 (79.6%)	0.088	27 (10.4%)	233 (89.6%)	0.976	42 (16.2%)	218 (83.8%)	0.015*	35 (13.5%)	225 (86.5%)	0.622
Private sector	69 (26.7%)	189 (73.3%)		27 (10.5%)	231 (89.5%)		64 (24.8%)	194 (75.2%)		31 (12.0%)	227 (88.0%)	
Specialization												
General dentist	58 (21.6%)	210 (78.4%)	0.289	19 (7.1%)	249 (92.9%)	0.010*	45 (16.8%)	223 (83.2%)	0.032*	36 (13.4%)	232 (86.6%)	0.693
Specialist dentist	64 (25.6%)	186 (74.4%)		35 (14.0%)	215 (86.0%)		61 (24.4%)	189 (75.6%)		30 (12.0%)	220 (88.0%)	

(n %): Categorical variables are expressed as frequencies and percentages, respectively.

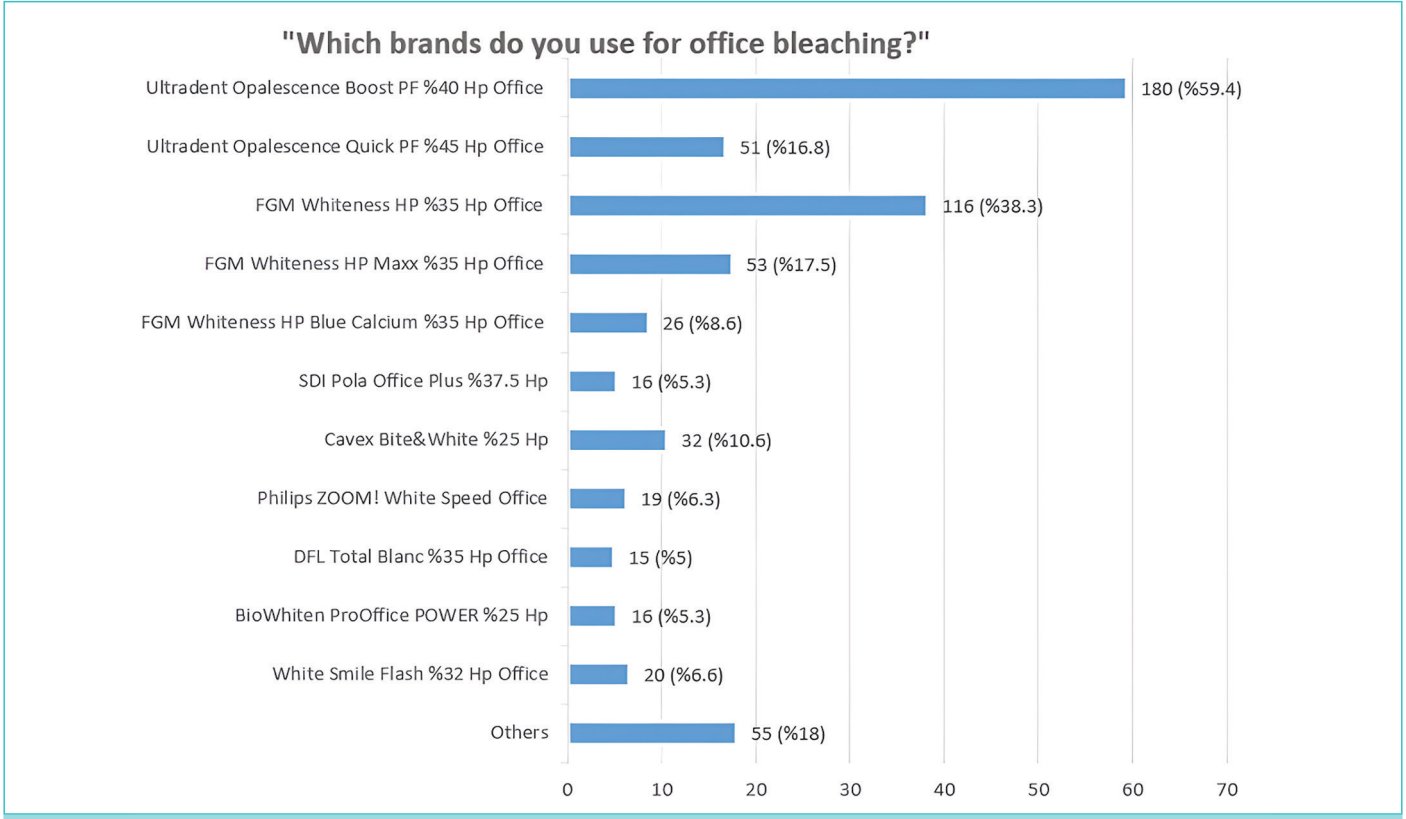

Figure 3. Distribution of commercial brands preferred by surveyed dentists.

between the sector in which dentists worked and their light activation preference (p<0.001). There was a relationship between the sector in which dentists worked and the preference for mixing bleaching gel preference (p<0.001). There was a relationship between the sector in which dentists worked and laser preference (p=0.025). General dentists preferred light activation in bleaching treatment more than specialist dentists (p=0.001) (Table 3).

The answers to the question "At which stage do you perform restoration in case of need?" were compared according to the professional experience, sector, and specialization status of the dentists. The obtained data are presented in Table 4. There was a relationship between the sector in which dentists worked and the preference for "7 days after bleaching" (p<0.001). There was a relationship between the sector in which dentists worked and the preference for "14 days after bleaching" (p<0.001). There was a relationship between the sector in which dentists worked and the preference for "+14 days after bleaching" (p<0.001). General dentists preferred restorations performed in the same session with bleaching compared with specialist dentists (p=0.039). General dentists preferred the "7 days after bleaching" option as restoration time more than specialist dentists (p<0.001) (Table 4).

"What complaints do you encounter during and after the application?" The answers to the questions were compared according to the dentists'

Table 2. Comparison of the answers to the question "How many office bleaching sessions do you perform?" based on interaction groups of specialty, place of work, and working time

Variables	Single session		p	Two session		p	Three session		p
	Yes, (n %)	No (n %)		Yes, (n %)	No (n %)		Yes, (n %)	No (n %)	
Professional experience									
≤5	68 (25.4%)	200 (74.6%)	0.092	106 (39.6%)	162 (60.4%)	0.460	29 (10.8%)	239 (89.2%)	0.206
>5	48 (19.2%)	202 (80.8%)		91 (36.4%)	159 (63.6%)		19 (7.6%)	231 (92.4%)	
Working institutions									
Public sector	28 (10.8%)	232 (89.2%)	0.001*	66 (25.4%)	194 (74.6%)	0.001*	23 (8.8%)	237 (91.2%)	0.741
Private sector	88 (34.1%)	170 (65.9%)		131 (50.8%)	127 (49.2%)		25 (9.7%)	233 (90.3%)	
Specialization									
General dentist	78 (28.8%)	193 (71.2%)	0.001*	167 (616%)	104 (38.4%)	0.865	30 (11.1%)	241 (88.9%)	0.138
Specialist dentist	38 (15.4%)	209 (84.6%)		154 (62.3%)	93 (37.7%)		18 (7.3%)	229 (92.7%)	

(n %): Categorical variables are expressed as frequencies and percentages, respectively.

Table 3. Comparison of the answers to the question "What do you use as an activator during the bleaching process?" according to the interaction groups of specialty, place of work, and working time

Variables	Light device		p	Mix the bleaching gel		p	Short time passed over teeth with LED		p	Laser		p
	Yes, (n %)	No (n %)		Yes, (n %)	No (n %)		Yes, (n %)	No (n %)		Yes, (n %)	No (n %)	
Professional experience												
≤5	114 (42.5%)	154 (57.5%)	0.153	83 (31.0%)	185 (69.0%)	0.801	39 (14.6%)	229 (85.4%)	0.647	18 (6.7%)	250 (93.3%)	0.696
>5	91 (36.4%)	159 (63.6%)		80 (32.0%)	170 (68.0%)		40 (16.0%)	210 (84.0%)		19 (7.6%)	231 (92.4%)	
Working Institutions												
Public sector	55 (21.2%)	205 (78.8%)	0.001*	56 (21.5%)	204 (78.5%)	0.001*	35 (13.5%)	225 (86.5%)	0.255	12 (4.6%)	248 (95.4%)	0.025*
Private sector	150 (58.1%)	108 (41.9%)		107 (41.5%)	151 (58.5%)		44 (17.1%)	214 (82.9%)		25 (9.7%)	233 (90.3%)	
Specialization												
General dentist	125 (46.1%)	146 (53.9%)	0.001*	90 (33.2%)	181 (66.8%)	0.371	36 (13.3%)	235 (86.7%)	0.192	20 (7.4%)	251 (92.6%)	0.826
Specialist dentist	80 (32.4%)	167 (67.6%)		73 (29.6%)	174 (70.4%)		43 (17.4%)	204 (82.6%)		17 (6.9%)	230 (93.1%)	

(n %): Categorical variables are expressed as frequencies and percentages, respectively, LED: Light emitting diode.

Table 4. Comparison of the answers given to the question "If there is a need for restoration, at what stage do you do it?" according to the interaction groups of the field of specialization, place of employment, and working time

Variables	Same session as bleaching		p	Seven days after bleaching		p	Fourteen days after bleaching		p	+Fourteen days after bleaching		p
	Yes, (n %)	No (n %)		Yes, (n %)	No (n %)		Yes, (n %)	No (n %)		Yes, (n %)	No (n %)	
Professional experience												
≤5	23 (8.6%)	245 (91,4%)	0.260	62 (23.1%)	206 (76.9%)	0.149	77 (28.7%)	191 (71.3%)	0.553	32 (11.9%)	236 (88.1%)	0.485
>5	15 (6.0%)	235 (94.0%)		45 (18.0%)	205 (82.0%)		66 (26.4%)	184 (73.6%)		35 (14.0%)	215 (86.0%)	
Working institutions												
Public sector	14 (5.4%)	246 (94.6%)	0.087	28 (10.8%)	232 (89.2%)	0.001*	52 (20.0%)	208 (80.0%)	0.001*	26 (10.0%)	234 (90.0%)	0.046*
Private sector	24 (9.3%)	234 (90.7%)		79 (30.6%)	179 (69.4%)		91 (35.3%)	167 (64.7%)		41 (15.9%)	217 (84.1%)	
Specialization												
General dentist	26 (9.6%)	245 (90.4%)	0.039*	75 (27.7%)	196 (72.3%)	0.001*	72 (26.6%)	199 (73.4%)	0.580	31 (11.4%)	240 (88.6%)	0.288
Specialist dentist	12 (4.9%)	235 (95.1%)		32 (13.0%)	215 (87.0%)		71 (28.7%)	176 (71.3%)		36 (14.6%)	211 (85.4%)	

(n %): Categorical variables are expressed as frequencies and percentages, respectively.

professional experience, the sector in which they work, and their specialization. The obtained data are presented in Table 5. There was a relationship between the professional experience of dentists and TMJ disorder (p=0.038). Dentists working in the private sector were more likely to experience pain, sensitivity, and irritation of soft tissues after bleaching than those working in the public sector (p<0.05). There was a relationship between the specialty status of dentists and sensitivity (p=0.016) (Table 5).

Table 5. Comparison of the answers to the question "Which complaints do you encounter during and at the end of the practice?" according to the interaction groups of field of specialization, place of employment and working time

Variables	Pain		p	Irritation of soft tissues		p	Sensitivity		p	TMJ disorder		p
	Yes, (n %)	No (n %)		Yes, (n %)	No (n %)		Yes, (n %)	No (n %)		Yes, (n %)	No (n %)	
Professional experience												
≤5	45 (16.8%)	223 (83.2%)	0.901	78 (29.1%)	190 (70.9%)	0.939	152 (56.7%)	116 (43.3%)	0.071	13 (4.9%)	255 (95.1%)	0.038*
>5	43 (17.2%)	207 (82.8%)		72 (28.8%)	178 (71.2%)		122 (48.8%)	128 (51.2%)		4 (1.6%)	246 (98.4%)	
Working institutions												
Public sector	33 (12.7%)	227 (87.3%)	0.009*	59 (22.7%)	201 (77.3%)	0.002*	90 (34.65.9	170 (65.4%)	0.001*	7 (2.7%)	253 (97.3%)	0.450
Private sector	55 (21.3%)	203 (78.7%)		91 (35.3%)	167 (64.7%)		184 (71.3%)	74 (28.7%)		10 (3.9%)	248 (96.1%)	
Specialization												
General dentist	44 (16.2%)	227 (83.8%)	0.633	78 (28.8%)	193 (71.2%)	0.927	157 (57.9%)	114 (42.1%)	0.016*	11 (4.1%)	260 (95.9%)	0.298
Specialist dentist	44 (17.8%)	203 (82.2%)		72 (29.1%)	175 (70.9%)		117 (47.4%)	130 (52.6%)		6 (2.4%)	241 (97.6%)	

(n %): Categorical variables are expressed as frequencies and percentages, respectively, TMJ: Temporomandibular joint.

DISCUSSION

In recent years, the number of people visiting dentists with the desire of having whiter teeth has been increasing rapidly, parallel to the increase in modernity and socialization. When indications and contraindications, materials used, application methods, and control and follow-up periods are considered together, bleaching should be considered as a form of treatment.

In a survey conducted among university students; 16.1% of the students had had bleaching at least once in their lives and 74.4% were wanting to have vital teeth bleaching.[15] In a survey among orthodontists, it was reported that 99.2% of patients undergoing orthodontic treatment were requesting bleaching.[16] In another survey searching the prevalence of the desire for teeth bleaching, 85% of 536 participants answered "yes" to the question asking if they want to whiten their teeth. The same study also reported that the number of people seeking vital bleaching had increased 2.3 times in one year.[17] As the interest in white teeth continues to grow, it is necessary to support this issue with new studies to improve the working principles of dentists and to protect patient comfort and health.

According to the results of the present study, most of the participating dentists applied vital bleaching treatment. According to the results obtained, general dentists applied bleaching treatment more frequently than specialists, and dentists with equal or less than 5 years of experience applied bleaching treatment more frequently than experienced dentists. In Türkiye, vital bleaching treatment is performed mostly in the private and secondary sectors. In a survey conducted in Pakistan, which reported different results from the present study, among dentists who perform vital bleaching, those working in the public sector perform more vital bleaching than those working in the private sector, and dentists with more clinical experience perform more vital bleaching than those dentists with equal or less than 5 years of experience.[18]

In the present study, in which dentists were grouped according to their specialty, institution, and professional experience, office-type vital bleaching was the most preferred method in all groups. The second-preferred method in all groups was the combined office and home bleaching, while home-type vital bleaching was preferred the third. According to the results of a survey conducted among Guatemalan dentists, dentists working in the private sector prefer office bleaching, whereas those working in the public sector prefer home bleaching.[19] According to a survey conducted among Palestinian dentists, dentists with equal or less than 5 years of experience prefer home bleaching, while dentists with more than 5 years of experience prefer office bleaching.[20] In a study conducted in Pakistan, dentist with 10-20 years of experience preferred the office-type with a statistically significant result.[18] As a reason for this, other researchers think that decision-making ability increases with experience and that the tendency to bleaching method applied in the office increases as a result of increased self-confidence with the effect of the trainings received over time.[20]

The microabrasion preference rates of the dentists who participated in this study were lower than those of the other methods. In a survey study among orthodontists, it was reported that most of them (78%) applied the microabrasion technique after orthodontic treatment for the removal of discoloration and white spot lesions.[21] The fact that the mentioned study was conducted only among orthodontists and the high probability of the need for microabrasion as a result of orthodontic treatments explains the different results obtained from the present study applied to all specialties.

According to the results of the present study, the most preferred office bleaching commercial product was "Ultradent Opalescence Boost PF 40% HP", followed by "FGM Whiteness HP 35%". These products are frequently preferred in clinical and in vitro studies.[1,22,23]

The number of bleaching treatment sessions is usually indicated in the manufacturer's instructions for use.[24] Nevertheless, the number of sessions may vary depending on the conditions deemed appropriate by the dentist and other patient and patient-related factors. In the present study, when asked how many sessions of vital bleaching treatment they usually perform, dentists in Türkiye responded "2 sessions" most frequently in all groups. In addition, general dentists and less experienced dentists generally preferred single-session applications over the other groups. According to the results of a telephone survey, 85% of dentists reported that a single session of vital bleaching treatment was performed.[25] According to the literature, 2 or 3 sessions are necessary to achieve and maintain effective office bleaching.[26]

In office bleaching treatment, high-concentration hydrogen peroxide is applied without activation or activation by methods such as heat, light, and laser. There are controversial results in the literature regarding the effectiveness and risk-benefit ratio of activation methods. Some studies claim that light activation improves bleaching efficacy in terms of color change, while others suggest that there is no difference between light-activated bleaching and conventional bleaching.[10,27] A recent study reported that there was no difference in tooth color change and

sensitivity increase in bleaching with and without the use of an LED/laser hybrid device. It is thought that no sensitivity difference occurred in this study due to the anti-inflammatory and analgesic effect of hybrid light.[10] In another study, it was stated that there was no difference in the effectiveness of light or non-light treatment in bleaching with high concentrations of hydrogen peroxide.[27]

According to the literature, contradictory results in the studies are due to the fact that variables such as the wavelength of the light, the type of light device, the duration of use, and the concentration of the agent cannot be fixed.[28] Today, as a result of the support of companies and the perception created, the bleaching process using light devices is becoming widespread in clinics in direct proportion to the amount of demand of patients. While the necessity of using light devices in bleaching treatment is a matter of debate, it has been supported by clinical and *in vitro* studies.

In the present study, the methods used for activation in bleaching treatment were questioned, and it was determined that "Light device" was preferred with the highest rate (67.3%) in all groups. Moreover, general dentists preferred light activation to specialists. Dentists working in the private sector prefer light activation over those working in the public sector. According to a survey study investigating the light device preferences of dentists in bleaching; 49.3% of dentists were using ultraviolet (UV) devices, 10.8% were using blue LED and laser, and 39.9% were preferring treatment without light activation.[25] According to the results of another survey, 58.6% of dentists were preferring light activation, while 41.4% were not using light devices for vital bleaching.[20] In the results of another study, 44.8% were using LED devices, 15.2% were using laser, and 11.7% were using halogen light sources, while 28.3% were not using light activation.[29]

According to the literature, residual peroxide that persists after vital bleaching interferes with adhesive polymerization and adversely affects restoration health. The restoration should be done 2 or 3 weeks after the bleaching procedure.[30] An *in vitro* study with six different waiting times after bleaching showed that there was no difference in the enamel bond strength of the composite restoration between the times.[31] In a recent study, it was shown that adhesion increased with the antioxidant applied immediately after bleaching.[13] Another study compared the bonding of resin composites applied to enamel treated with 10% ascorbic acid after vital bleaching with resin composites applied to enamel that had never been bleached and reported that there was no difference.[32] In another clinical study, a 1-year follow-up of the restoration on a lateral tooth treated with sodium ascorbate for 1 hour after bleaching showed high clinical success.[33]

In the present study, we questioned on which day the dentists would restore the teeth if restoration was needed after vital teeth bleaching treatment. In all groups, the answer "after 14 days" was mostly given without any significant difference. It was also found that general dentists gave the answers "the same session as bleaching" and "after 7 days" more often than specialist dentists. In another survey of Romanian dentists, which also asked about the use of antioxidants, 88.8% answered "after 14 days", 4.8% answered "immediately without antioxidants" and 3.4% answered "immediately with antioxidants" when asked how long it would take to restore teeth after vital bleaching.[29]

In the present study, when dentists were asked which complications they encountered the most during and at the end of vital teeth bleaching application, "sensitivity" was the most common answer (90.1%) and "soft tissue irritations" was the second most common answer. In the present study, we found that dentists working in the private sector encountered pain, sensitivity, and soft tissue irritation at a higher rate than those working in the public sector. In addition, general dentists received more sensitivity feedback from their patients than specialist dentists. According to another survey with similar results, 75.7% of dentists were experiencing sensitivity and 29.7% were experiencing gingival burns.[25] In another study, sensitivity and soft tissue inflammation were the most common side effects reported by dentists, with an increase in sensitivity with the use of UV light.[29] According to a Nigerian survey study on hypersensitivity, 80.3% of dentists identified teeth bleaching treatment as a predisposing factor for sensitivity.[34]

Study Limitation

This survey was completed by 518 dentists. Although the study included more participants, the sample size was limited to 518 due to dentists who did not prefer to complete the questionnaire. The fact that the study was completed with fewer participants than expected can be considered a limitation of the study.

CONCLUSION

According to the results of the study, differences were found between the methods for vital bleaching treatment and materials preferred by dentists in Türkiye according to their specialization status, sector of employment, and interaction groups in professional experience. Among the vital bleaching methods, office bleaching was the most preferred method in all groups. As the professional experience of dentists increases, their preference for home bleaching and combined office and home bleaching also increases. Two-session in-office vital bleaching was the most preferred option among all dentist groups. In all groups, bleaching with light activation was the most preferred option. Dentists usually apply restorations 14 days after vital bleaching. The most common complication encountered by dentists during vital teeth bleaching treatment was sensitivity, and the second most common complication was irritation of soft tissues. Dentists working in the private sector were more likely to experience pain, sensitivity, and soft tissue irritation than those working in the public sector. It is thought that it would be useful to support this study with new studies with larger sample sizes and multicenter studies.

MAIN POINTS

- In-office bleaching was the most preferred vital bleaching method in all groups.

- Dentists working in the private sector preferred light activation during vital tooth bleaching more than those working in the public sector and general practitioners more than specialists.

- Most dentists found a total of 2 sessions sufficient for office-type vital bleaching.

- All dentists identified sensitivity as the most common complication of vital tooth bleaching.

ETHICS

Ethics Committee Approval: The study protocol was approved by Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (approval number: 49, date: 15.02.2022).

Informed Consent: It was obtained.

Footnotes

Authorship Contributions

Concept: M.B.T., B.C.Y., H.T., Design: M.B.T., B.C.Y., Data Collection and/or Processing: M.B.T., B.C.Y., Analysis and/or Interpretation: M.B.T., B.C.Y., Ö.Ç., Literature Search: M.B.T., B.C.Y., H.T., Writing: M.B.T., B.C.Y., Ö.Ç.

DISCLOSURES

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RESEARCH ARTICLE

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Assessment of Community Pharmacists' Awareness of Antibiotic Resistance and Practice of Antibiotic Use for Urinary Tract Infections in North Cyprus

Basma Omar[1], Nevzat Birand[2], Meryem Deniz Aydın[1]

[1]Department of Clinical Pharmacy, Near East University Faculty of Pharmacy, Nicosia, North Cyprus
[2]Department of Clinical Pharmacy, Cyprus International University Faculty of Pharmacy, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: Uncontrolled antibiotic use significantly contributes to antimicrobial resistance, thereby impacting public health and healthcare costs. Given the rise in antimicrobial resistance, community pharmacists should adhere to regulations on antibiotic dispensing. Community pharmacists should actively educate patients about appropriate antibiotic use. This study aimed to assess the awareness of community pharmacists regarding antibiotic resistance and to investigate their practices in dispensing antibiotics for urinary tract infections (UTIs) in North Cyprus.

MATERIALS AND METHODS: This cross-sectional study was conducted over a 3-month period. The proposed sample size was 184 community pharmacies, calculated using Raosoft® software.

RESULTS: Two hundred and seven out of 350 community pharmacists agreed to participate in this study. 188 (90.8%) had good awareness about antibiotic resistance, while 19 (9.17%) had poor awareness. Furthermore, 65.7% of community pharmacists agreed that antibiotic resistance is a public health issue. There was a statistically significant association between gender and awareness ($p=0.006$), as well as between age and awareness ($p=0.02$). Additionally, a statistically significant association was found between education status and awareness ($p<0.001$), as well as between experience and awareness ($p<0.001$).

CONCLUSION: This study showed that community pharmacists dispense antibiotics without prescription because they are confident in their knowledge of antibiotic use for treating UTIs. We suggest that educational programs to promote reasonable antibiotic use should be organized by the Ministry of Health of North Cyprus and the Cyprus Turkish Pharmacists Association.

Keywords: Antibiotic, urinary tract infections, community pharmacists, North Cyprus

INTRODUCTION

Urinary tract infections (UTIs) are one of the most prevalent bacterial infections globally, constituting 25% of all infections. UTIs are the most recurrent bacterial infections among females, and antibiotic resistance rates have been increasing in recent years.[1] UTIs can affect the urethra, bladder, or kidneys, with symptoms varying depending on the location, and are classified as uncomplicated or complicated. Complicated UTIs are linked to structural or neurological abnormalities which increase the susceptibility to infections.[2] Uncomplicated UTIs, also known as cystitis or lower UTIs, present with symptoms like painful

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ORCID IDs of the authors: B.O. 0009-0008-6088-7092; N.B. 0000-0001-5785-2333; M.D.A. 0009-0006-2142-9975.

Address for Correspondence: Meryem Deniz Aydın
E-mail: meryem.denizaydin@neu.edu.tr
ORCID ID: orcid.org/0009-0006-2142-9975

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voiding, urgency, frequent urination, suprapubic pain, and hematuria. Uncomplicated UTIs, which affect up to 50% of women during their lifetime, are primarily caused by *Escherichia coli* by the fecal flora. This bacterium colonizes the vagina and urethra before infecting the bladder.[3] Although most cases of uncomplicated UTI resolve without treatment,[4] most individuals with UTIs visit pharmacies either before or after seeing their general practitioner (GP). Therefore, pharmacist interventions can improve antimicrobial use for UTIs by enhancing patient knowledge, preventive care, and self-care skills and offering appropriate consultations.[5] Global guidelines discourage routine urine cultures, and GPs often start empirical antibiotic therapy based on the likely consideration of possible infecting organisms and local resistance patterns.[6] As a result, diagnosis of UTI is based primarily on signs and symptoms. When a patient presents with both dysuria and increased frequency of urination, the probability of a UTI is greater than 90%.[7] Community pharmacists often are the primary source of information regarding UTI symptoms. In some countries, such as Canada, Australia, and the United Kingdom, they can independently manage lower UTIs from diagnosis until follow-up. Thus, pharmacists, as well as other health professionals, must understand UTI clinical presentation, diagnosis, and treatment options.[8] Approximately 80% of global antibiotic consumption occurs outside hospital settings, and more than 50% of antibiotics are sold without a prescription.[9,10] Access to antibiotics without prescriptions significantly contributes to the development of antimicrobial resistance.[11] Although studies have focused on the public's understanding and awareness of antibiotic resistance, the practices of community pharmacists in North Cyprus have not been assessed. This study aimed to assess the awareness of community pharmacists regarding antibiotic resistance and to investigate their practices in dispensing antibiotics for UTIs in North Cyprus.

MATERIALS AND METHODS

A cross-sectional study was conducted over a three-month period from November 2022 to January 2023. North Cyprus has six districts: 131 out of 350 community pharmacies in Nicosia, 97 in Famagusta, 131 in Girne, 20 in Güzelyurt, 17 community pharmacies in İskele, and 11 community pharmacies in Lefke.

The number of community pharmacists in North Cyprus was 350. Sample size calculation was performed using Raosoft, Inc. (Seattle, WA, USA), based on a margin of error of 5%, a 95% confidence level, and a population of 350 community pharmacists. The proposed sample size was 184 community pharmacies, calculated using Raosoft® software.[12] All community pharmacists actively working in North Cyprus were included in this study. However, community pharmacists who did not complete the survey were excluded. The study was explained to the participants in detail by the researchers, and verbal consent was obtained from the participants.

An expert panel was formed to develop the questionnaires, consisting of three clinical pharmacists, one pharmacologist and one active community pharmacist from North Cyprus. The questionnaire was developed and modified from previous studies.[13-16] The questionnaires were administered to 20 randomly selected community pharmacists. The pilot study data were included in the total dataset. Although the recommended sample size was 184, we aimed to increase the validity of our findings by inviting all community pharmacists in North Cyprus to participate. Two hundred and seven out of 350 community pharmacists, 207 agreed to participate in the survey in this study. The final sample size exceeded the minimum recommended sample size and provided a more comprehensive assessment of the population in this study.

The survey in this study had four parts. The first part consisted of five questions on the demographic information of community pharmacists. The second part included eight questions about the practice of antibiotic use by community pharmacists for UTI. The third section contained 5 questions about the reasons for prescribing antibiotics without prescription. The fourth part consisted of four questions on the awareness of community pharmacists of antibiotic resistance.

Ethical approval was obtained from the Scientific Ethics Committee of the Near East University (approval number: NEU/2022/107-1614, date: 10.11.2022).

Statistical Analysis

The study data were evaluated using SPSS version 21. Demographic information of community pharmacists and data on other questionnaire parts are presented as percentages and frequencies. Cronbach's alpha was used to measure the internal consistency or reliability in this study. The pearson chi-square test was used to determine the association between demographic characteristics and awareness. The significance level was accepted as 0.05.

RESULTS

Three hundred fifty community pharmacists were reached, and only 277 agreed to participate in the survey. In this study, 66.2% of community pharmacists were female, and 46.9% were younger than 30 years old (Table 1).

Table 1. The demographic characteristics of community pharmacists

	n	%
Gender		
Male	70	33.8%
Female	137	66.2%
Age		
<30 years old	97	46.9%
30-39 years old	72	34.8%
40-50 years old	21	10.1%
>50 years	17	8.2%
Nationality		
Turkish Republic of North Cyprus	191	92.3%
Republic of Türkiye	2	1.0%
Others	14	6.8%
Education status		
Bachelor of pharmacy	75	36.2%
Master's in pharmacy	104	50.2%
PhD	21	10.1%
Others	7	3.4%
Experience		
<5 years	90	43.5%
6-10 years	64	30.9%
11-15 years	17	8.2%
16-20 years	8	3.9%
>20 years	28	13.5%

The community pharmacist practice of dispensing antibiotics for UTI treatment had a total score was 2.43±0.40, and Cronbach's alpha was 0.64. Furthermore, 93.7% stated that they inquired about patients' history of drug allergies before dispensing antibiotics for UTIs, while 92.3% stated that they inform patients about the side effects of antibiotics and how to manage them when dispensing antibiotics for UTIs (Table 2).

Regarding community pharmacist awareness of antibiotic resistance, the total score was 2.65±0.52 and Cronbach's alpha was 0.74. The study revealed that out of the 277 community pharmacists surveyed, 188 (90.8%) demonstrated good awareness of antibiotic resistance, whereas 19 (9.2%) had poor awareness. In addition, 87.4% of patients who self-administered antibiotics had an increased risk of developing antibiotic resistance. 79.2% agreed that discontinuation of antibiotics either before or after treatment may increase antibiotic resistance (Figure 1).

Regarding community pharmacist reasons for dispensing antibiotics without a prescription, the total score was 2.52±0.45 and Cronbach's alpha 0.61 was 0.61 (Figure 2).

There was a statistically significant association between gender and awareness (p=0.006), as well as between age and awareness (p=0.02). There was a statistically significant association found between education status and awareness (p<0.001), as well as between experience and awareness (p<0.001) (Table 3).

DISCUSSION

UTIs are one of the most common infections among the public. The most common symptoms in patients with UTIs are pain and burning during urination, fatigue, fever, frequent urination, and pain in the lower abdomen.[17] Patients with UTIs frequently prefer to visit community pharmacies to control and manage their infections.

A study conducted in different regions in 2021 found that Lebanese pharmacists had good knowledge of UTIs. In addition, they showed that they have a good attitude and practice in this field.[18] The findings from Swart et al.'s[19] systematic review indicated that pharmacist-led UTI management provides a cost-effective alternative to GP-led management, benefiting patients with UTIs. Beahm et al.'s[20] study findings revealed that UTI management by pharmacists was effective and safe. On the other hand, a previous study showed that patient satisfaction with patient care was high level.[20] This study revealed that 90.3% of community pharmacists are confident in their knowledge of antibiotic use for UTI treatment. We believe that continuous training on UTI management and prevention can be provided by organizing

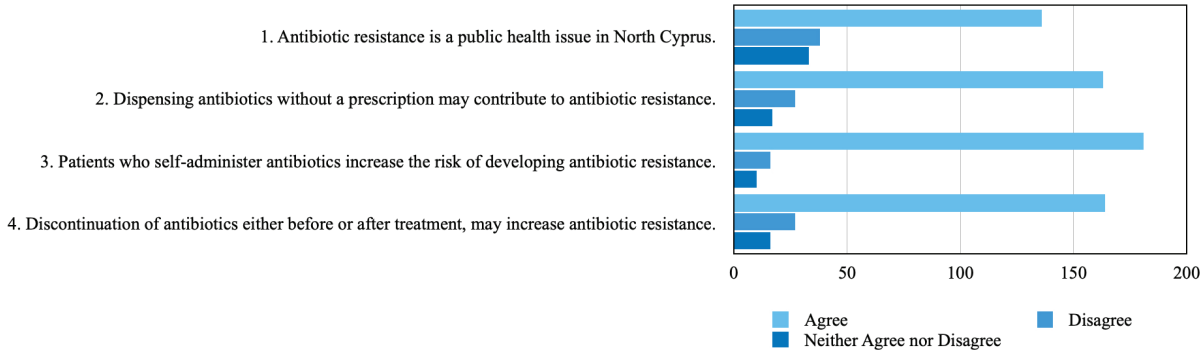

Figure 1. Community pharmacists' awareness of antibiotic resistance.

Table 2. Antibiotics used for UTI treatment

	Yes (%)	No (%)	Don't remember (%)	Score (mean ± SD)
1. Is dispensing antibiotics without prescription a common practice in UTI treatment in pharmacies?	85 (41.1%)	120 (58%)	2 (1.0%)	1.83±0.98
2. Do you dispense antibiotics without prescription at the patient's request for UTI treatment?	85 (41.1%)	120 (58%)	2 (1.0%)	1.83±0.98
3. Do you recommend or dispense antibiotics without prescription based on the patient's situation and symptoms?	91 (44.0%)	112 (54.1%)	4 (1.9%)	1.9±0.99
4. Do you recommend referring patients with symptoms of urinary tract infections to a physician?	172 (83.1%)	27 (13.0%)	8 (3.9%)	2.70±0.69
5. Do you recommend over-the-counter treatment for patients with UTI symptoms?	153 (73.9%)	50 (24.2%)	4 (1.9%)	2.50±0.86
6. Do you have a history of drug allergies before dispensing antibiotics for UTIs?	194 (93.7%)	12 (5.8%)	1 (0.5%)	2.88±0.47
7. Do you provide information to your patients regarding the potential side effects and their management when prescribing antibiotics for UTIs?	191 (92.3%)	9 (4.3%)	7 (3.4%)	2.88±0.44
8. Do you recommend that your patients complete the full course of antibiotics dispensed for their UTI treatment?	200 (96.6%)	1 (0.5%)	6 (2.9%)	2.96±0.22
Total score				2.43±0.40

UTI: Urinary tract infections, SD: Standard deviation.

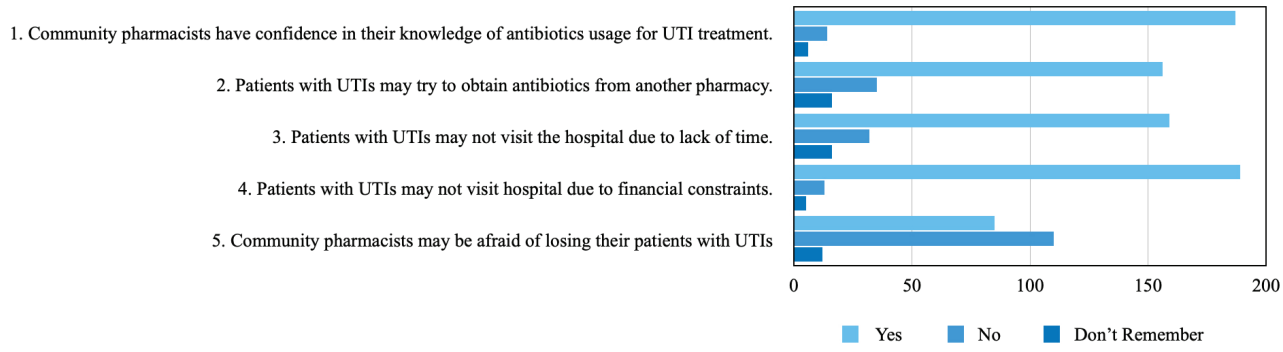

Figure 2. Reasons for dispensing antibiotics without prescription for urinary tract infection treatment.

Table 3. Relationship between demographic factors and community pharmacists' antibiotic resistance awareness

	Good	Poor	p
Gender			
Male	69	1	0.006
Female	119	18	
Age			
<30 years old	93	4	0.020
30-39 years old	65	7	
40-50 years old	16	5	
>50 years	14	3	
Nationality			
Turkish Republic of North Cyprus	173	18	0.867
Republic of Türkiye	2	0	
Others	13	1	
Education			
BPharm or PharmB	65	10	0.0001
MPharm	100	4	
PhD	20	1	
Others	3	4	
Experience			
<5 years	85	5	0.0001
6-10 years	64	0	
11-15 years	11	6	
16-20 years	7	1	
>20 years	21	7	

training programs for community pharmacists and the public facilitated by pharmacy faculties, the Ministry of Health, and the Pharmacists' Association in North Cyprus. Such programs can enhance the knowledge and awareness of UTIs and their management.

A study conducted in Jordan in 2016 showed that most antibiotics are dispensed without prescription in Jordan. Of the antibiotics dispensed with a prescription (31.5%) or without a prescription, 24.6% were appropriate for dosage and duration.[21] In another study conducted with community pharmacists in Jordan, there was insufficient knowledge about antibiotics and antibiotic resistance.[22] In this study, 65.7% of community pharmacists stated that antibiotic resistance is a public health concern. Given their awareness of antibiotic resistance, we believe that community pharmacists can effectively manage UTIs in North Cyprus by implementing continuous training programs.

The presence of resistant bacteria in UTIs can cause significant challenges in treatment. Overuse or misuse of antibiotics can lead to the development of antibiotic-resistant strains, such as extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, as well as Methicillin-Resistant *Staphylococcus aureus*. Inappropriate treatment of UTIs due to antibiotic resistance can cause several significant problems, such as persistent infections, increased morbidity and mortality, and higher healthcare costs.[23,24] In addition, community pharmacists can no longer dispense antibiotics without a prescription in North Cyprus. The justifications for this regulation include preventing antibiotic resistance, ensuring proper diagnosis and treatment, and promoting the rational use of drugs.

Study Limitations

The study was conducted with only 207 community pharmacists actively working in North Cyprus. Therefore, the data in this study cannot be generalized to the entire Cypriot population.

CONCLUSION

According to the findings, community pharmacists dispense antibiotics without prescription due to their confidence in their knowledge of antibiotic use for treating UTIs. In response to this situation, we suggest that educational programs for rational antibiotic use should be jointly organized by the Ministry of Health of North Cyprus, Cyprus Turkish Pharmacists Association, and pharmacy faculties.

MAIN POINTS

- Most of community pharmacists had good awareness of antibiotic resistance in North Cyprus.
- Antibiotic resistance is a common public health concern according to community pharmacists in North Cyprus.
- Community pharmacists dispense antibiotics without prescriptions because they are confident in their knowledge of antibiotic use for treating urinary tract infections in North Cyprus.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Scientific Ethics Committee of the Near East University (approval number: NEU/2022/107-1614, date: 10.11.2022).

Informed Consent: Verbal consent was obtained from the participants.

Authorship Contributions

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

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RESEARCH ARTICLE

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Pediatric Dentists' Approaches to Dental Treatment of Children with Dental Fear and Anxiety

Damla Akşit-Bıçak[1], Twana Othman Hussein[2], Gyanendra Kumar[3]

[1]Department of Pediatric Dentistry, Final International University Faculty of Dentistry, Nicosia, North Cyprus
[2]Private Practice, B & R Dental Center, Suleymaniyah, Iraq
[3]Department of Pediatric and Preventive Dentistry, Maulana Azad Institute of Dental Sciences, New Delhi, India

Abstract

BACKGROUND/AIMS: Dental fear and anxiety (DFA) are important facets of pediatric dental treatment and may cause oral health neglect and dental treatment evasion. This study aimed to collect and share opinions and experiences of pediatric dentists in treating children with DFA worldwide.

MATERIALS AND METHODS: Using the Google form survey tool (Google LLC, Mountain View, USA), an online questionnaire was created in five different languages and submitted to pediatric dentistry specialists. The questionnaire included 9 questions in total and gathered data on demographics, causes of DFA, preferred non-pharmacological and pharmacological behavior management techniques, used systems for local pain control, and methods while treating children.

RESULTS: A total of 1,054 pediatric dentists completed the questionnaire. For treating pediatric patients with DFA, >50% reported utilizing both pharmacological/non-pharmacological approaches, whereas 41.8% reported using only non-pharmacological techniques. The most frequently reported causes of DFA were extraction (55.7%), seeing a syringe (55.5%), and injection with a syringe (54.3%). Most participants (84.06%) preferred the conventional syringe technique, whereas only 15.08% reported using other delivery systems of local anesthetics for dental treatments of children with DFA. The most commonly utilized minimally invasive techniques were atraumatic restorative treatment (62.5%), silver diamine fluoride (55.2%), and hall technique (49.4%).

CONCLUSION: Our findings demonstrated that pediatric dentists mostly used behavior management techniques for the dental treatment of children with DFA. However, various minimally invasive dentistry approaches and advanced systems for local pain control could be used more extensively.

Keywords: Behavior management, children, dental fear and anxiety, pediatric dentistry

INTRODUCTION

Dental fear is a normal, unpleasant reaction to certain threatening stimuli associated with dental treatment. It refers to the response to a specific external threat. However, dental anxiety is a tense, pessimistic, and uncertain feeling that is not related to any object. Dental fear and anxiety (DFA) are often used interchangeably with each other; or used together as DFA.[1,2] Both environmental and genetic factors may play a role in the etiology of DFA.[3,4] In a recent systematic review, the prevalence of DFA was reported as 12.2% among 0-13-year-olds.[5]

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ORCID IDs of the authors: D.A.B. 0000-0002-0375-9026; T.O.H. 0000-0003-4565-4406; G.K. 0000-0002-2881-8555.

Address for Correspondence: Damla Akşit-Bıçak
E-mail: damlaaksit@gmail.com
ORCID ID: orcid.org/0000-0002-0375-9026

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For many children, a visit to the dentist's office might be stressful. Dental treatments are considered a threatening event and a source of fear, anxiety, pain, and discomfort for some patients. Children who are tense cooperative may exhibit disruptive behaviors, which can be a key indicator of DFA, increasing the child's risk of injury and treatment time.[6,7] Positive thoughts established during childhood also positively affect children's behavior. Therefore, many factors, such as the impression of the child about dental treatments or the clinic environment, experiences in the dental clinic, and the attitude of the parent and dentist, determine the child's behavior and may play a role in the development of dental anxiety in the future.[2] If DFA is effectively managed in childhood, dental anxiety may not continue into adulthood.[8] This suggests that pediatric dentists should employ suitable treatment modalities and provide effective behavioral shaping.[9]

Hence, DFA have been proven to be one of the most fundamental and challenging situations in pediatric dentistry, consequently making it pivotal to share experiences in this field with colleagues. According to all this information, this study aimed to collect and share opinions and experiences of pediatric dentists regarding causes of DFA among children, preferred non-pharmacological and pharmacological behavior management techniques, used systems for local pain control, and methods of pediatric dentists while treating children with DFA worldwide.

MATERIALS AND METHODS

Ethical Considerations

The study was approved by Near East University Scientific Research Ethics Committee (approval number: YDU/2021/98-1440, date: 23.12.2021).

Questionnaire Design

An online questionnaire was prepared using the Google form survey tool (Google LLC, Mountain View, USA). The objectives of the study and the willingness to participate were included at the beginning of the questionnaire. Participants who provided consent were allowed to proceed to the questionnaire. Five languages were used in the questionnaire: Turkish, English, Russian, Spanish, and Portuguese.

The self-administered questionnaire prepared in each language was first piloted on 10 colleagues for feasibility and clarity. After necessary corrections, the questionnaire was accepted as appropriate and understandable, and no further corrections were applied.

The questionnaire included 9 questions in total. An English version of the questionnaire is available as a supplementary file. The first part of the questionnaire gathered data on demographics and asked participants if they had ever treated a child with DFA. The causes of DFA among children, preferred non-pharmacological and pharmacological behavior management techniques, used systems for local pain control, and methods while treating children with DFA were asked. The questionnaire included closed-ended and open-ended questions. In this way, the participants were given the opportunity to share their methods that were not included in the questionnaire.

Participants

The online questionnaire was sent to pediatric dentistry specialists' societies and groups throughout the world. A convenience sample of subjects was obtained through heads of pediatric associations in different countries, by posting the survey to social media platforms (Facebook, WhatsApp and Telegram-based dental pediatric groups), and through referral of participating pediatric dentists who had already completed the questionnaire. No information revealing the identity of the participants was not obtained. No reminder was sent. The average time required to complete the questionnaire is 5-10 minutes.

The appropriate sample size was determined to be 384 using Cochran's sample size calculation algorithm for cross-sectional design with a 95% confidence interval and a 5% margin of error. Finally, we determined 460 individuals to be the required sample size after factoring in 20% for possible non-respondents. After completing the forms, they were translated back to English by dentists with dual languages.

Statistical Analysis

Data were evaluated using a Google Form Survey tool and Microsoft Excel (2016). Frequency and percentage were used as descriptive statistics. Statistical analysis was performed using the SPSS software version 24 (IBM SPSS Statistical Package for the Social Sciences) (Chicago, Illinois, USA).

RESULTS

Demographics Features

A total of 1,204 dentists completed the questionnaire. Of the 1,054 patients, 1,054 were pediatric dentists. The remaining 150 participants were not pediatric dentistry specialists, and their questionnaire answers were not included in the final analysis. Participants were from 90 countries distributed in Asia (n=288; 27.3%), Europe (n=261; 24.7%), North America (n=220; 20.8%), South America (n=185; 17.5%), Africa (n=97; 9.2%), and Oceania (n=3; 0.2%). The geographic distribution of participants is presented in Table 1.

The sample of pediatric dentists consisted of 824 female (78.2%) and 230 male (21.8%) (Table 2). The average number of years of experience was 10 among participants. It was observed that all respondents had experience treating patients with DFA.

The Causes of DFA in Children

More than 50% of respondents (n=588; 55.7%) reported extraction as the main cause of DFA, making it the most prevalent reported cause. The remaining causes of DFA as reported by respondents are, in descending order of frequency: seeing a syringe (n=585; 55.5%), injection with a syringe (n=573; 54.3%), root canal treatments (n=204; 19.3%), previous medical treatments performed in the hospital (n=195; 18.5%), restorative treatments (n=91; 8.6%), dental cleaning (n=16; 1.51%), and preventive treatments (n=12; 1.3%) (Table 2). In addition to these causes of DFA enumerated in the questionnaire, 50 respondents (4.7%) mentioned other causes of DFA: pain and ineffective local anesthesia during dental treatments (n=21; 1.9%), previous negative dental experience (n=20; 1.8%), family and parents' negative effects (n=5; 0.4%), using restraints (n=3; 0.2%), placing rubber dam (n=3; 0.2%), sound of the dental handpiece and suction (n=3; 0.2%), parent separation during dental treatment (n=2; 0.1%), dental traumatic injuries (n=2; 0.1%), and numbness after anesthesia (n=1; 0.09%) (Table 3).

Non-Pharmacological Behavior Management Techniques

Of the 1,054 total respondents, 441 participants (41.8%) reported using non-pharmacological techniques alone for treating pediatric patients

with DFA. 611 (57.9%) patients used both pharmacological and non-pharmacological techniques. When asked to select a preferred non-pharmacological behavior management technique used to treat a child with DFA, 920 respondents (88.2%) selected the tell-show-do technique, 822 (77.9%) selected positive reinforcement, and 629 (59.6%) selected distractions. The remaining results in descending order of selection are: modeling (n=453; 42.9%); relaxation (n=428; 40.6%), voice control (n=426; 40.4%), systematic desensitization (n=386; 36.6%), music (n=188; 17.8%), signaling (n=178; 16.8%), video modeling (n=100; 9.5%), physical restraint (n=100; 9.4%), videogame (n=64; 6.07%), negative reinforcements (n=40; 3.7%), and virtual reality (n=38; 3.6%) (Table 4). When respondents chose another technique, they reported

Table 1. Geographic distribution of pediatric dentists who participated

Continents	Country (n)	Total n (%)
Asia	India (115), Jordan (78), Iraq (15), Iran (14), Saudi Arabia (10), Lebanon (7), Syria (7), Nepal (6), Malaysia (5), Qatar (3), Oman (3), Philippine (3), Japan (3), Indonesia (3), Thailand (2), Pakistan (2), United Arab Emirates (2), Yemen (2), Myanmar (2), Kuwait (1), Bahrain (1), Taiwan (1), Palestine (1), Kyrgyzstan (1), Kazakhstan (1)	288 (27.32%)
Europe	Ukraine (33), Turkey (32), Spain (25), Russia (26), Germany (21), Romania (21), Portugal (21), Greece (15), Italy (12), United Kingdom (6), Poland (5), France (6), Slovakia (5), Israel (5), Switzerland (3), Belarus (3), Netherland (3), Czech public (3), Serbia (2), Austria (2), Belgium (2), Slovenia (2), Cyprus (1), Sweden (1), Ireland (1), Romania (1), Lithuania (1), Croatia (1), Armenia (1), Transnistrian (1)	261 (24.76%)
North America	Mexico (136), United States of America (54), Canada (16), Cost Arica (3), Honduras (3), Cuba (3), Guatemala (2), Trinidad and Tobago (1), Panama (1), Puerto Rico (1)	220 (20.87%)
South America	Brazil (106), Ecuador (21), Peru (19), Argentina (12), Columbia (10), Bolivia (6), Paraguay (4), Chile (3), Venezuela (3), Uruguay (1)	185 (17.55%)
Africa	Egypt (57), South Africa (7), Nigeria (7), Kenya (7), Sudan (5), Libya (4), Uganda (3), Morocco (2), Tanzania (2), Ghana (1), Zimbabwe (1), Botswana (1)	97 (9.20%)
Oceania	New Zealand (1), Australia (2)	3 (0.28%)
Total	(n=90)	**1054** (100%)

Table 2. Distribution of answers from pediatric dentists regarding their gender and whether they had ever seen a child with DFA

Questions	Answers	n (%)
What is your gender?	Male	230 (21.8%)
	Female	824 (78.2%)
Have you ever seen a child with dental fear and anxiety?	Yes	1,054 (100%)
	No	0

DFA: Dental fear and anxiety.

Table 3. Distribution of answers from pediatric dentists regarding the causes of DFA in children

Question	Answers	n (%)	Answers	n (%)
What are the causes of dental fear and anxiety in children? (You can choose more than one option)	Extraction	588 (55.7%)		
	Seeing a syringe	585 (55.5%)		
	Injection using a syringe	573 (54.3%)		
	Root canal treatment	204 (19.3%)		
	Medical treatments	195 (18.5%)		
	Restorative treatments	91 (8.6%)		
	Dental cleaning	16 (1.51%)		
	Preventive treatments	12 (1.3%)		
	Other (please specify in the blank)	50 (4.7%)	Pain and ineffective local anesthesia during dental treatments.	21 (1.9%)
			Previous negative dental experience.	20 (1.8%)
			Negative effects of family and parents.	5 (0.4%)
			Using restraints.	3 (0.2%)
			Placing a rubber dam.	3 (0.2%)
			Sound of dental handpiece and suction.	3 (0.2%)
			Parental separation during dental treatment.	2 (0.1%)
			Dental trauma.	2 (0.1%)
			Numbness after anesthesia.	1 (0.09%)

DFA: Dental fear and anxiety.

aromatherapy (n=5; 0.4%), a combination of techniques (n=5; 0.4%), hypnosis (n=4; 0.3%), parent separation (n=2; 0.1%), time out policy (n=1; 0.09%), and storytelling (n=1; 0.09%) (Table 4).

Pharmacological Behavior Management Techniques

The preferred pharmacological technique for treating children with DFA was general anesthesia, as reported by 527 respondents (50%). Nitrous oxide oxygen sedation was preferred by 419 respondents (39.7%), and other types of sedation were preferred by 330 respondents (31.3%) (Table 5).

Systems for Local Pain Control

Of the participants, 886 (84.06%) preferred the conventional syringe technique, whereas 159 (15.08%) reported using other delivery systems for local anesthetics. The Wand STA System was preferred by most pediatric dentists who reported using other delivery systems (Table 6).

Minimally Invasive Dentistry Approaches

For treating pediatric patients with DFA, minimally invasive techniques were preferred by most respondents. The techniques preferred, in descending order, were: Atraumatic restorative treatment (n=659; 62.5%), silver diamine fluoride (n=582; 55.2%), hall technique (n=521; 49.4%), laser application for caries removal (n=143; 13.5%), air abrasion (n=66; 6.2%), chemo mechanical caries removal (n=7; 0.6%), preventive treatments (n=5; 0.4%), selective caries removal without dental anesthesia (n=3; 0.2%), lesion sterilization and tissue repair (n=3; 0.2%), interim therapeutic restorations (n=2; 0.1%), ozone application (n=1; 0.09%) (Table 6). Some pediatric dentists suggested aromatherapy, psychological therapy, and cognitive behavioral therapy for behavioral support, and buffered anesthesia solution to decrease pain during anesthesia (Table 6).

DISCUSSION

This study aimed to collect, analyze, and share the opinions and experiences of pediatric dentists worldwide regarding DFA experienced by children during dental treatments. Pediatric dentists frequently encounter disruptive behaviors in children when conducting dental treatments. These children often report a history of unfavorable treatment experiences.[2] All of our respondents in this study had experienced pediatric patients with DFA.

Cademartori et al.[10] stated because of the possibility of painful/forceful removal of the tooth; extractions may cause DFA during dental treatments, thus resulting in uncooperative behavior among children.[11]

Table 4. Distribution of answers from pediatric dentists regarding non-pharmacological behavior management techniques used among children with DFA

Question	Answers	n (%)	Answers	n (%)
Which non-pharmacological behavior management techniques do you use in children with dental fear and anxiety? (You can choose more than one option)	Tell-show-do technique	920 (88.2%)		
	Positive reinforcement	822 (77.9%)		
	Video and audio distractions	629 (59.6%)		
	Modeling	453 (42.9%)		
	Relaxation	428 (40.6%)		
	Voice control	426 (40.4%)		
	Systematic desensitization	386 (36.6%)		
	Music	188 (17.8%)		
	Signaling	178 (16.8%)		
	Video modeling	100 (9.4%)		
	Physical restraint	101 (9.5%)		
	Videogames	64 (6.07%)		
	Negative reinforcements	40 (3.7%)		
	Virtual reality	38 (3.6%)		
	Other (please specify in the blank)	21 (1.57%)	Aromatherapy	5 (0.4%)
			Combination of the above techniques	5 (0.4%)
			Hypnosis	4 (0.3%)
			Parent separation	2 (0.1%)
			Time-out policy	1 (0.09%)
			Storytelling	1 (0.09%)

DFA: Dental fear and anxiety.

Table 5. Distribution of answers from pediatric dentists regarding pharmacological behavior management techniques used among children with DFA

Question	Answers	n (%)
Which pharmacological behavior management techniques do you use in children with dental fear and anxiety? (You can choose more than one option)	General anesthesia	527 (50%)
	Nitrous oxide oxygen sedation	419 (39.7%)
	Other types of sedation	330 (31.3%)

DFA: Dental fear and anxiety.

Table 6. Distribution of answers from pediatric dentists regarding the use of systems for local pain control and minimally invasive dentistry approaches among children with DFA

Question	Answers	n (%)	Answers	n (%)
What do you use to control pain in children? (You can choose more than one option)	Conventional syringe technique	886 (84.06%)		
	Other local anesthetic delivery systems (please specify in the blank)	159 (15.08%)	The Wand STA system	38 (3.6%)
			The Quick Sleeper® system	14 (1.32%)
			Morpheus anaesthesia unit	7 (0.6%)
			Insulin injector	6 (0.56%)
			Needleless pressure injection technique	6 (0.56%)
			Dentapen-powered injector	4 (0.37%)
Which minimally invasive dental approach is most appropriate for children with dental fear and anxiety? (You can choose more than one option)	Atraumatic restorative treatment	659 (62.5%)		
	Silver diamine fluoride	582 (55.2%)		
	Hall technique	521 (49.4%)		
	Laser treatment for caries removal	143 (13.5%)		
	Air abrasion	66 (6.2%)		
	Chemomechanical caries removal	7 (0.6%)		
	Preventive treatments	5 (0.4%)		
	Selective caries removal	3 (0.2%)		
	Interim therapeutic restoration	2 (0.1%)		
	Ozone application	1 (0.09%)		
	Lesion sterilization and tissue repair	3 (0.2%)		

DFA: Dental fear and anxiety.

In the present study, extraction was the most common cause of DFA. This study also indicated that seeing a syringe before injection and injection with a syringe were the second and third most reported causes of DFA, respectively. In line with this, Ghibban et al.[12] reported dental injection as the major reason of DFA. Peng et al.[13] reported that preschoolers have a high rate of dental anxiety and show a significant fear of needles, dentists, tooth extraction, drilling, and oral anesthesia.

The quality of dental treatment is affected by pain during dental procedures. Children frequently cite the conventional syringe as an image of pain and fear. New technologies have been developed to provide near-painless injections and reduce dental anxiety.[14] Therefore, we asked our study participants about their usage of different systems for local pain control that could be more acceptable, suitable, and effective. The Wand System was preferred by most pediatric dentists who reported using other local anesthetic delivery systems in this study. Previous studies[15,16] have evaluated the advantages of different systems for local pain control. In the study of Chavhan et al.[15] the Wand system was found to be superior in terms of lower pain for 12-year-olds compared with the conventional injection technique, but no difference was detected in the 6- and 9-year-old age groups. Patini et al.[16] reported that dental anesthesia administered to children using a computer-controlled delivery system reduced pain better than that administered with a conventional syringe. Vitale et al.[17] compared the discomfort felt by patients using a conventional syringe with the computer-controlled local anesthetic delivery system SleeperOne. Researchers have reported that the SleeperOne device is beneficial for reducing pain related to anesthetic injection, especially in children. Muller-Bolla et al.[18] reported computer-controlled local anesthetic delivery systems as preferable for primary dentition. Despite all the developments in this field, the participants of this study mostly preferred the conventional syringe technique. The conventional syringe technique may still be preferred due to the pain-reducing effect of topical anesthesia prior to injection and their price/accessibility.

Among the non-pharmacological behavior management techniques, Dhar et al.[19] reported tell-show-do, audiovisual distraction, breathing relaxation, biofeedback relaxation, cognitive behavior therapy, animal-assisted therapy, positive reinforcement, and modeling showed a significant reduction in anxiety among patients undergoing dental treatments. Nagaveni et al.[20] demonstrated videos of various non-pharmacological behavior management techniques to 68 children between 9 and 12 years. These techniques included tell show do, voice control, magic trick, parental presence/absence, non-verbal communication, positive reinforcement, distraction, and protective stabilization. Researchers reported that the least accepted techniques were voice control and protective stabilization; however, positive reinforcement was the most accepted technique, followed by distraction and magic trick. It was recommended that the opinions of children should always be considered. In another study, the use of virtual reality notably decreased the pain and anxiety of children and the duration of dental treatment.[21] Hypnosis is also recommended to resolve anxiety during dental treatments.[22] In this study, participating pediatric dentists preferred the tell-show-do method as the most effective technique for treating children with DFA. There has been confirming proof for the tell-show-do approach to decreasing anxiety in children.[12,23] This could be from the step-by-step principle of this technique, which gives the child an idea about what is going to happen in the next step and helps the child believe that the dentist will not hurt them. This supports the building of a trust relationship between the child with DFA and the dentist. In contrast, Abbasi et al.[24] reported most widely used "tell-show-do" technique did not help reduce anxiety levels. Greeshma et

al.[25] reported that children were most relaxed in virtual reality, followed by audio recordings, and were least relaxed in "tell-show-do" technique during dental visits. Positive reinforcement, video-audio distractions, modeling, relaxation, voice control, and systemic desensitization were detected as the other widely used non-pharmacological behavior management techniques among participants in their study.[25] The combined use of behavioral guidance techniques is also recommended for successful results.[26] In the current study, the most preferred techniques after the tell-show-do were, positive reinforcement and distraction. Then, modeling, relaxation, voice control, systematic desensitization, music, and signaling were conducted. The least preferred techniques were video modeling, physical restraint, video games, negative reinforcement, and virtual reality. When respondents chose another technique, few reported aromatherapy, hypnosis, parent separation, time-out policy, or storytelling. Following current developments in this field and using various behavioral support techniques together may help clinicians manage the behaviors of pediatric dental patients.

Pharmacological management techniques are the only options available to children who cannot overcome dental anxiety using non-pharmacological management approaches.[27,28] A retrospective cross-sectional study reported that one-third of patients were treated with pharmacological interventions. General anesthesia was used most frequently. Patients treated with general anesthesia required restorative treatment and extractions that involve pain. However, two-thirds of the patients were treated with non-pharmacological interventions, which required treatments with less pain.[29] In the current study, half of the participants reported that they conducted dental treatment for children with DFA under general anesthesia if necessary. Moreover, nearly 40% of participants preferred nitrous oxide oxygen sedation, while 30% used other types of sedation.

Conventional methods for the restoration of dental caries may cause distress in patients. To lower the levels of anxiety experienced by children, minimal intervention dentistry principles can be used to minimize dental anxiety.[30] To manage caries in young children, minimally invasive dentistry (MID) approaches should be considered as a junction between restorative treatments and preventive strategies. This way of thinking has a favorable effect on how well a child behaves in the dentist chair since many procedures can be completed without the use of high-speed rotating equipment, rubber-dam isolation, or local anesthetic, which all help patients feel less scared and anxious. MID approaches should be promoted and used in the pediatric dentistry community because of their advantages over conventional restorative treatments, even though many dental professionals are still resistant to it.[31] According to Arrow et al.[32] minimally invasive treatments that support family- and child-centered care are a suitable option for general anesthesia and should be considered for the management of early childhood caries. The use of atraumatic restorative treatment may reduce the risk of worsening dental anxiety in children and may therefore be a valuable alternative to dental practice.[33] However, Barreto et al.[34] reported no significant difference in the anxiety of children related to the types of treatment and observed higher anxiety levels during atraumatic restorative treatment and silver diamine fluoride applications. The current study demonstrated that participants preferred minimally invasive procedures that do not involve sound/drilling and avoided painful stimuli. In the current study, the most preferred techniques were atraumatic restorative treatments, silver-diamine fluoride applications, and the Hall Technique. In this way, children may be able to overcome DFA and eliminate previous traumatic dental experiences.

With this study, we provided a perspective on current management strategies for DFA, which is a situation most frequently encountered by pediatric dentists, with participants from all around the world. The experiences of more than one thousand pediatric dentistry specialists from different regions of the world gave us an opportunity to provide an overview of the current situation of DFA management strategies. The provision of questionnaire forms in most spoken languages in the world made the current study available to non-English speakers.

However, we could not get samples from every part of the world. Using an online questionnaire causes some details to be lost, which can be overcome by face-to-face sample taking. This study was conducted immediately after the COVID-19 lockdowns, and there were many online questionnaire studies. Therefore, we made our questionnaire as short as possible to get enough sample. In addition, the questionaire did not ask about the age of the participants and whether they worked in a private or government institution. However, further studies including a larger sample of participants from all parts of the world with more detailed analysis of the findings are needed to share the most possible and diverse experiences about dental treatment of children with DFA.

CONCLUSION

Applying dental treatments with the desire, harmony, and happiness of children is the key point of success in pediatric dentistry today. For this reason, pediatric dentists make an effort to perform the necessary treatments without causing fear and anxiety in children. The fact that all participants encountered a child with DFA in our study indicates that this situation is indeed quite widespread. Our findings demonstrated that pediatric dentists mostly use behavior management techniques for the dental treatment of children with DFA. However, various MID approaches and advanced systems for local pain control could be used more extensively. We believe that the findings of our investigation provide a mechanism needed to better understand the issue of DFA and to design a proper method for its avoidance and treatment among children and adolescents.

MAIN POINTS

- In the current study, the extraction procedures and conventional syringe appearance/injection were the most reported causes of dental fear and anxiety (DFA). However, the conventional syringe technique was preferred by participating pediatric dentists.
- Tell-show do, positive reinforcement, and video/audio distractions are the most commonly used non-pharmacological behavior management techniques.
- The most preferred pharmacological technique for treating children with DFA was general anesthesia followed by nitrous oxide-oxygen sedation.
- Atraumatic restorative treatment, silver diamine fluoride, and the Hall technique are the most commonly used minimally invasive treatment approaches for children with DFA.

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ETHICS

Ethics Committee Approval: The study was approved by Near East University Scientific Research Ethics Committee (approval number: YDU/2021/98-1440, date: 23.12.2021).

Informed Consent: It was obtained.

Authorship Contributions

Concept: D.A.B., T.O.H., G.K., Design: T.O.H., Data Collection and/or Processing: T.O.H., Analysis and/or Interpretation: D.A.B., T.O.H., G.K., Literature Search: D.A.B., T.O.H., G.K., Writing: D.A.B., T.O.H., G.K.

Footnotes

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RESEARCH ARTICLE

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Knowledge and Attitudes Related to COVID-19 Vaccine Uptake and Hesitancy of Attendants of a Healthcare Center in North Cyprus

Özen Asut, Songül Vaizoğlu, Gulifeiya Abuduxike, Sanda Cali

Department of Public Health, Near East University Faculty of Medicine, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: Vaccination is the most effective method for controlling infectious diseases, including coronavirus disease-2019 (COVID-19). The aim of this study was to investigate COVID-19 vaccine uptake status as related to knowledge and attitudes, including vaccine hesitancy, in a healthcare center in North Cyprus, where no previous data among the general population was available during the study period.

MATERIALS AND METHODS: This descriptive study included 428 patients and their companions presenting to a healthcare center between October 4, 2021 and October 31, 2021. The data collection tool was a questionnaire designed by the researchers that utilized international documents. The data were analyzed using SPSS 18.0.0 software.

RESULTS: Of the participants, 52.3% were female, 50.0% were 25-44 years of age and 25.2% were in the 45-64 age group, with a median age of 36. Regarding vaccine coverage, we have 93% had received at least one dose of the COVID-19 vaccine and 64.5% had received two doses. The one-dose vaccination rate was higher than the global average. Of the vaccinated, 64.5% had received CoronaVac and 37.6% received Comirnaty. The majority believed that vaccines are effective, and correct knowledge of COVID-19 vaccines was a predictor of higher vaccine uptake. Nevertheless, most of the participants displayed hesitancy for a variety of reasons, led by the speedy authorization of the vaccines by the World Health Organization (40%), adverse effects (22%), and speedy development of the vaccines (18%), while 42.1% indicated no hesitancy.

CONCLUSION: This study clarified the factors influencing COVID-19 vaccination uptake among the general population in this region.

Keywords: COVID-19 vaccine intention and uptake, knowledge and attitudes, COVID-19 vaccine hesitancy, North Cyprus, general population

INTRODUCTION

Vaccination is the most effective method for controlling morbidity and mortality due to infectious diseases, including coronavirus disease-2019 (COVID-19).

A total of 13.4 billion vaccine doses had been administered by May 2023 according to World Health Organization (WHO) data[1] and 70% of the world population had received at least one dose of a COVID-19 vaccine. According to other international data, only 29.9% of low-income people had received at least one dose of the vaccine as of May 2023.[2]

By 2022, the percentages of vaccinated people were 88.95% in China, 88.67% in Cuba, 86.48% in Portugal, 80.96% in Italy, 76.02% in Germany, 75.13% in the United Kingdom, 62.67% in Türkiye, and 67.18% in the USA.[3]

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ORCID IDs of the authors: Ö.A. 0000-0002-9604-4037; S.V. 0000-0001-9279-1740; G.A. 0000-0002-9798-7459; S.C. 0000-0001-9929-2637.

Address for Correspondence: Özen Asut
E-mail: ozen.asut@neu.edu.tr
ORCID ID: orcid.org/0000-0002-9604-4037

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However, vaccination problems continue to occur in low- and middle-income countries.[4] According to data from Cyprus in general, 50.2% of the population were fully vaccinated, whereas 64.6% had received at least the first dose in 2021.[5]

Vaccine hesitancy should be monitored in all countries by relevant measures according to WHO.[6,7] Vaccine hesitancy was previously defined as "the delay in acceptance or refusal of vaccination services despite their availability" which was modified in May 2022 by the WHO as "a motivational state of being conflicted about, or opposed to getting vaccinated".[8]

In high-income countries with adequate vaccination services, vaccine hesitancy is the most important factor in decreasing vaccination rates, ranging from 7 to 77.9%.[9-12] However, data from low- and middle-income countries on this issue are limited.[13] A study conducted in Türkiye among the general population found that 37.9% were not willing to have a COVID-19 vaccine.[14] A similar study conducted in Cyprus illustrated vaccination hesitancy among nurses and midwives as 70.0%.[15]

To the best of our knowledge, no previous study has been conducted to establish COVID-19 vaccine uptake, vaccination intention, and vaccine hesitancy in North Cyprus among the general population. The COVID-19 epidemic was continuing at a moderate level in Cyprus at the time of the study. The leading COVID-19 variant in North Cyprus was the Delta variant (B.1.617.2), a severe acute respiratory syndrome-coronavirus-2 strain. The number of weekly cases increased from 562 in the 1st week to 798 in the 4th week of the study. Cases per 100,000 were 147.12 in the 1st week and 208.9 in the 4th week. The case fatality rate was 0.26 per 100,000 in the last week.[16,17]

CoronaVac and Comirnaty vaccines have been available in the country since February 2021. CoronaVac, Comirnaty, AstraZeneca, Jannsen, and Moderna vaccines are available from time to time. The main reason for getting the specific vaccine types was the availability of the vaccines at the time of need.

Objective

The current study aimed to investigate COVID-19 vaccine uptake status in terms of knowledge and attitudes, including vaccine hesitancy, in a healthcare center in North Cyprus.

MATERIALS AND METHODS

This study was carried out during 4-31 October 2021 at a central healthcare facility in Nicosia, North Cyprus.

This descriptive epidemiological study included patients and their companions who applied to the healthcare center for any reason. The dependent variables were knowledge and attitudes regarding COVID-19 vaccination, including acceptance of vaccination and vaccine hesitancy. Independent variables included age, gender, nationality, marital status, occupation, unemployment, educational status, socioeconomic status, history of chronic disease, and knowledge of COVID-19 and vaccines.

Sampling

A non-probability convenience sampling method was used, and individuals 15 years of age and older who were attending the healthcare center during the study period were included. A total of 503 people were approached, but 75 were refused to participate in the study.

The selected healthcare unit is a comprehensive primary healthcare center in the region. The people visiting the health facility included all age groups, nationalities, ethnicities, and genders, resembling the population distribution of the city.

Outcome Measurement

The primary outcome of the study was the uptake frequency of COVID-19 vaccines.

Data Collection Tools and Methods

The data collection tool was a questionnaire designed by the researchers based on international documents (Supplementary 1)[18-22]. The first 12 questions are about the participants' sociodemographic characteristics. Occupations were classified according to the International Labor Organization classification.[18] During the evaluation, participants were grouped as health professionals and others for comparison.

The following 10 questions are about the COVID-19 history and vaccination status of the participants. The type of COVID-19 vaccine and the number of doses was discussed in this section. The intention or willingness was measured by Question 23, which covers 11 items: protection of oneself, family, and community; belief in science, returning to normal life, and reducing the costs of the pandemic.

The hesitancy data were derived from the answers to question 24 of the questionnaire ("the reasons for not being vaccinated"). This question included 13 items as reasons for not receiving the vaccine, including adverse effects, novelty of the vaccines, suspicion of effectiveness, and false or non-relevant perceptions.

The next section comprises 25 questions about the participants' attitudes (17Qs) and knowledge (8Qs) of theCOVID-19 vaccination. The attitude questions (Qs26-43) are in Likert format and cover questions on vaccine benefits, efficacy, and side effects, involvement in a vaccine trial, and belief in public health professionals and community leaders.

The last 8 questions (Qs44-51) are on the knowledge of COVID-19 and vaccines. Correct knowledge of COVID-19 vaccines was obtained from questions 28, 48, and 51.

Q28: This is a Likert-type question asking about the influence of the vaccine on preventing the spread of the disease. The answer was accepted as satisfactory if the respondent responded "I strongly agree" or "I agree".

Q48: The response was accepted as satisfactory if the participant answered "yes" to Q48, inquiring about the vaccination necessity for people who recovered from a COVID-19 infection. Q51 tested the opinion of the participant about the effectiveness of COVID-19 vaccines. If the participant responded "very effective" or "effective", the response was considered satisfactory.

Pre-test: The pre-test was conducted on 20 patients and their companions who were attending a hospital in Nicosia. Minor revisions were made in the revised manuscript. The pre-test questions were understood sufficiently by the participants, and the questionnaire was completed in about 10 minutes on average.

Questionnaires were completed anonymously under observation after obtaining written informed consent. Permission to conduct the

research was provided by the Ministry of Health. The study protocol was approved by Near East University Faculty of Medicine Scientific Research Ethics Committee (approval number: 2021/95-1416, date: 30.09.2021). The Declaration of Helsinki was complied with.

Statistical Analysis

Data were analyzed using SPSS 18.0.0 (Statistical Package for the Social Sciences). For the analysis, descriptive statistics were calculated and marginal and cross-tabulated. The categorical data were evaluated using the chi-square test, with the significance level set as $p<0.05$.

RESULTS

Of the total of 503 participants, 428 were accepted to participate and 75 were rejected to be included in the study. The acceptance rate is 85%.

The sociodemographic characteristics of the participants are presented in Table 1. The majority of the participants were citizens of North Cyprus and Türkiye. Of the total, 52.3% were female, 50.0% were 25-44 years of age and 25.2% were in the 45-64 age group, with a median age of 36. The 65 age group comprised 5.9% of the participants.

The participants' history of chronic diseases and COVID-19 is presented in Tables 2, 3. Of the participants, 12.9% stated that they had recovered from a COVID-19 of, and 61.4% stated that they knew people who had died of COVID-19. There was no statistically significant difference between participants with chronic disease and those with COVID-19.

The vaccination uptake status of the participants according to demographic variables is presented in Table 4. A total of 93.2% of those aged below 45 years and 92.5% of those aged 45 and above were vaccinated for COVID-19. The differences between age groups were not statistically significant. Similarly, the differences between the groups regarding some categorical variables, such as vaccination status according to nationality, sex, having a chronic disease, having children, economic and employment status, and education, were not found statistically significant. The difference between health workers and members of other occupations in vaccine uptake was also not significant. The only demographic variable found to be significant was marital status, with married people being significantly more vaccinated compared to single people.

The knowledge of COVID-19 vaccination was inquired by 3 questions and satisfactory responses were compared between vaccinated and unvaccinated participants. The results indicated that there was a significant difference between participants with satisfactory responses and those with non-satisfactory responses regarding vaccination rates. People who answered these questions satisfactorily were vaccinated significantly more than those in the other group:

1. Vaccination will prevent the spread of the disease: $\chi^2=92.14$, $p=0$.

2. Vaccination is necessary for people who have had COVID-19: $\chi^2=40.625$, $p=0$.

3. COVID-19 vaccination is effective: $\chi^2=73.93$, $p=0$.

Table 5 presents the COVID-19 vaccination status of the participants. Of the total, 93.0% were vaccinated with one or more doses for COVID-19, 64.5% had 2 doses, 19.4% had 3 doses, and 10.3% received only one dose.

Table 1. Socio-demographic characteristics of the participants (Nicosia, October 2021) (n=428)

Socio-demographic characteristic	n	%
Gender		
Female	224	52.3
Male	204	47.7
Age group		
15-24	81	18.9
25-44	214	50.0
45-64	108	25.2
≥65	25	5.9
Mean ± SD: 38.3±14.8; median: 36; min.-max.: 15-83		
Country of origin		
North Cyprus	237	55.4
Türkiye	184	43.0
Other countries	7	1.6
Marital status		
Married	225	52.6
Single	193	45.1
Divorced/Widower	10	2.3
Having children		
Yes	227	53.0
No	201	47.0
Educational status		
Primary school and below	68	15.9
Junior high school: The students' voices were heard	51	11.9
High school	132	30.8
University and above	177	41.4
Work status		
Working	216	50.5
Not working	161	37.6
Retired	51	11.9
Number of household members		
1-2	140	32.7
3-4	222	51.8
≥5	66	15.5
Mean ± SD: 3.2±1.4; median: 3; min.-max.: 1-8		
The economic status of households		
High	31	7.2
Middle	312	72.9
Low	85	19.9

SD: Standard deviation, min.: Minimum, max.: Maximum.

Table 2. Chronic disease history of the participants (Nicosia, October 2021) (n=428)

Chronic disease distribution	n	%*
Cardiovascular system	48	11.2
Endocrine system	31	7.2
Respiratory system	24	5.6
Gastrointestinal system	5	1.2
Other	8	1.9
Total number of participants with chronic diseases	86	20.1

*Row percentages over 428.

Among the vaccinated participants, 64.5% had received the CoronaVac COVID-19 and 37.6% received the Comirnaty vaccine. The reasons for being vaccinated were expressed as personal protection from the infection (79.6%), protecting family members (79.1%), normalizing life (72.0%), protecting the community (67.3%), believing in science (53.5%), to be able to travel again (46.4%), and to be able to participate in social activities (40.5%).

Of the participants, 22.4% expressed no concern about acquiring the COVID-19 infection while 16.1% were seriously concerned. However, most (61.4%) of the participants were moderately concerned. Similar to the rationale for being vaccinated, confidence in some leaders, as expressed by the participants, was 71.1% for public health workers, 36.7% for politicians, and 29.9% for religious leaders. Regarding the source of information about COVID-19 vaccines, 46.7% stated that they received information from television and newspapers, 40.2% from social media and the internet, 31.1% from the Ministry of Health, 7.2% from primary healthcare physicians, or 4.7% from universities.

Factors related to hesitancy about vaccines (question 24) were indicated as concerns about adverse effects by 22.4%, the rapid development of the COVID-19 vaccines by 18.0%, vaccine ineffectiveness for prevention

Table 3. Past-COVID-19 infection status among participants with chronic diseases compared with patients without chronic diseases (n=428)

Chronic disease status	Past-COVID-19 (+), (n, %)	Past-COVID19 (-), (n, %)	Total, (n, %)*
Participants with chronic disease (n=86)	11 (12.8)	75 (87.2)	86 (20.1)
Participants without chronic disease (n=342)	44 (12.9)	298 (87.1)	342 (79.9)
Total	55 (12.8)	373 (87.2)	428 (100)
			χ^2=0, p=0.98

*Column%; others row%, COVID-19: Coronavirus disease-2019.

Table 4. The vaccination uptake status of the participants according to demographic variables (Nicosia, October 2021) (n=428)

	COVID-19 vaccination status				
Variable	**Vaccinated**	**Not vaccinated**	**Total**	**χ^2**	**p**
	n (%)	n (%)		0.08	0.78
Age (years)					
Under 45	275 (93.2)	20 (6.8)	295		
45 & over	123 (92.5)	10 (7.5)	133		
Marital status					
Married	195 (96.1)	8 (3.9)	203	55.58	**0.018**
Single	203 (90.2)	22 (9.8)	225		
Gender				0.42	0.52
Male	188 (92.2)	16 (7.8)	204		
Female	210 (93.8)	14 (6.3)	224		
Chronic disease				0.24	0.63
Yes	317 (92.7)	25 (7.3)	342		
No	81 (94.2	5 (5.8)	86		
Having children				7.23	0.07
Yes	204 (89.9)	23 (10.1)	227		
No	194 (96.5)	7 (3.5)	201		
Economic status				0.25	0.62
Total of high and medium response	320 (93.3)	23 (6.7)	343		
Low responses	78 (91.8)	7 (8.2)	85		
Employment				1.41	0.23
Employed	204 (94.4)	12 (5.6)	216		
Unemployed	194 (91.5)	18 (8.5)	212		
Occupation				0.55	0.46
Health professionals	8 (88.9)	1 (11.1)	9		
Others	196 (94.7	11 (5.3)	207		
Education				0.342	0.56
Junior high & <	228 (92.3)	19 (7.7)	247		
High school & >	166 (93.8)	11 (6.2)	177		

COVID-19: Coronavirus disease-2019.

by 9.6%. Of the total, 58% expressed some kind of hesitancy about the vaccines, whereas 42% displayed no hesitancy.

The factors influencing confidence in vaccines negatively (question 25) were the speedy emergency use authorization by the WHO (40.2%), use of new technologies in producing the vaccines (28.7%), the speedy development of new measures and techniques (24.1%), and some misleading or fake information (19.6%).

Regarding vaccine efficacy, 81.8% believed vaccines are beneficial for protection from the infection. and 68.9% of the respondents expressed that vaccination should be mandatory for all people, and 79.9% thought vaccines should be mandatory for health professionals.

Likert-type attitudes and knowledge questions showed that higher education would not indicate better knowledge and attitude in general, except for better knowledge of the fatality rate and incubation period of the disease (Table 6).

Of the participants, 23.5% of those whose education level was junior high school and below and 46.6% of those with education of high school and above stated that they received information about COVID-19 vaccines from social media and the internet. The difference between the groups according to education levels regarding receiving information on vaccines from social media and the Internet was statistically significant. Higher educated people received information from social media and the internet significantly more frequently than the less educated group.

DISCUSSION

In this study, 93.0% of the participants were vaccinated with one or more vaccine doses for COVID-19. The overall one–dose rate was much

Table 5. The vaccination status of the participants according to vaccine type and the number of doses uptaken (Nicosia, October 2021) (n=428)

COVID-19 vaccination status	n	%
At least one dose	398	93.0
Vaccine type		
CoronaVac (Sinovac)	276	64.5
Comirnaty (Pfizer-BioNTech)	161	37.6
Jannsen	22	5.1
AstraZeneca (Vaxzevria)	13	3.0
Moderna	4	0.9
Number of vaccine doses		
1	44	10.3
2	276	64.5
3	83	19.4
4	2	0.5
No difficulty in accessing the vaccines	304	71.0

COVID-19: Coronavirus disease-2019.

Table 6. Attitudes and knowledge about COVID-19 and COVID-19 vaccines by educational status (Nicosia, October 2021) (n=428)

Attitude, knowledge	Educational status					
	Junior high school and below		High school and above			
	n*	%*	n	%	χ^2	p
Would you like to learn more about vaccines						
	111	93.3	289	93.5	0.72	0.70
COVID-19 vaccination is important for curbing the spread of the disease						
	102	85.7	275	89.0	0.9	0.64
COVID-19 vaccines are important for community health						
	109	91.6	267	86.4	2.16	0.34
I received COVID-19 vaccination because it is mandatory						
	63	52.9	118	38.3	12.6	**0.02**
COVID-19 vaccination is unnecessary because most people will contract COVID-19						
	25	21.0	52	16.8	7.3	0.26
Correct knowledge of the COVID-19 fatality rate						
	56	47.1	179	57.6	24.1	**0.04**
Correct knowledge of the COVID-19 incubation period						
	24	20.2	96	31.1	5.1	**0.02**

*n and (%) reveal the sum of the number and percentage of people who strongly agreed and agreed with the statements below (Likert scale).

higher than the global average of 70%.[2] Of the participants in the study, 81.8% indicated that vaccines are beneficial and effective for protection from infection.

Our findings are in compliance with a broad survey of low- and middle-income countries. A survey of 15 studies in 2020-2021 compared low-income, lower-middle-income, and upper-middle-income countries with Russia and the USA.[4] Similar to the 93% vaccine uptake rate in our study, the average acceptance rate in all studies in low and middle income countries was 80.3%, higher than samples from the United States (64.6%) and Russia (30.4%).[4] Another study covering 15 African countries found that the majority of the respondents (79%) were willing to receive a COVID-19 vaccine.[13] The highest acceptance rates were found in Malaysia (94.3%), Indonesia (93.3%), and China (91.9%). In the Eastern Mediterranean Region, confidence rates in the general population ranged from 29.4% to 64.7%.[21,23] The lowest rates of vaccine confidence in the general population were found in Hong Kong, the Middle East, and the Democratic Republic of Congo in a systematic review of 2021.[19]

Our findings revealed that 79.6% of the respondents expressed the reason for being vaccinated as being protected personally from the infection, followed by protection of family members (79.1%). Data from other surveys indicated similar results in that vaccine acceptance and uptake are related to the intention for protection against COVID-19. However, contrary to our survey, higher vaccine acceptance was associated with sociodemographic factors such as older age, male gender, higher education, high income, having older children with vaccine coverage, health insurance coverage, and not having any chronic illnesses.[24] In our study, only the marital status among sociodemographic features was found to affect vaccine uptake.

Suspicion about safety and efficacy, hasty development of vaccines, and cost-effectiveness were among the main predictors of both vaccine acceptance and vaccine hesitancy,[24] similar to our study. Other factors like trust in authorities and vaccine safety, risk perception of COVID-19, and previous influenza vaccination positively affected vaccine acceptance positively.[25]

In our study, hesitancy was indicated even by people who were vaccinated, which might have prevented full-dose vaccination. Thus, although the one-dose vaccination rate was high, hesitancy findings rates were also high: 22.4% of the participants indicated concern about adverse effects, 18% were concerned that the COVID-19 vaccines had been hastily developed, and 9.6% believed that vaccines may be ineffective for protection from the infection. In total, 42% of the participants expressed no hesitancy. In the literature, concerns about adverse effects are the most common reasons for hesitancy.[4,13,23]

Of the participants in our study, 46.7% stated that they received information about COVID-19 from television and newspapers, 40.2% from social media and the internet, and 31.1% from the Ministry of Health.

However, according to the literature, healthcare professionals are considered the most reliable sources for vaccination against COVID-19.[10,15] A systematic review on COVID-19 uptake intention found that the leading confidence factor was physician recommendations, influencing 80% of the Chinese population and 62% of the Americans.[24] Health workers were found to be the most trusted sources for COVID-19 vaccines in another study.[7] The higher proportion of media and social media influences may be due to the younger age of the study population. As the group of people involved is a young population, this might be the reason for the social media impact, and as isolation was a reality, many of them could not go to the hospitals or primary care, which might have influenced the result.

The influence of knowledge about COVID-19 vaccines on vaccination uptake was also investigated. People who answered the relevant questions satisfactorily were vaccinated significantly more than the other group. Similarly, in another study, half of the participants stated that they would reconsider getting vaccinated if they were more informed about the vaccine.[9] However, even if health messages are adequate, opinions of people about the vaccine may change over time.[26]

Our findings are in compliance with other research on COVID-19 vaccination issues in Cyprus.[27]

Study Limitations

The study is a convenience sample and thus not representative of the North Cyprus population. The study size is small, from a single country during a certain short period of the pandemic. The vaccine uptake rate is based on one dose of COVID-19 vaccination. Hesitancy questions were asked to all participants, including those who were vaccinated. The vaccine type was not questioned. The economic status question is subjective, relying on self perception of the economic status of the participant.

CONCLUSION

This study on COVID-19 vaccination in North Cyprus revealed the vaccination uptake and associated factors among the general population in this region, illustrating findings similar to those in the medical literature. In summary, the one-dose vaccination rate was high, but the full-dose vaccination rate was lower than the world average.

The predictors of higher vaccine acceptance and uptake were marital status and correct knowledge of COVID-19 vaccination. A closer monitoring and implementation of COVID-19 vaccination and achievement of full-dose vaccination are needed among the general population of the people of North Cyprus, given the uncertain progress of the COVID-19 epidemic worldwide.

MAIN POINTS

- Vaccination is the most effective method for controlling infectious diseases, including COVID-19.
- No previous data on COVID-19 vaccine uptake and associated factors among the general population of North Cyprus were available during the study.
- Regarding vaccine coverage, 93% had received at least one dose of a COVID-19 vaccine, a rate higher than the world average, and 64.5% had received two doses.
- The majority believed that vaccines are effective and that correct knowledge of COVID-19 vaccines, together with concern for personal protection from the infection, were predictors of higher vaccine intention and uptake.
- Most participants displayed hesitancy for a variety of reasons, including speedy authorization of the vaccines by the WHO (40%),

adverse effects (22%), and speedy development of the vaccines (18%), whereas 42.1% stated no hesitancy for vaccination.

ETHICS

Ethics Committee Approval: The study protocol was approved by Near East University Faculty of Medicine Scientific Research Ethics Committee (approval number: 2021/95-1416, date: 30.09.2021).

Informed Consent: It was obtained.

Footnotes

Authorship Contributions

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

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

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Supplementary 1 Links:

https://l24.im/9Ej3Zm

RESEARCH ARTICLE

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Evaluation of the Frequency and Awareness of Using Tobacco Products in Parents of Primary School and Preschool Students in Girne

Ayşe Baha[1], Fisun Yıldız[2]

[1]Department of Chest Diseases, Near East University Faculty of Medicine, Nicosia, North Cyprus
[2]Department of Chest Diseases, Cyprus International University Faculty of Medicine, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: In this study, we aimed to investigate the frequency of smoking and extent of awareness of second-hand smoke (SHS) among parents.

MATERIALS AND METHODS: This is a descriptive study. A total of 2,602 questionnaires were administered to the parents of students in 7 different schools. The questionnaire included 8 questions and collected demographic data. The findings were analyzed using appropriate statistical methods.

RESULTS: Participation rate was 61.9% among all parents. 23.2% of mothers and 43.1% of fathers were active smokers. 31% of mothers and 33.8% of fathers were aware of the fact that their children could have many diseases related to SHS. 98.6% of mothers and 98.8% of fathers did not want their children to be exposed to SHS. 60% of mothers and 54.5% of fathers who were active smokers thought that smoking outside the home did not harm their children. 90.9% of mothers (n=1162) and 91.5% of fathers (n=1129) wanted their children to receive education about the harms of tobacco products (HTPs). 60.9% of active smoker mothers, 69% of exsmoker, and 68.6% of never smoked mothers did not want to receive education about the HTPs (p=0.025). These rates were 63.2%, 75%, and 68.9% among fathers, respectively (p=0.002).

CONCLUSION: Childhood exposure to SHS in our study is similar to that of previous studies. We think that parents should be educated about SHS, and for those who refuse the education, the reasons behind this should be investigated.

Keywords: Secondhand smoking, exposure, children, parents

INTRODUCTION

Second-hand smoking (SHS) refers to exposure to smoke emitted from the tip of a cigarette or smoke exhaled out by people who are smoking. SHS contains more than 4000 chemicals, such as insecticide dichloro-diphenyl-trichloroethane, nail polish remover (acetone), rat poison (cyanide), toilet cleaner (ammonia), and exhaust fumes (carbon monoxide).[1,2] This is a very dangerous situation for all age groups, and its negative effects on health have been proven by many studies.[1-3] SHS kills approximately 1.2 million people per year, and 65,000 of these preventable deaths are seen in children under 15 years of age. Children with parents who are active smokers are nearly 70% more likely to attempt smoking by the age of 15.[4]

Although all age groups are affected, the most serious adverse effects are observed in infants and young children. The main reasons for this are summarized below. Due to the dynamics of developmental physiology, babies require more energy and breathe more frequently.[4] Thus, they are more affected by air pollution because 80% of the

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ORCID IDs of the authors: A.B. 0000 0002 9649 250X; F.Y. 0000-0003-4810-7301.

Address for Correspondence: Ayşe Baha
E-mail: dr_aysedemir@hotmail.com
ORCID ID: orcid.org/0000 0002 9649 250X

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alveoli are formed after birth, and lung development continues during adolescence. The developing lung is extremely vulnerable to pollutants during the neonatal period. Due to the high respiratory rate and activity level, a large number of pollutants reaches the lungs of infants.[5]

Prenatal active smoking and SHS among women are the most common preventable causes of neonatal morbidity, prematurity, and low birth weight (LBW).[6] A recent study showed that the babies of women who smoked during pregnancy were 142 g lower than those of non-smokers.[7] The risk of LBW was 1.6 times higher in embryos exposed to cigarette smoke.[7] Because, carbon monoxide in cigarette smoke binds to hemoglobin and reduces the blood's oxygen-carrying capacity.[8]

Recent studies have shown an association between intrauterine and childhood SHS and an elevated risk of attention-deficit/hyperactivity disorder.[9,10] The U.S. The Environmental Protection Agency has declared that SHS increases the risk of lower respiratory tract infections, such as pneumonia and bronchitis. It is estimated that between 150,000 and 300,000 annual cases of lower respiratory tract infections in children aged 18 months can be attributed to exposure to SHS. Approximately 7,500-15,000 of these cases require hospitalization.[11] In addition, SHS is associated with school absenteeism among children with asthma because of increased respiratory problems.[12] Moreover, the likelihood of being an active smoker later in life, cancer and sleep breathing disorders are increased among children who were exposed to SHS.[4,13,14]

Studies have shown that parents' perceptions of exposure to SHS differ from one another.[15-17] Different perceptions of SHS exposure can explain parents' understanding of their children's health risks and, consequently, why they are smoking in the same environment with their children.[18]

One of the most striking issues of recent years is the increasing use of electronic cigarettes, which are becoming increasingly widespread worldwide. Efforts to combat the use of e-cigarettes and scientific articles on the subject are increasing daily. There are currently a multitude of both legitimate and illegitimate products on the market, offering over 8,000 different vape varieties whose additives have not been tested, reviewed, or regulated, and the safety-toxicity profile of which is unknown.[19] E-cigarettes are designed to heat nicotine and produce vapor that contains carcinogens and harmful toxins, including formaldehyde, acetaldehyde, and caroline. This vapor may also contain other substances such as aerosolized particles, polycyclic aromatic hydrocarbons, carbonyls, aldehydes, metals, volatile organic compounds, and tobacco-specific nitrosamines. Children and other non-users are at risk of inhaling this vapor.[20] *In vitro* studies have shown a dose-dependent reduction in the viability of normal human bronchial epithelial cells following exposure to vapor from vaping (e-cigarette) devices.[19]

We designed this study because there are no epidemiological data in North Cyprus regarding SHS exposure in children or parents' awareness of this issue.

MATERIALS AND METHODS

This descriptive study was conducted between January 1, 2020 and January 30, 2020 in 7 schools including 5 primary schools (6-10 years old) and 2 pre-schools (3-5 years old) in the central and rural areas of Girne. Written approval for the study was obtained from the Ministry of Education and the Ethics Committee of Dr. Burhan Nalbantoğlu State Hospital (approval number: YTK.1.01-EK 35/20, date: 16.07.2024).

Questionnaire

The questionnaires were distributed to the classroom teachers by the school principals and to the parents via the students.

A total of 2100 questionnaires were distributed to 7 schools, and 1301 responses were received. Each questionnaire consists of 8 questions that should be answered separately by the mother and father, as well as the parents' age, occupation, comorbidity, tobacco product use history (conventional cigarettes, electronic cigarettes and other tobacco products), and whether the mother smoked during pregnancy. Six of the 8 questions were closed-ended and 2 were multiple-choice questions. The 8 questions answered separately by both mother and father answered separately were as follows:

1. Were you exposed to SHS when you were a child? (yes or no).

2. Do you accept the exposure of your child to tobacco smoke? (yes or no).

3. Do you accept the use of tobacco products by your child in the future? (yes or no).

4. What symptoms or diseases might develop in your child when exposed to tobacco smoke? Asthma/bronchitis, COPD (chronic asthma), Frequent respiratory infections, Snoring, Allergy, Otitis media, Leukemia, All.

5. Does smoking outside the home (balcony, garden, workplace) harm your child? (yes or no).

6. Does your child have any of the following? (You can select more than 1 option); Frequent respiratory tract infections, Frequent ear infections, Snoring, Allergy, Asthma, Sleep disorder, or restlessness/hyperactivity.

7. Would you like your child to be educated about the harmful effects of tobacco products? (yes or no).

8. Would you like to be educated about the harmful effects of tobacco products? (yes or no).

Inclusion and Exclusion Criteria

The inclusion criteria are; (1) being literate in Turkish, (2) agreeing to fill out the questionnaire, (3) having no visual/reading/writing or comprehension impairments, (4) being over 18 years of age, (5) having a child studying at preschool or primary school.

Exclusion criteria are; (1) lack of literacy in Turkish, (2) not accepting to fill out the questionnaire, (3) visual, reading, writing, or comprehension disability, (4) age under 18.

Statistical Analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences Statistics software, version 23.0 (IBM Corp.; Armonk, NY, USA). In statistical analyses, categorical variables are presented as numbers and percentages, and continuous variables are presented as mean ± standard deviation and median (minimum-maximum value)

for descriptive analyses. For data that did not fit the normal distribution, the Mann-Whitney U test was used for comparative analysis between the 2 independent groups, and the independent sample t-test was used for data that fit the normal distribution. One-Way ANOVA was used to compare these parameters among the smoking status (active smoker, exsmoker, never smoked) of the mothers and fathers. An overall p-value 0.05 was considered statistically significant.

RESULTS

The participation rate was 61.9% (n=1301). Six questions in the mother section and 57 questions in the father section were unanswered because of death or divorce. The mean ages of the mothers and fathers were 36.4±5.3/year (23-50/year) and 40.3±5.6/year (26-65/year) respectively. The demographic data of the parents are presented in Table 1.

23.2% (n=302) of mothers and 43.1% (n=561) of fathers were active smokers. In 193 (15.3%) households, both mothers and fathers were active smokers. The frequency of respiratory tract infections (p<0.001), snoring (p=0.001) and allergies (p=0.001) were higher in the children of smokers than in non-smoking households. The rate of electronic cigarette usage was 3.4% (n=44). 5.3% (n=69) of the mothers had smoked during pregnancy. The frequency of respiratory infections (p<0.001), snoring (p<0.001), asthma (p<0.001) and hyperactivity (p<0.001) were higher in children whose mothers smoked during pregnancy.

31% of mothers (n=403) and 33.8% of fathers (n=440) thought that if their children were exposed to SHS, they could develop many diseases. Moreover, 98.7% of mothers (n=1258) and 98.4% of fathers (n=1194) did not want their children to be exposed to SHS. If their children were exposed to SHS, 81.7% (n=1063) of mothers thought that their children may have asthma, 56.9% (n=740) COPD, 66.8% (n=869) respiratory tract infections, 41.8% (n=544) snoring, 48.5% (n=631) allergy, 33.1% (n=430) otitis media, 37.4% (n=486) leukemia, and 31% (n=403) all of them. If their children are exposed to SHS, 76.5% (n=995) of fathers think that their children may have asthma, 55.3% (n=719) COPD, 64.6% (n=840) respiratory tract infections, 44.7% (n=569) snoring, 47.3% (n=615) allergy, 35.6% (n=463) otitis media, and 37.4% (n=486) leukemia.

64.2% (n=823) of mothers and 66.1% (n=412) of fathers were exposed to SHS when they were children. Of these, 5.1% (n=41) of mothers had asthma, 4.3% (n=35) hypertension, and 5.8% (n=47) other diseases. Of these, 2.4% (n=19) of fathers had asthma, 6.8% (n=53) hypertension, and 6.2% (n=48) other diseases.

Mothers' answers to the questionnaire are shown in Table 2. Most mothers who were active smokers (n=242, 78.8%) were exposed to SHS when they were children. Most mothers who were not exposed to SHS during childhood were non-smokers (p<0.001). Additionally, most mothers exposed to SHS during childhood were also non-smokers (p<0.001). Regardless of the smoking status, most mothers did not want their children to be exposed to SHS (0.019). Most mothers who were active smokers (n=177, 60%) believed that outside smoking would not harm children. This rate was higher among mothers who had never smoked (p=0.018). Furthermore, 90.9% of mothers (n=1162) wanted their children to receive education about the harms of tobacco products (HTP). This rate was higher among mothers who had never smoked, but the difference was not statistically significant (p=0.210). 9.1% of mothers (n=117) did not want their children to receive education about the HTP. This rate was higher in mothers who had never smoked than in those who did (p=0.470). Most mothers who were active smokers did not want to receive education about the harmful effects of smoking (p=0.025).

Fathers' answers to the questionnaire are shown in Table 2. The rate of active smoking was high among fathers who were exposed to SHS when they were children (p<0.001). Regardless of their smoking status, almost all fathers did not want their children to be exposed to SHS (p=0.149). Most fathers who were active smokers (n=301, 54.5%) thought that outside smoking would not harm their children. Fathers who had never smoked were more aware than others of the harms of outside smoking (p<0.001). Regardless of the smoking status, most fathers wanted their children to be educated about the harmful effects of smoking (p=0.173). Most fathers who did not want to receive education about the harms of smoking were active smokers (p=0.002). Mothers and fathers were similar in this respect.

Table 1. Demographic characteristics of the mothers and fathers

		Mother, (n=1295)	Father, (n=1244)
Situation during occupation	Not working	675 (51.9%)	27 (2.1%)
	Civil servant	69 (5.3%)	210 (16.1%)
	Private sector	440 (33.8%)	746 (57.3%)
	Other	100 (7.7%)	261 (20.1%)
Situation of tobacco products using	Never smoked	861 (66.2%)	481 (37%)
	Exsmoker	128 (9.8%)	217 (16.7%)
	Active smoker	302 (23.2%)	561 (43.1%)
Comorbidities	None	1079 (82.9%)	1053 (80.9%)
	Chronic lung disease	57 (4.4%)	28 (2.2%)
	Cardiovasculary disease	55 (4.2%)	75 (5.8%)
	Other	79 (6.1%)	65 (5%)

Table 2. Parents' answers to the questionnaires according to their smoking status					
		Never smoked	Exsmoker	Active smoker	p
Mother					
Did you become exposed to SHS at home as a child?	Yes	502 (61.4%)	79 (77.5%)	242 (78.8%)	<0.001
	No	315 (38.6%)	33 (22.5%)	65 (21.2%)	<0.001
Do you approve of your child being exposed to tobacco smoke?	Yes	7 (0.9%)	4 (3%)	6 (2.2%)	0.140
	No	810 (99.1%)	117 (97%)	267 (97.8%)	0.019
Does smoking outside the home (balcony, garden, workplace) harm your child?	Yes	527 (64.6%)	75 (60.5%)	118 (40%)	<0.001
	No	289 (35.4%)	49 (39.5%)	177 (60%)	0.018
Would you like your child to be educated about the harms of tobacco products?	Yes	766 (91.1%)	117 (92.9%)	279 (89.5%)	0.210
	No	75 (8.9%)	9 (7.1%)	33 (10.6%)	0.470
Would you like to learn more about the harms of tobacco products?	Yes	266 (31.4%)	40 (31%)	117 (39.1%)	0.013
	No	581 (68.6%)	89 (69%)	182 (60.9%)	0.025
Father					
Did you become exposed to SHS at home as a child?	Yes	278 (57.8%)	133 (64.3%)	391 (74.3%)	<0.001
	No	203 (42.2%)	74 (35.7%)	135 (25.7%)	<0.001
Do you approve of your child being exposed to tobacco smoke?	Yes	6 (1.3%)	1 (0.5%)	8 (1.5)	0.372
	No	456 (98.7%)	212 (99.5%)	526 (98.5%)	0.149
Does smoking outside the home (balcony, garden, workplace) harm your child?	Yes	316 (69.3%)	132 (67.7%)	251 (45.5%)	<0.001
	No	140 (30.7%)	63 (32.3%)	301 (54.5%)	0.034
Would you like your child to be educated about the harms of tobacco products?	Yes	424 (90.4%)	190 (92.2%)	515 (92.1%)	0.173
	No	45 (9.6%)	16 (7.8%)	44 (7.9%)	0.559
Would you like to learn more about the harms of tobacco products?	Yes	152 (31.1%)	54 (25%)	204 (36.8%)	0.033
	No	337 (68.9%)	162 (75%)	351 (63.2%)	0.002
SHS: Second-hand smoke.					

DISCUSSION

The SHS exposure rate in children aged 11 years was 43.1%. In a study designed in 2013-2016 by measuring blood cotinine levels, it was determined that 35.4% of non-smoking children and adolescents in the USA were exposed to SHS.[21] In another study conducted in 2017, 36.3% of children aged between 7 and 12 years were exposed to SHS anywhere, 27% were exposed to SHS in public areas, and 23.8% were exposed at home.[22] In Oberg's study, which was conducted in 192 countries in 2004, the frequency of SHS exposure in children was found to be 40%.[2] In the study conducted by Kuntz and Lampert[23] on children who were 0-6, between 2003 and 2006, the rate of children whose at least one parent smoked was 49.8%. This rate was found to be 41.8% between 2009 and 2012. When we look at data from various countries, the frequency of exposure of children to SHS is similar around the world. The results of our study are consistent with worldwide data.

Another important issue is the mother's smoking habit during pregnancy. Smoking during pregnancy is associated with maternal, fetal, and infant morbidity and mortality. Pineles et al.[24] showed that smoking during pregnancy is associated with an increased risk of prenatal and perinatal death. In addition, it has been proven that smoking during pregnancy leads to telomere shortening. Telomere shortening is associated with many adverse outcomes, from cancer to type 2 diabetes, cardiovascular diseases, and Alzheimer's disease.[25] In the United States, the smoking rate in the last trimester of pregnancy is 12.8%, which is considered a very high rate.[25] In Switzerland, the rate of women smoking in pregnancy was 13%, indicating that 11,000 babies per year are exposed to fetal tobacco.[26] Smoking during pregnancy is lower in low- and middle-income countries.[27] The mean prevalence of smoking among pregnant women worldwide is 1.7%. This rate is estimated to be highest in Europe (8.1%) and lowest in Africa (0.8%).[27] In our study, 5.9% of mothers who smoked in pregnancy was 5.9%. The intermediate frequency observed in our study is attributed to the heterogeneous population of our country.

There are only few studies on second-hand e-cigarette exposure in children. An experimental study suggested that both the alveolar areas of the lungs and total lung growth are impaired by exposure to e-cigarettes in neonatal mice[28] and that exposure to e-cigarettes during early life may cause persistent behavioral changes in adult mice.[29] In our study, we did not investigate whether e-cigarette exposure had a negative effect on children, but we contributed to the data on the frequency of e-cigarette use in students' homes. The sale of e-cigarettes is legal in our country, but despite this freedom, the rate of e-cigarette use among the parents in our study was only 3.4%. In America, where the sale of e-cigarettes is legal, the frequency of e-cigarette use in adults over the age of 18 years was 7.7%.[30] Garbutt et al.[31] administered a questionnaire to parents in 33 pediatric outpatient clinics and found that e-cigarettes were used in 1 in 8 homes, with 4% of parents using only e-cigarettes and 8.3% using both e-cigarettes and conventional cigarettes.

SHS exposure may cause some adverse health effects in children, such as asthma, coughing, wheezing, lower respiratory tract diseases, allergy, decreased lung function, middle ear disease, nasal irritation, sleeping disturbance, attention-deficit/hyperactivity disorder, leukemia, and obesity.[25] In our study, 1 in 3 of parents knew that their children would have chronic diseases due to SHS exposure. The most fundamental

issue affecting the prevention of SHS exposure in children is parental risk perception and awareness. In a study from Malaysia, 35.4% to 59.3% of parents knew that SHS exposure poses risks to child health.[32] In the study, 33.7% of parents considered smoking near their child while the balcony door open as "high-risk" and 35.4% as "extremely high-risk".[32] In addition, 42.3% of parents considered smoking near their child in the playground to be a high-risk behavior, and 34.1% considered smoking outdoors at a distance from the child as high-risk.[32] In another study, approximately 52% of parents who were active smokers reported a lack of belief or awareness about the negative health effects of SHS exposure on children.[33] In our study, the rate of idea that outside smoking (balcony, garden, workplace) could be harmful to children was highest among fathers who never smoked fathers (n=316), lowest (n=132) in exsmoker. The frequency of idea that outside smoking could be harmful to children was highest among mothers who had never smoked and lowest among exsmokers. This finding is similar to that of fathers. Another important finding of our study was that 78.8% of active smoking mothers and 74.3% of fathers were exposed to SHS when they were children.

In our study, the proportion of fathers (n=1129, 91.5%) who wanted their children to be educated about the harms of smoking was similar to that of mothers (n=1162, 90.0%). The fathers who were active smokers emphasized the importance of education about the harms of smoking compared to the fathers who had never smoked. The situation was the opposite for mothers. We could not find any other study that examined parents by categorizing them according to their smoking status. Therefore, we cannot make comparative comments on these results. However, the reluctance of mothers who are active smokers to teach children about the harms of tobacco is surprising and a matter of research. Another surprising finding was that parents who were active smokers were less likely to be willing to receive education about the HTP than non-smokers. This is also a subject that deserves further research. These surprising results are open to interpretation. People's education level, health literacy, beliefs, and living conditions may affect these results.

This study is important because it is the first epidemiological data on SHS exposure in children aged 11 years in North Cyprus. The main results of our study are as follows; 1) SHS exposure in our region is similar to the world average; 2) awareness about the HTP on health varies depending on the parent's smoking status; 3) the frequency of chronic diseases in children who were exposed to SHS is similar to the literature; and 4) the proportion of parents who want to get education about the HTP varies according to their smoking status.

Study Limitations

First, this study was conducted in a single region of the country and only in public schools. However, a new study will be conducted nationwide and in both private and public schools, which may affect some results in terms of awareness. Second, we asked a small number of questions to increase participants' participation. It is known that questionnaire participation rates decrease as the number of questions increases. Due to the small number of questions, we only had the opportunity to determine the situation; the reasons for the answers could not be questioned. The strengths of the study can be listed as follows; 1) the participation rate was relatively high; 2) the questions were answered by both mothers and fathers; and 3) parents were categorized according to their smoking status.

CONCLUSION

This study not only revealed the health problems associated with SHS in children but also provided a different perspective on parents' exposure to SHS when they were children. In addition, parental awareness of the harmful effects of tobacco products was examined according to their smoking status. This is an important point. We believe that parents should receive training on SHS and, in those who do not want to receive training, the reason for this should be investigated.

MAIN POINTS

- In this pilot study, the rate of SHS exposure among preschool and primary school children was similar to the global average.
- Parents' awareness of the health hazards of tobacco products varies according to their smoking status. Parents who have never smoked are more aware of the hazards of smoking.
- Most of the parents who are active smokers were exposed to SHS when they were children.
- The proportion of parents who want to be educated about the harmful effects of tobacco products varies according to their smoking status. Active smokers are less willing to be educated.

ETHICS

Ethics Committee Approval: The study protocol was approved by Dr. Burhan Nalbantoğlu State Hospital Ethics Committee (approval number: YTK.1.01-EK 35/20, date: 16.07.2024).

Informed Consent: Written approval for the study was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.B., F.Y., Concept: A.B., F.Y., Design: A.B., F.Y., Data Collection and/or Processing: A.B., Analysis and/or Interpretation: A.B., Literature Search: A.B., F.Y., Writing: A.B.

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RESEARCH ARTICLE

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Elbow Arthroscopy: Where are We Today? A Bibliometric Analysis

Sercan Çapkın[1], Ali İhsan Kılıç[1], Fatih Şeker[2], Mehmet Akdemir[3], Mahmud Aydın[4], Ertuğrul Şahin[5]

[1]Department of Orthopaedics and Traumatology, İzmir Bakırçay University Faculty of Medicine, İzmir, Türkiye
[2]İzmir Bakırçay University Sciences Education, İzmir, Türkiye
[3]Department of Orthopaedics and Traumatology, İzmir Ekol Hospital, İzmir, Türkiye
[4]Clinic of Orthopaedics and Traumatology, University of Health Sciences Türkiye, Haseki Training and Research Hospital, İstanbul, Türkiye
[5]Clinic of Orthopaedics and Traumatology, Kafkas University Faculty of Medicine, Kars, Türkiye

Abstract

BACKGROUND/AIMS: Elbow arthroscopy is a critical procedure for the treatment of elbow disorders, largely due to advancements in arthroscopic technology. While the field has seen significant growth, no comprehensive bibliometric analysis has been conducted to map research trends, key contributions, and gaps in this area. This study aimed to fill this gap by conducting a bibliometric analysis of articles published on elbow arthroscopy between 1986 and 2023, with the goal of understanding the evolution of the field, identifying influential research, and guiding future studies.

MATERIALS AND METHODS: Articles on elbow arthroscopy published between 1986 and 2023 from the Web of Science database were retrieved and subjected to bibliometric scrutiny. After an initial retrieval of 343 articles, we excluded irrelevant categories and focused on the 312 studies that were most relevant to the field. Using VOSviewer software, bibliometric network visualizations and specific result mappings were conducted. Citation analysis was employed to discern prominent journals and articles, while keyword clustering and trend analyses were performed to investigate the thematic landscape of the research.

RESULTS: Our analysis of 312 articles on elbow arthroscopy published between 1986 and 2023 revealed a significant increase in the number of publications after 2006. The majority of these publications (82.5%) were original research articles. The average citation count per article was 13.14, with an H-index of 36. The most frequently used keywords were “elbow” and “arthroscopy,” with “Complications of Elbow Arthroscopy” being the most cited study. Prominent journals such as “Arthroscopy: The Journal of Arthroscopic & Related Surgery” and influential authors like “Van Den Bekeron MPJ” and “O’Driscoll SW” were identified. Additionally, the United States was found to be the leading contributor in this field.

CONCLUSION: This study offers insights into the evolution and trends of elbow arthroscopy research. The findings serve as a valuable resource for guiding future investigations in this field, while the keyword analysis provides a roadmap for researchers in formulating new studies.

Keywords: Elbow arthroscopy, bibliometric analysis, citation analysis, Web of Science, VOSviewer

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ORCID IDs of the authors: S.Ç. 0000-0001-6957-5927; A.İ.K. 0000-0001-7491-6044; F.Ş. 0000-0003-0427-9208; M.A. 0000-00019638-4907; M.Ay. 0000-0002-2235-1480; E.Ş. 0000-0002-8509-3570.

Address for Correspondence: Sercan Çapkın
E-mail: sercancapkn@gmail.com
ORCID ID: orcid.org/0000-0001-6957-5927

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INTRODUCTION

Knee and shoulder arthroscopy is a long-established primary treatment modality for various joint pathologies. In contrast, elbow arthroscopy has historically faced limitations in terms of both case volume and widespread acceptance as a viable treatment option.[1] Originally employed primarily for diagnostic purposes due to the complexities inherent in the elbow joint,[1-4] elbow arthroscopy has undergone significant advancements in recent decades, driven by improved surgical techniques, enhanced equipment, and a deeper understanding of arthroscopic principles.[5-9]

As highlighted by pioneering cadaver studies conducted by Burman[2], early indications for elbow arthroscopy have primarily focused on diagnostic exploration and removal of loose bodies.[1] However, subsequent research has broadened the scope of elbow arthroscopy to encompass a broader spectrum of pathologies, ranging from lateral epicondylitis and synovitis to osteochondritis dissecans and contracture release.[6,10,11] Despite the challenges posed by the complex anatomy of the elbow joint and its proximity to vital neurovascular structures, elbow arthroscopy has steadily increased in recent years.[7,12]

Indeed, indications for elbow arthroscopy have expanded to include the management of complex disorders, such as arthroscopically assisted open reduction of intra-articular fractures, ligament repair or reconstruction, and total synovectomy.[13-17] This evolution reflects not only advancements in surgical technique but also a growing recognition of elbow arthroscopy's efficacy and versatility in addressing a diverse array of elbow pathologies.

The internet's accessibility has revolutionized research in many fields, particularly medicine, providing researchers with unprecedented access to a vast amount of up-to-date literature and data. However, this abundance of information also presents challenges such as information overload and difficulty in identifying relevant research despite the shear volume of publications.

A comprehensive bibliometric analysis is warranted to address these challenges and contribute to the understanding of research trends in elbow arthroscopy. Although significant developments have occurred in this field in recent years, current and comprehensive bibliometric analysis literature must be improved. Therefore, we aimed to summarize global research output on elbow arthroscopy by conducting a bibliometric analysis of publications published between 1986 and 2023. This analysis will examine countries and authors with the highest publication output and explore highly influential articles and leading scholarly journals.

Given the increasing utilization of elbow arthroscopy and the vast amount of literature currently available, a comprehensive bibliometric analysis is needed to map the research landscape in this field. Despite significant advancements in elbow arthroscopy, no detailed bibliometric study has systematically analyzed global research trends, identified key contributors, or highlighted influential publications. Therefore, the aim of this study was to conduct a bibliometric analysis of elbow arthroscopy publications published between 1986 and 2023. Specifically, this analysis addresses the following research questions: 1) Which countries and authors have the highest publication output? 2) What are the most influential articles and leading scholarly journals in this field? 3) How has the research focus evolved over time, and what are the emerging trends?

MATERIALS AND METHODS

We conducted a comprehensive systematic literature search using the Web of Science [(WoS); Clarivate Analytics, Philadelphia, Pennsylvania] database, covering SCI-expanded, SSCI, AHCI, CPCI-S, CPCI-SSH, ESCI, BKCI-S, and BKCI-SSH (accessed on February 16, 2024). Our search targeted all articles related to elbow arthroscopy. We extracted publications containing the keyword "elbow arthroscopy" in the title, spanning the period from 1986 to 2023, from the WoS database. These publications were then subjected to bibliometric analysis, including network visualizations conducted using VOSviewer software (version 1.6.15; Center for Science and Technology Studies, The Netherlands).[18]

We specifically selected the WoS database due to its established reputation and comprehensive coverage of high-quality academic literature. WoS is widely regarded as the gold standard for bibliometric research, providing reliable and robust tools, such as citation analysis, H-index calculation, and impact factor metrics, which are critical for ensuring the accuracy and consistency of research outcomes. Although databases such as Scopus, PubMed, and Google Scholar offer valuable insights, they vary in scope and may not always provide the same level of analytical depth or reliability. By focusing on the WoS, we aimed to maintain the integrity and rigor of the study by leveraging a singular, well-respected source to produce findings that are both credible and widely recognized in the academic community.[19]

We analyzed publications using various research parameters, including publication year, authors' affiliations, keywords, and citation counts. Notably, ethical approval was not obtained for this research because it utilized publicly accessible databases. This study involved online databases; thus, no informed consent was obtained.

Statistical Analysis

The network visualization map represents the outcomes using labels, circles, and lines. Larger circles indicate higher contributions by respective items, whereas dense clusters of items are represented by thicker lines, indicating strong relationships. In addition, we employed a density visualization map, which assigned colors on a scale from blue to red based on item density. Points with higher densities and greater neighboring item weights are depicted on the red end of the scale.

RESULTS

We accessed 343 scientific studies. However, we limited our study to 1986-2023 and excluded categories such as "Veterinary Sciences," "Medicine General Internal," "Zoology," and "Agriculture Dairy Animal Science," which are irrelevant in the WoS database. As a result, we analyzed 312 scientific studies.

A total of 257 (82.5%) of these publications were journal articles, 23 (7.4%) were review articles, 12 (4%) were editorial material, 7 (2.1%) were book chapters, 6 (1.8%) were proceeding papers, and 7 (2.2%) were corrections and other publications. A total of 286 (91.7%) of the articles were published in English. The rest were published in other languages (German: 18, French: 5, Czech: 2, and Russian: 1). The journal articles had 4101 citations (without self-citations: 2547). The average number of citations per article was 13.14, and the overall H-index for all included journal articles was 36.

Trends of Annual Articles and Citations

Figure 1 shows the distribution of the number of articles and total citations by years. The number of articles on elbow arthroscopy and their total citations significantly increased in 2006 compared with the preceding years. Furthermore, the highest number of citations and studies related to this field was recorded in 2016. Additionally, there has been a clear trend of increasing studies and citations related to the field over the years.

To better understand the trend of scientific studies conducted on this subject between 1986 and 2023, an exponential trend line was drawn for the publications. Upon examining the results, the exponential function Y=1,272e0,0808x (where Y represents annual publications and x represents years, R^2=0.6161) indicates the potential of studies related to elbow arthroscopy and suggests that research trends will continue.

Keywords and Trends

Our analysis included 312 scientific publications that collectively employed 93 distinct keywords. Table 1 lists the five most frequently used keywords and their total link strength. In addition, Figure 2 illustrates the network visualization map derived from the citation analysis of these articles. The total link strength represents the frequency at which keywords appear together in the analyzed publications.

The most prominent keywords regarding scientific studies on elbow arthroscopy are "elbow," "arthroscopy," "elbow arthroscopy," "complication," and "osteochondritis dissecans." In addition, "nerve injury," "fracture," "arthritis," "pediatric," and "diagnostic" are among the most frequently used keywords.

Citation Analysis

Table 2 presents the 10 most cited articles and their respective citation counts. Each of these articles has garnered more than 50 citations. The article with the highest number of citations (212) was published in the Journal of Bone and Joint Surgery by Kelly et al.[20] in 2001. Furthermore, it is noteworthy that five out of the top 10 most cited articles were published in the journal Arthroscopy: The Journal of Arthroscopic & Related Surgery.

Active Journals

Thirty-two journals have published 312 scientific publications. Table 3 presents the top 10 journals that produced the most publications. The table lists the total number of publications and citations for each article. The total link strength indicates the article's citation or that the article is related to other studies and has a place in the literature. Figure 3 shows a citation network visualization map of the most active journals.

Active Authors

The productivity of authors within the scope of elbow arthroscopy by year is presented in Figure 4. When analyzing the productivity of authors who have published in the field of elbow arthroscopy, the most prominent ones were "Van Den Bekeron MPJ," "Eygandal D," "Hilgersom NFC," "Oh LS," "King GJW" and "Steinmann SP" in that order. Additionally, authors such as "Bishai SK," "Plancher KD," "Hobgood ER," "O'driscoll SW," and "Field LD" were also found to have notable contributions in this area.

Figure 5 presents a co-citation network analysis of authors publishing in the field of elbow arthroscopy. The authors with the most significant number of shared citation networks within the realm of elbow arthroscopy were "O'driscoll SW," "Andrews JR," "Savoie FH," "Ruch DS," "Baker CL," "Morrey BF," "Ogilvie-Harris, DJ," "Field LD," "Stothers K," and "Thomas MA."

Table 1. The top five trend keywords on elbow arthroscopy

Keyword	Occurrence	Total link strength
Elbow	18	69
Arthroscopy	17	65
Elbow arthroscopy	15	61
Complications	7	27
Osteochondritis dissecans	5	22

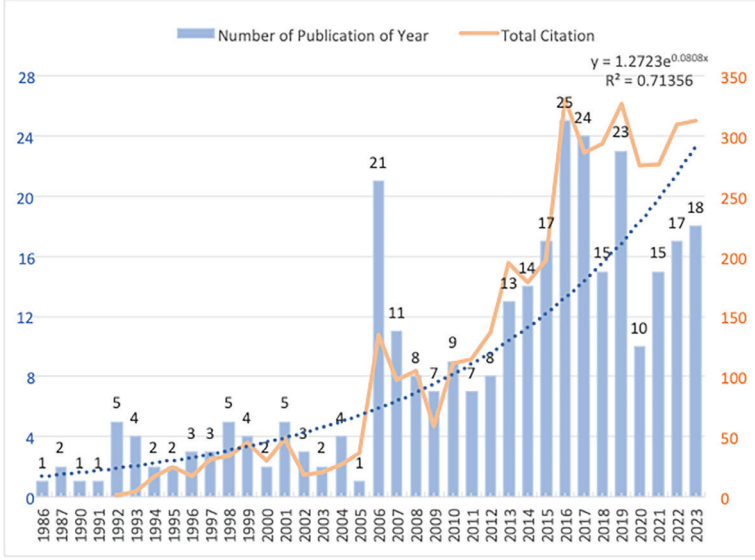

Figure 1. The distribution of the number of articles and total citations on elbow arthroscopy by years.

Active Countries

A total of 312 scientific publications were published with addresses from 18 countries. The United States ranked first in terms of productivity. The active countries producing publications and citations are the United States (publications: 28, citations: 700), the Netherlands (publications: 3, citations: 39), Canada (publications: 4, citations: 114), Japan (publications: 4, citations: 15), and France (publications: 2, citations: 12). The international collaboration network map among countries that have published articles together is shown in Figure 6.

DISCUSSION

In this study, we conducted comprehensive bibliometric analyses, including keyword analysis, citation analysis for articles and journals, and an examination of international collaborations, marking the first time such analyses have been performed in this area. Our research is the most exhaustive examination of the literature, analyzing the highest number of articles on this subject.

Our comprehensive bibliometric analysis covering 312 scientific publications revealed that the annual publication count ranged from 1 to 25 between 1986 and 2023. A significant increase in articles on elbow

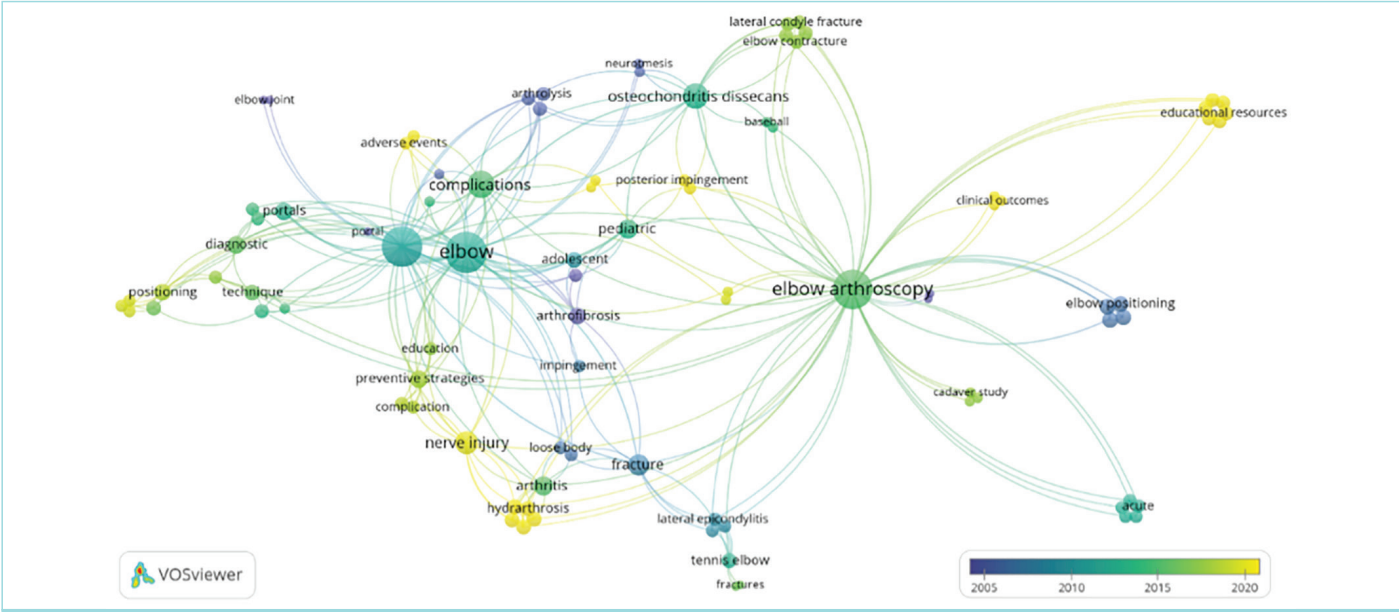

Figure 2. Network visualization map depicting the citation analysis of keywords in the field of elbow arthroscopy (the clustering among keywords is represented by six distinct colors. The size of the circles denotes the frequency of keyword usage, and the thickness of the lines reflects the strength of the relationships.

Table 2. The 10 most cited articles on elbow arthroscopy

Name of the article	Author(s)	PY	Journal	TC
1. Complications of elbow arthroscopy	Kelly et al.[20]	2001	Bone and Joint Surgery	215
2. Complete transection of the median and radial nerves during arthroscopic release of post-traumatic elbow contracture	Haapaniemi et al.[21]	1999	Arthroscopy: Journal of Arthroscopic and Related Surgery	88
3. Arthroscopy of the elbow: anatomy, portal sites, and a description of the proximal-lateral portal	Stothers et al.[22]	1995	Arthroscopy: Journal of Arthroscopic and Related Surgery	86
4. Intraarticular capacity and compliance of stiff and normal elbows	Gallay et al.	1993	Arthroscopy: Journal of Arthroscopic and Related Surgery	84
5. Snapping plica associated with radiocapitellar chondromalacia	Antuna and O'Driscoll	2001	Arthroscopy: Journal of Arthroscopic and Related Surgery	79
6. Magnetic resonance imaging of the elbow	Murphy	1992	Radiology	76
7. Elbow arthroscopy: early complications and associated risk factors	Nelson et al.	2014	Journal of Shoulder and Elbow Surgery	74
8. Anterior interosseous nerve injury following elbow arthroscopy	Such and Poehling	1997	Arthroscopy: Journal of Arthroscopic and Related Surgery	72
9. Osteochondritis dissecans of the capitellum	Baker III et al.	2010	The American Journal of Sports Medicine	70
10. Arthroscopic treatment of post-traumatic elbow contracture	Ball et al.	2002	Journal of Shoulder and Elbow Surgery	70

PY: Publication year; TC: Total citation.

Table 3. The 10 most active journals on elbow arthroscopy

Journals	NP	TC	TL	C	CQ
Arthroscopy: Journal of Arthroscopic and Related Surgery	10	184	1075	SCIE	Q1
Knee Surgery Sports Traumatology Arthroscopy	3	39	653	SCIE	Q1
World J Orthopedics	1	14	527	ESCI	-
Journal of Shoulder and Elbow Surgery	4	96	517	SCIE	Q2
Operative Techniques in Sports Medicine	2	1	480	SCIE	Q4
Orthopedic Techniques	2	8	444	ESCI	-
Journal of the American Academy of Orthopedic Surgeons	2	94	369	SCIE	Q1
Sports Medicine and Arthroscopy	1	3	343	SCIE	Q3
Journal of Bone and Joint Surgery-American Volume	1	215	312	SCIE	Q1
Arthroscopy Techniques	1	9	274	ESCI	-

NP: Number of publications, TC: Total citation, TL: Total link strength C: Category, CQ: Category Quartile.

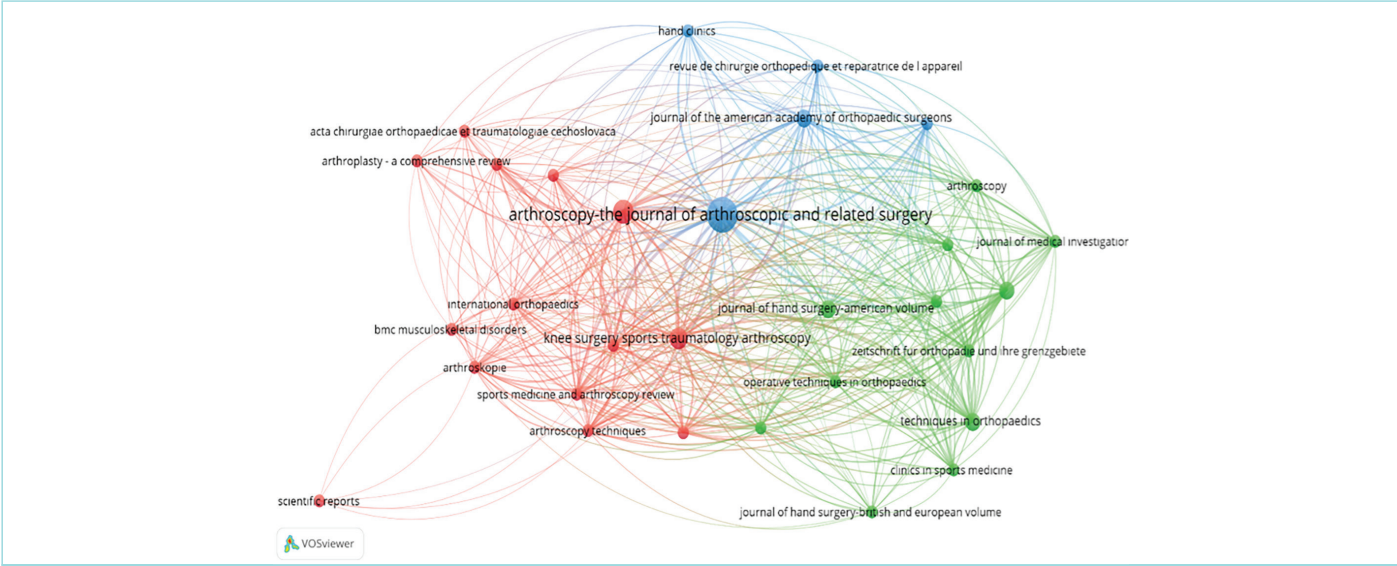

Figure 3. A network visualization map illustrating the citation analysis of the most active journals in the field of elbow arthroscopy (the size of the circles indicates the frequency of each journal, while the thickness of the lines reflects the strength of the relationships).

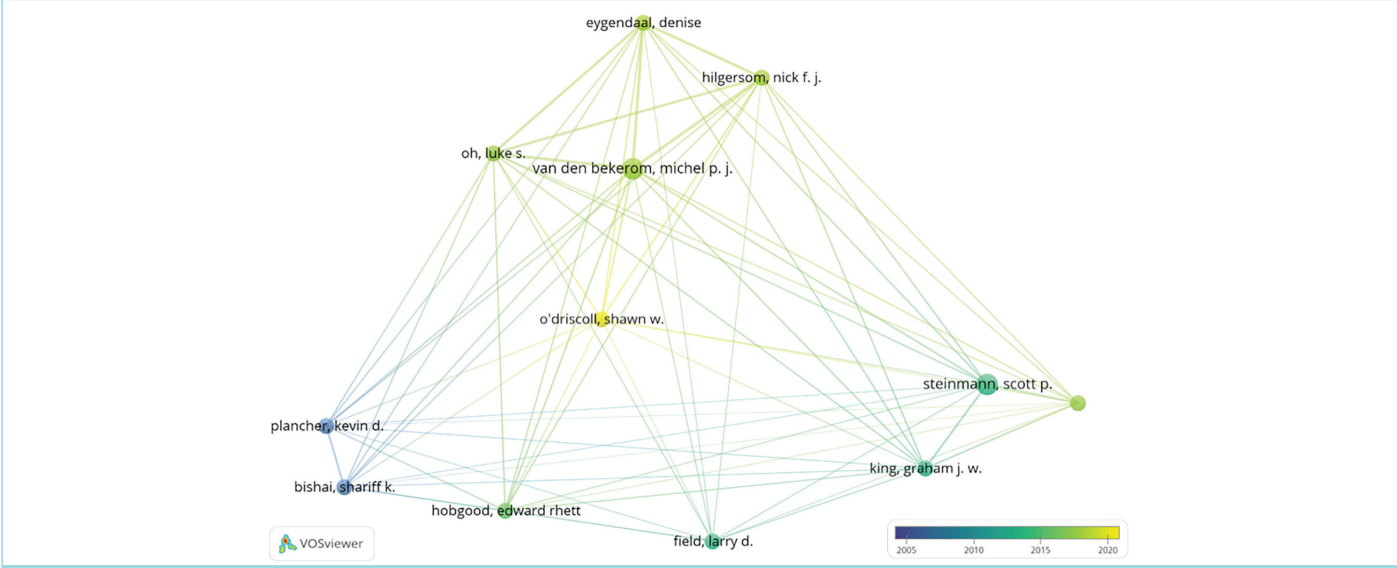

Figure 4. A network visualization map showing the analysis of the productivity of authors within the scope of elbow arthroscopy by year.

arthroscopy was particularly notable after 2006. This trend suggests that advances in arthroscopic techniques and growing clinical interest have driven more research in this area, potentially leading to improved patient outcomes.

Furthermore, our evaluation of keyword analysis results identified the top five topics investigated in relation to elbow arthroscopy: "elbow," "arthroscopy," "elbow arthroscopy," "complication," and "osteochondritis dissecans."

The article with the most significant impact, measured by the mean of the total number of citations, was "Complications of elbow arthroscopy," published by Kelly et al.[20] in the Journal of Bone and Joint Surgery-American Volume in 2001. The second most cited article was "Complete transection of the median and radial nerves during arthroscopic release of post-traumatic elbow contracture," which was published by Haapaniemi et al.[21] in Arthroscopy: The Journal of Arthroscopic & Related Surgery in 1999. The third most cited article was "Arthroscopy of the Elbow: Anatomy, Portal Sites, and a Description of the Proximal Lateral Portal," which was published by Stothers et al.[22] in Arthroscopy: The

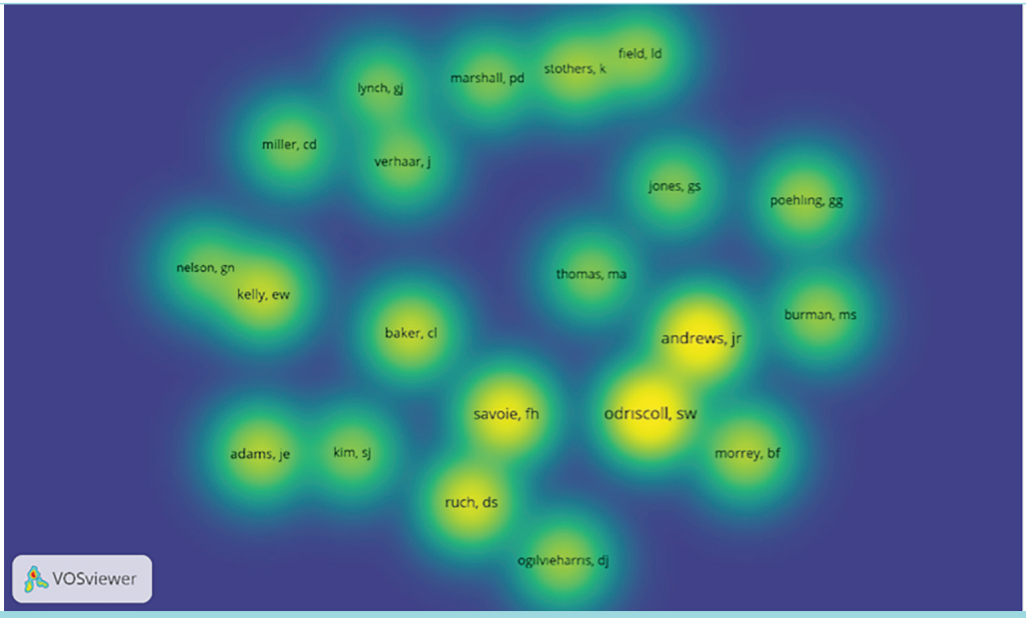

Figure 5. Density visualization map showing co-citation analysis in the field of elbow arthroscopy [number of citations are represented on a scale ranging from green (low) to yellow (high)].

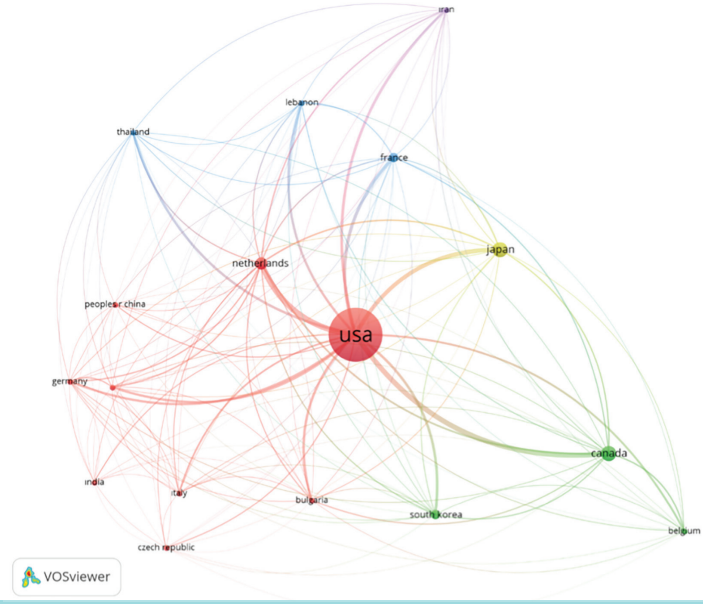

Figure 6. Showcases a network visualization map illustrating international collaboration among countries worldwide in the field of elbow arthroscopy (circle size denotes the volume of publications, colors represent collaboration clusters, and line thickness indicates the strength of collaboration).

Journal of Arthroscopic & Related Surgery in 1995. The remaining highly cited articles are presented in Table 2. Interestingly, five out of the top 10 most cited articles were published in the same journal, "Arthroscopy: The Journal of Arthroscopic & Related Surgery." Researchers interested in this subject should review these studies because their significance is primarily determined by attribution and co-citation analysis. Therefore, the articles presented in Table 2 can be considered as the cornerstone research on elbow arthroscopy.

Table 3 lists the most active journals in the field. Researchers seeking to publish manuscripts on this subject may find it helpful to consider these journals. Among the most active journals, those producing 10 or more publications were Arthroscopy: The Journal of Arthroscopic & Related Surgery. When evaluating journals based on the number of citations per article, the three most active journals were the Journal of Bone and Joint Surgery-American Volume, Arthroscopy: The Journal of Arthroscopic & Related Surgery, and the Journal of Shoulder and Elbow Surgery. Researchers who want their articles to be cited more frequently can first consider these journals. Publishing in these journals may increase the visibility and impact of future research because these platforms are recognized for their high citation rates and relevance.

When the analyzed articles were evaluated based on the total number of citations, the most cited study was Kelly et al.'s[20] "Complications of elbow arthroscopy," published in the Journal of Bone and Joint Surgery-American Volume in 2001.

When analyzing the publication distributions of countries worldwide, we observed that developed countries are the most prolific producers of publications in elbow arthroscopy, with notable contributors including the United States, the Netherlands, Canada, Japan, and France. This observation aligns with the findings of previous bibliometric analyses. This finding supports the notion that the economic size or developmental level of countries can indeed have a notable impact on academic publication productivity.[23,24] This finding suggests that future research should explore ways to support scientific output in developing countries, potentially enhancing global collaboration and knowledge sharing. Additionally, the analysis of coauthorship between countries revealed that geographic region was the main factor associated with collaboration on elbow arthroscopy, which is consistent with previous evidence.[23,24]

Study Limitations

This study has some limitations that need to be acknowledged. This study only reviewed articles published in the WoS database without including PubMed and Scopus. Although bibliometric studies often analyze many articles, excluding multiple databases may limit the comprehensiveness of the findings. However, it is essential to note that using multiple databases can lead to the inclusion of the same articles from different sources, potentially skewing the results by duplicating data. The decision to focus exclusively on WoS was made to ensure the consistency and reliability of the data. Nonetheless, future studies could consider incorporating multiple databases to provide a more comprehensive analysis while addressing potential duplication issues to ensure the reliability of the results.

CONCLUSION

Our study on elbow arthroscopy, reflecting the increasing volume of literature on this topic, summarized 312 scientific publications published between 1986 and 2023. The United States has emerged as the most active publishing country. At the same time, the top three journals for publishing articles were the Journal of Bone and Joint Surgery-American Volume, Arthroscopy: The Journal of Arthroscopic & Related Surgery, and the Journal of Shoulder and Elbow Surgery. By examining the development of topics studied over the years, identifying trending topics, and noting topics with higher citation rates, researchers can gain insights into new studies in this field. Therefore, our study is valuable for clinicians and scientists who wish to understand the global research landscape on elbow arthroscopy. Furthermore, keyword analysis can help professionals in designing new studies and enhance the overall advancement of knowledge in this field.

MAIN POINTS

- Although significant developments have occurred in the field of elbow arthroscopy in recent years, current and comprehensive bibliometric analysis still needs to be improved in the literature. This study includes global research output in elbow arthroscopy by conducting a bibliometric and visuality analysis.
- Our study on elbow arthroscopy, reflecting the increasing volume of literature on this topic, summarizes 312 scientific publications published between 1986 and 2023.
- This study will guide clinicians and scientists seeking to better understand the global research landscape on elbow arthroscopy.

ETHICS

Ethics Committee Approval: Notably, ethical approval was not obtained for this research because it utilized publicly accessible databases.

Informed Consent: This study involved online databases; thus, no informed consent was obtained.

Footnotes

Authorship Contributions

Concept: S.Ç., A.İ.K., M.A., M.Ay., Design: S.Ç., A.İ.K., E.Ş., Data Collection and/or Processing: S.Ç., A.İ.K., F.Ş., M.Ak., M.Ay., E.Ş., Analysis and/or Interpretation: S.Ç., F.Ş., Literature Search: S.Ç., A.İ.K., F.Ş., M.Ak., M.Ay., E.Ş., Writing: S.Ç., A.İ.K., M.Ak., M.Ay., E.Ş.

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RESEARCH ARTICLE

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Multidisciplinary Management of Patients with Brain Abscesses: A Retrospective Analysis

Alper Tabanlı

Department of Neurosurgery, İzmir Tınaztepe University Faculty of Medicine, İzmir, Türkiye

Abstract

BACKGROUND/AIMS: We aimed to evaluate general management strategies for brain abscesses via the integration of several disciplines to improve patient outcomes. Furthermore, this study addresses the need to optimize therapeutic interventions for different risk factors and diagnostic methods.

MATERIALS AND METHODS: Sixty-nine patients who were diagnosed with brain abscesses between December 2013 and December 2023 at our hospital. The demographic characteristics, predisposing factors, treatment options (surgical interventions and antibiotic therapy), and outcomes of the patients were analyzed. Neurological status was assessed using normative scales such as Glasgow Coma Scale, NIH Stroke Scale, and modified Rankin Scale. The primary outcome variables measured were postoperative resolution of abscesses, changes in neurological status, and survival rates.

RESULTS: The neurological function of all patients significantly improved after treatment. Surgeries such as aspiration and craniotomy were successful in resolving symptoms in 84% and 76% of patients, respectively. Furthermore, antibiotic therapy (ceftriaxone and metronidazole regime) cured all microbial infections in 92% of the patients. There was a strong correlation between abscess formation and the presence of comorbidities, such as diabetes mellitus, immunosuppression, and recent neurosurgery. These conditions are associated with a high mortality rate and complex management.

CONCLUSION: Effective coordination between multiple specialists and the use of sophisticated techniques for the early diagnosis of brain abscesses. Furthermore, appropriate antibiotic administration and timely surgical intervention are required to ensure favorable outcomes. The findings of this study emphasize the importance of patient-specific care that considers patient characteristics and risk factors to decrease mortality rates and increase quality of life.

Keywords: Brain abscess, treatment, diagnosis

INTRODUCTION

The challenge of clinically managing brain abscesses is that they require a complex multidisciplinary approach to ensure good results. A brain abscess is a severe neurological condition that can cause several complications and death if poorly managed. For example, the treatment of brain abscesses usually requires the combined efforts of neurosurgery experts, such as infectious disease consultants and neuroradiologists, to ensure an all-inclusive medical approach.[1,2]

The identification and management of brain abscesses have greatly improved with recent technological advancements in imaging and microbial diagnosis. Nevertheless, the condition is associated with considerable morbidity, especially among older adults or those with comorbidities such as diabetes mellitus (DM), immunosuppression, or a history of trauma/surgery. These factors can complicate the treatment of brain abscesses.[3,4]

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ORCID ID of the author: A.T. 0000-0002-2378-507X.

Address for Correspondence: Alper Tabanlı
E-mail: dralpertabanli@hotmail.com
ORCID ID: orcid.org/0000-0002-2378-507X

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Despite advances in technology, a gap remains in the optimal integration of these technologies and clinical practices to effectively improve patient outcomes. Furthermore, better diagnostic strategies need to be developed, especially for cases of failure of traditional cultures or the presence of ambiguous symptoms such as cranial pressure or signs of neurological impairment.[5,6]

In this study, we examined how the efficacy of current diagnostic and therapeutic approaches for brain abscesses can be improved via an integrated interdisciplinary system. Furthermore, we aimed to overcome the lack of comprehensive data on the effects of predisposing factors on treatment outcomes. Moreover, we aimed to evaluate the impact of newer less-invasive surgical techniques, such as burr hole drainage, and compare it to the impact of craniotomies.[7,8]

Our findings may bridge the existing gap by providing data-based guidelines for improving the management of brain abscesses, which may reduce the morbidity and mortality associated with the condition. Furthermore, high-risk groups can benefit from current evidence-based practices, which can optimize the care of these patients.

MATERIALS AND METHODS

In this retrospective study, the clinical data of 69 patients who were diagnosed with brain abscesses and underwent surgery between December 2013 and December 2023 at the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital, Department of Neurosurgery, were examined.

Ethics Statements

This study was conducted in accordance with the principles of the 1964 Helsinki Declaration. The study was approved by the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital Institutional Review Board (approval number: 2023/40, date: 29.03.2023). Informed consent was obtained from all patients before study enrollment.

Demographic Information About the Patients

The following data were analyzed: age, sex, predisposing factors, brain abscess location and volume, neurological status at presentation, biological organisms, surgical procedures performed, duration and type of antibiotic therapy administered, and neurological results. In this study, standardized methods were applied to evaluate neurological status. The levels of awareness, motor and sensory skills, and functions such as speech and language capacity were assessed using a series of tests. Furthermore, the visual fields and other neurological functions were evaluated. To objectively measure the state of consciousness and severity of stroke-related neurological deficits, the Glasgow Coma Scale and National Institutes of Health Stroke Scale were used, respectively. Furthermore, the modified Rankin Scale (mRS) was used to assess the overall neurologic functional status and independence in activities such as domestic chores. Using these scales, the neurological condition of each patient was systematically recorded. This evaluation established a baseline neurological state before initiating treatment, which helped monitor patient recovery objectively. Neurological assessment was performed by a multidisciplinary team at the time of admission and at specific timepoints postoperatively. These tools were selected because they can reliably assess different aspects of brain injuries among patient populations in previous studies. In this study, consistency in assessment was required, which was ensured using these tools.

The largest diameters on the X, Y, and Z axes were measured and converted to millimeters (mm). Using these measurements, the brain abscess volume (mm^3) was calculated as follows: 0.5 ´ X ´ Y ´ Z. The measurements were performed using high-resolution computerized tomography (CT) and magnetic resonance imaging (MRI). Accurate information on abscess size and site was obtained to help prepare for neurosurgical intervention. Radiologists with several years of experience evaluated the images. Three-dimensional images were used to determine the X, Y, and Z diameters of each abscess, which helped determine its exact position and volume within the cerebral parenchyma tissue. This approach was standardized for all participating patients to ensure uniformity of the volumes. The formulas and methods used to calculate abscess volume were selected to provide objective data for clinical decision-making during the treatment and follow-up periods. Intraoperative drainage of the abscess is shown in Figure 1, and preoperative and postoperative MRI are shown in Figure 2.

Standard laboratory tests, including complete blood count, high-sensitivity C-reactive protein (CRP) level, blood and cerebrospinal fluid (CSF) cultures, and serum biochemistry, were performed. Advanced CT and MRI are emerging diagnostic imaging modalities. Subsequently, aspiration with resection and craniotomy were performed under general anesthesia using neuronavigational technology. Empirical antibiotic treatment was initiated for all patients based on the condition, antibiotic susceptibility test results, clinical and radiological response to treatment, and inflammatory laboratory parameters. Antibiotics were administered intravenously for 4-8 weeks. The first postoperative CT scan was performed 24 hours after the surgery. Subsequently, follow-up CTs were performed weekly to monitor the treatment. Furthermore, the white and red blood cell counts and CRP levels during these intervals were evaluated. The mRS scores were also determined.

Statistical Analysis

SPSS (version 22.0) was used for all statistical analyses. Continuous data are presented as means and standard deviations. Continuous data were analyzed using the independent t-test or Mann-Whitney U test. The categorical data were analyzed using the chi-square test. Multivariate logistic regression analysis was performed to identify significant predictors of treatment outcome. Statistical significance was sent as $p<0.05$.

RESULTS

Over the course of 10 years, 69 patients were diagnosed with a brain abscess at University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital. The present study focused on the different demographics, risk factors, and effects of different therapies. Thus, we aimed to provide an overview of the optimal method for managing brain abscesses while considering the factors that determine patient outcomes.

Patients aged between 18 and 75 (mean age: 45±15 years) were included in the study. Most patients (58%) were male. Brain abscesses were found in the frontal (30%), parietal (25%), and temporal (20%) lobes, and the average abscess volume was 35±20 mm^3 (range, 30-40 mm^3) (Table 1).

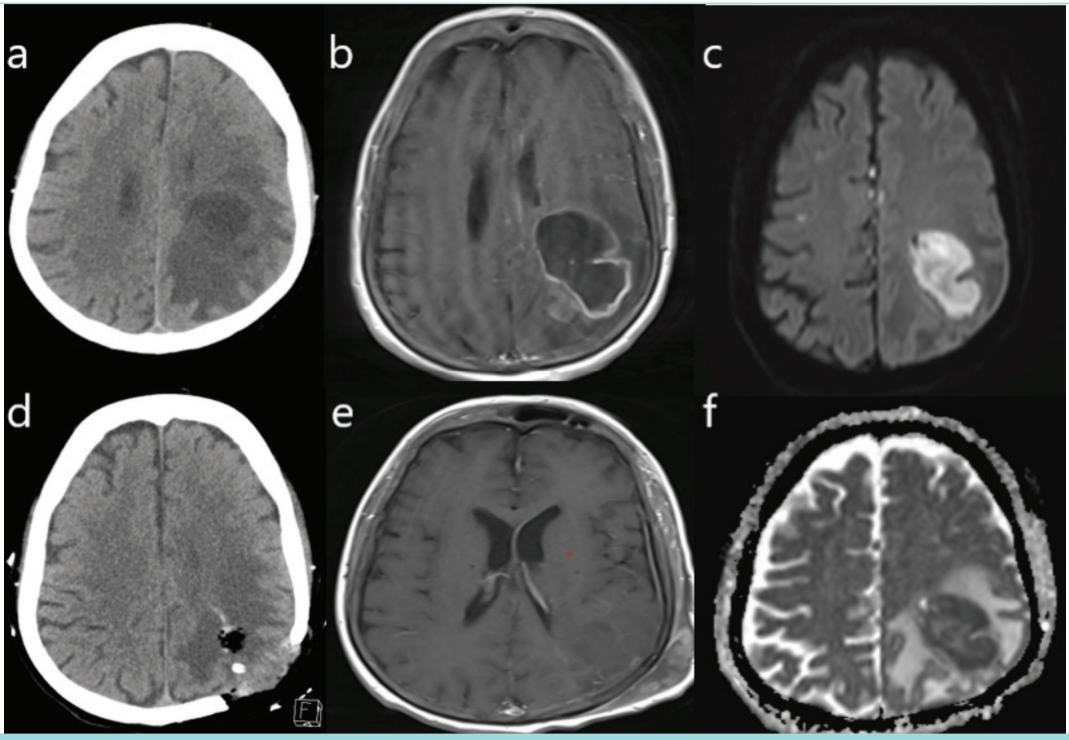

Figure 1. Intraoperative drainage of the abscess.

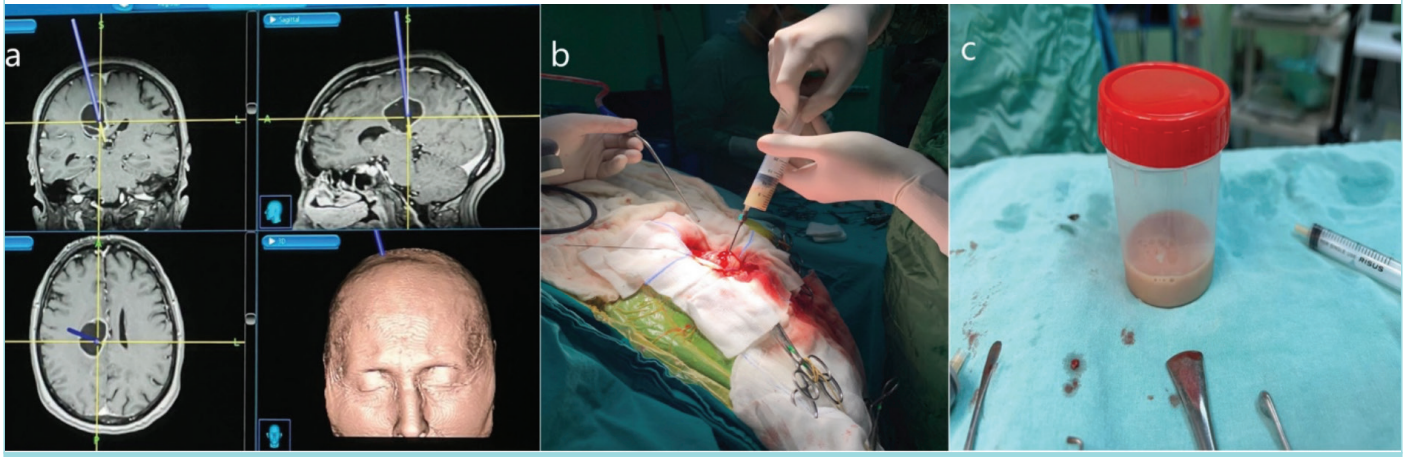

Figure 2. Preoperative and postoperative magnetic resonance imaging.

The factors that significantly predisposed patients to brain abscesses were DM (20%) and immunosuppression (15%). There was a significant association between brain abscess development and the presence of DM [p=0.045; adjusted odds radio (AOR), 1.8; confidence interval (CI): 1.1-2.9] or an immunocompromised state (p=0.033; AOR: 2.1; CI: 1.2-3.6) (Table 2).

White blood cell count, CRP level, and erythrocyte sedimentation rate (ESR) were elevated in 67%, 73%, and 64% of patients, respectively. There was a significant correlation between these laboratory values and abscess severity [correlation coefficient of CRP, 0.50 (0.007)]. Imaging studies revealed that abscess capsule enhancement was observed in most patients (85%) in addition to surrounding edema, which was critical to the diagnosis and subsequent evaluation of the impact of the abscess (Table 3).

In 84% of the aspirations and 76% of the craniotomies, surgical intervention was associated with abscess resolution and favorable outcomes. The efficacy of these interventions was demonstrated by the high success rates and strong AORs (aspiration: AOR: 2.5, CI: 1.8-3.4; craniotomy: AOR: 1.8, CI: 1.3-2.5). The microorganism were eradication with antibiotics in 92% of the patients. Furthermore, supportive measures such as steroids and analgesics improved the condition of 86% and 94% of patients, respectively. For example, in 50% of patient's rehabilitative services, the functional outcomes illustrate the need for a holistic approach toward brain abscess management (Table 4).

Table 1. Demographic and clinical characteristics of the patients

Variable	Description	Additional statistics
Age	Mean ± SD: 45±15; range 18-75 (years)	95% CI: 42-48
Gender	Males: 40 (58%); females: 29 (42%)	-
Location of brain ablation	Frontal (30%), parietal (25%), temporal (20%), cerebellar (15%), other (10%)	-
Volume of brain ablation	Mean ± SD: 35±20; range 10-70 (mm^3)	95% CI: 30-40; 25th percentile: 20 mm^3; 75th percentile: 45 mm^3
Neurological status at presentation	GCS: Mean 12±3; NIHSS: Mean 8±4; mRS: Mean 3±1	GCS, 95% CI: 11-13; NIHSS, 95% CI: 7-9; mRS, 95% CI: 2.8-3.2
Pathogens identified	Bacterial (*Staphylococcus aureus* 30%, *Streptococcus* spp. 20%), mixed infections (10%), and others (40%)	-
Surgical procedures	Aspiration: 40 (58%); craniotomy: 29 (42%)	-
Duration and type of antibiotic therapy	Average duration: 6 weeks; common antibiotics: ceftriaxone, metronidazole	-
Neurological outcomes	mRS 0-2: 35 (51%); mRS 3-5: 20 (29%); mRS 6 (death): 14 (20%)	-
Imaging modalities	CT: 69 (100%); MRI: 50 (72%)	-

GCS: Glasgow Coma Scale, NIHSS: National Institutes of Health Stroke Scale, mRS: Modified Rankin Scale, CT: Computed tomography, MRI: Magnetic resonance imaging, SD: Standard deviation, CI: Confidence interval.

Table 2. Predisposing factors and comorbidities

Predisposing factor/comorbidity	Number of patients	Percentage, (%)	p	Adjusted OR (95% CI)
Diabetes mellitus	14	20%	0.045	1.8 (1.1-2.9)
Immunocompromised state	10	15%	0.033	2.1 (1.2-3.6)
Otogenic infections	7	10%	0.080	1.5 (0.9-2.5)
Chronic ear infections	5	7%	0.120	1.3 (0.8-2.1)
Sinusitis	8	12%	0.095	1.4 (0.9-2.2)
Head trauma	4	6%	0.200	1.2 (0.7-2.0)
The recent neurosurgery	6	9%	0.050	1.7 (1.0-2.8)
Dental infections	3	4%	0.250	1.1 (0.6-2.1)
Other	12	17%	0.110	1.4 (0.8-2.3)
Total patients	69	-	-	-

Patients may have more than one predisposing factor or comorbidity. The "Other" category includes less common or unspecified factors that contribute to the development of brain abscesses. OR: Odds ratio, CI: Confidence interval.

Table 3. Laboratory and imaging findings

Finding type	Description	Mean value or range	Percentage of patients affected	Correlation coefficient	p	CI
Laboratory findings						
White blood cell count	Elevated (>10,000/µL)	12,000-18,000/µL	67%	0.45	0.012	0.15-0.75
C-reactive protein	High (>10 mg/L)	20-50 mg/L	73%	0.50	0.007	0.20 to 0.80
Erythrocyte sedimentation rate	Elevated (>20 mm/hr)	30-70 mm/h	64%	0.35	0.025	0.05-0.65
Blood cultures	Positive for pathogens	-	28%	0.25	0.080	-0.05 to 0.55
CSF analysis	Elevated protein and reduced glucose	Protein: 45-80 mg/dL	16%	0.40	0.020	0.10-0.70
Imaging findings (CT/MRI)						
Abscess location	Frontal, parietal, temporal, other	-	-	-	-	-
Volume of brain ablation	Mean ± SD	35±20 mm^3	-	0.55	**0.002***	0.30-0.80
Abscess capsule enhancement	Present on contrast imaging	-	85%	0.60	**0.001***	0.35 to 0.85
Surrounding edema	Visible edema around the abscess	-	90%	0.65	**<0.001***	0.45 to 0.85
Other lesions	Identification of additional lesions	-	10%	0.20	0.150	-0.10 to 0.50

CI: Confidence interval, CSF: Cerebrospinal fluid, CT: Computed tomography, MRI: Magnetic resonance imaging, SD: Standard deviation.

Table 4. Treatment approaches and outcomes

Treatment type	Description	Percentage of patients treated	Outcome measures	Success rate	Adjusted OR	95% CI	Success rate CI
Surgical intervention							
Aspiration		58%	Resolution of abscess	84%	2.5	1.8-3.4	79-89%
			Complication rate				
Craniotomy		42%	Resolution of abscess	76%	1.8	1.3-2.5	70-82%
			Complication rate				
Antibiotic therapy		100%	Microbial eradication,	92%	3.0	2.1-4.2	88-96%
	Common antibiotics used		Duration of treatment				
	Ceftriaxone, metronidazole						
Supportive care							
Steroids for edema		30%	Reduction in cerebral edema	86%	2.2	1.6-3.0	81-91%
Management							
Analgesics for pain		60%	Pain relief	94%	4.0	3.2 to 5.0	90-98%
Management							
Rehabilitative services							
Physical therapy		50%	Improvement in functional	71%	1.5	1.0-2.2	65-77%
Occupational therapy			Status				
Outcome tracking							
Modified rankin		-	mRS 0-2: Good outcome	51%	1.0	0.8-1.3	46-56%
Scale (mRS) post-treatment			mRS 3-6: Poor outcome				

OR: Odds ratio, CI: Confidence interval, mRS: modified Rankin Scale.

The results of this study demonstrate the treatment of brain abscesses and the importance of a multidisciplinary approach to optimize patient outcomes. The analysis spanned a decade, included 69 patients, and evaluated the demographic characteristics and predisposing factors of brain abscesses. We found a significant relationship between treatment efficacy and modality. Furthermore, accurate initial assessments and meaningful interventions are crucial. Advanced diagnostic tools, such as logistic regression models and correlation coefficients, ensure precision, and appropriate methodologies ensure a true reflection of the results. When combined with a strong antibiotic regime, surgical techniques exhibited a better outcome toward abscess resolution. Furthermore, the combination exhibited a higher likelihood of better outcomes than curettage alone or a less effective drug therapy (intravenous infusions). Our results also indicate that individualized treatment plans are significantly associated with improved neurological outcomes and reduced mortality. Furthermore, our findings advocate for the improvement of current treatment protocols and support ongoing studies aimed at reforming therapeutic strategies for brain abscesses.

DISCUSSION

The management of brain abscesses poses numerous challenges that significantly impact patient outcomes and healthcare practice. Because its diagnosis and treatment are inherently challenging, understanding its pathogenesis and evolution is essential. Thus, a detailed evaluation of the condition is required.[9] Brain abscesses significantly affect the health and quality of life of patients because they cause long-term neurological deficits, reduced functionality, and increased morbidity.[10] The clinical characteristics of patients with brain abscesses should also be known. Thus, the patient's initial neurological status, cause of infection, and response to the different treatment alternatives should be thoroughly evaluated.[11] In this study we have focused on these aspects and the need for precision in diagnostic and treatment protocols to improve outcomes and enhance the quality of life of patients with brain abscesses.[12]

In our study, brain abscesses were most prevalent among males aged 18-75 years, indicating the need for targeted public health interventions are required.[13] These abscesses often develop in critical cognitive areas, such as the frontal and parietal lobes. Thus, precise surgeries are required to minimize neuronal damage.[14] Abscesses caused by *Staphylococcus aureus* or *Streptococcus* species responded favorably to a six-week regimen of ceftriaxone and metronidazole (good results, 51%). However, the mortality rate associated with this condition was 20%. Furthermore, >50% of the patients required surgical interventions such as aspiration or craniotomy for symptomatic relief. This indicates that better non-invasive treatments and early detection methods are required. Together, these findings demonstrate the importance of an integrated multidisciplinary approach to enhance recovery and reduce fatalities.[15-17]

The factors predisposing patients to brain abscesses were identified. Approximately 20% of our patients had DM, confirming the link between poor glucose metabolism and higher chances of infections due to impaired immune response.[18] Furthermore, most of our patients were older adults with comorbidities, indicating that this population requires targeted preventive measures and therapy.[19] A weakened immune system, observed in 15% of our patients, also significantly increased the risk of brain abscesses. Patients with severe complex skull fractures or other conditions are usually immunocompromised. In such patients, the primary infection must be treated meticulously to prevent complications such as brain abscesses.[20] These various risk factors highlight the need for a multifaceted approach to prevent and manage brain abscesses, which are associated with high morbidity and mortality rates.

In this study, laboratory tests and imaging studies were used to expound on the underlying inflammatory processes in brain abscesses. White blood cell count, CRP level, and ESR were elevated in 67%, 73%, and 64% of patients, respectively. These findings indicate systemic inflammation and infection. Positive blood cultures were obtained in only 28% of the patients, demonstrating the effectiveness of blood-based diagnostics in identifying the causative pathogens. However, the low rate also demonstrates that culturing organisms from some patients may be challenging.[21,22] CSF analysis revealed elevated protein and reduced glucose content in 16% of patients, which can help differentiate bacterial infection from other central nervous system pathologies. Furthermore, brain MRI revealed capsular enhancement and edema around the abscess in 85% of the patients, which confirmed our diagnosis and helped evaluate the extent and size of the abscess. Based on these findings, a comprehensive laboratory analysis must be complemented with advanced brain imaging techniques to improve diagnostic accuracy and guide effective treatment of brain abscesses.[23,24]

Our findings confirmed the effectiveness of a multidisciplinary approach for treating brain abscesses. Furthermore, treatment success depends on the coordinated efforts of the three specialties of neurosurgery, infectious diseases, and neuroradiology. Aspiration and craniotomy effectively resolved the symptoms in 76% and 84% of patients, respectively. Therefore, timely surgical intervention can reduce the size of abscesses and relieve symptoms. This will prevent long-term neurological damage due to cranial compression or failure of culture to demonstrate the causative agents. Therefore, surgical interventions remain fundamental in the management of this condition. Furthermore, patients with negative blood cultures or apparent neurological signs who exhibit signs of increased intracranial pressure might require prompt surgical decompression for symptom relief and diagnosis. The choice between burr hole drainage and craniotomy depends on outcomes, including the incidence of complications, less-invasive nature of the surgery, and faster recovery. Furthermore, the management of brain abscesses after head trauma or surgery is associated with high mortality and reoperation rates. Thus, cautious preoperative planning and vigilant postoperative care are required in such patients. Although this can be achieved with technological developments, strategic surgical decision-making should be based on patient-specific factors.[25,26]

In most of our patients, supportive care measures, such as steroids for edema reduction and painkillers for analgesia, were effective in 86% and 94% of patients, respectively. These interventions improve patient comfort and possibly hasten recovery by controlling the consequences of abscesses. Furthermore, >50% of patients experienced significant improvement in their functional status after undergoing rehabilitative services. This indicates that rehabilitation is necessary to facilitate recovery and improve quality of life. Thus, these patients require an all-inclusive care approach. These findings indicate that an integrated management strategy involving surgery, drug therapy, and other forms of treatment, such as palliative care, could be useful when treating patients with brain abscesses.[27,28]

Study Limitations

This retrospective study had several limitations that affected its generalizability. First, the study was conducted at a single center, which did not reflect the differences in demographic characteristics. Second, the retrospective nature of the study may have introduced selection bias and increased the risk of data inaccuracy by relying on historical medical records. Furthermore, changes in the standards of care during the study period might have affected the treatment outcomes. Future studies could also benefit from a multicentric approach or prospective data collection, which would make the results robust.

CONCLUSION

The management of brain abscesses requires a comprehensive multidisciplinary approach involving neurosurgery, infectious diseases, and neuroradiology disciplines to optimize patient outcomes. The average patient with a brain abscess in this study was older with comorbid conditions that often caused infections following immunosuppression or complex skull fractures. Thus, primary infections must be carefully managed because they can lead to brain abscess formation if left untreated. Despite technological advancements, surgical interventions remain the mainstay of management, particularly for decompression in patients with cranial compression-induced neurological symptoms or negative blood cultures. Furthermore, surgical intervention can also aid in diagnosis. Although techniques such as burr hole drainage are favored for their less-invasive nature, craniotomy may be preferred in patients with recurrent or trauma-induced abscesses. The high mortality rate associated with posttraumatic or postsurgical brain abscesses highlights the importance of careful surgical planning and early intervention to improve survival and minimize reoperation.

MAIN POINTS

- Primary infections must be carefully managed because they can lead to brain abscesses if left untreated.
- Although techniques such as burr hole drainage are favored for their less-invasive nature, craniotomy may be preferred for recurrent or trauma-induced abscesses.
- The high mortality rate associated with posttraumatic or postsurgical brain abscesses highlights the importance of careful surgical planning and early intervention to improve survival and minimize reoperation.

ETHICS

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, İzmir Bozyaka Training and Research Hospital Institutional Review Board (approval number: 2023/40, date: 29.03.2023).

Informed Consent: Informed consent was obtained from all patients before study enrollment.

Footnotes

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RESEARCH ARTICLE

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Evaluating Soluble CD25 as a Diagnostic Biomarker for Severe Aplastic Anemia: A Retrospective Analysis

Amin A. Alamin

Department of Pathology, Taif University, College of Medicine, Taif, Saudi Arabia

Abstract

BACKGROUND/AIMS: Severe aplastic anemia (SAA) is a critical marrow failure syndrome characterized by pancytopenia and bone marrow failure (BMF). Soluble CD25, which is involved in immune regulation, has been proposed as a potential biomarker of SAA. This study evaluated the diagnostic performance of soluble CD25 for differentiating SAA from other BMF failure syndromes.

MATERIALS AND METHODS: This retrospective study included 150 patients: 50 with SAA and 100 with other BMF syndromes. Demographic, clinical, and laboratory data were obtained, and soluble CD25 was measured using an ELISA kit. The diagnostic accuracy of soluble CD25 was assessed using receiver operating characteristic curve analysis.

RESULTS: The soluble CD25 concentration was significantly greater in the SAA group (3245 pg/mL) than in the BMF syndrome group (1250 pg/mL) ($p<0.001$). Soluble CD25 showed excellent diagnostic performance, with an area under the curve of 0.92 (95% confidence interval: 0.89-0.95). Using a cut-off value of 2500 pg/mL, the sensitivity was 84%, the specificity was 88%, the positive predictive value was 72%, and the negative predictive value was 93%. Soluble CD25 levels are correlated with disease severity, with higher levels linked to more severe cytopenia and lower bone marrow cellularity.

CONCLUSION: Soluble CD25 can be a useful non-invasive biomarker for the diagnosis of SAA because it is very accurate in distinguishing SAA from other marrow failure syndromes. The association of this parameter with disease severity makes it useful for early and accurate diagnosis, which enhances treatment.

Keywords: Soluble CD25, IL-2 receptor, severe aplastic anemia, bone marrow failure syndromes, diagnostic biomarker

INTRODUCTION

Aplastic anemia (AA) is a rare and frequently fatal disorder classified within the bone marrow failure (BMF) syndrome group. It is characterized by cytopenia and hypocellular bone marrow.[1] The incidence of AA displays two age peaks: childhood, at which age 10-25 years, is one such stage, and in elderly people, particularly those above 65 years. The global epidemiology of AA varies. In Western countries, the estimated annual incidence is 1. Five-2 cases per million people, whereas in Asia, the rate is 2-3 times greater, with 3.0-7.5 cases per million people. 0-7.[2] The cause of AA can be immunological, and its chief effect is on hematopoietic stem cells, which lead to BMF.[3,4] Therefore, the exact cause of the disorder has not yet been clearly defined, even though the disorder is believed to be polygenetic in origin, as indicated by the fact that several genes, environmental factors, and immune factors are known to be associated with its development.[5]

Severe aplastic anemia (SAA) is characterized by certain clinical and laboratory features that distinguish it from other types of AA. The criteria for diagnosis included a bone marrow cellularity of less than 25% and at least two of the following: a corrected reticulocyte count of less than 20×10^9/L, a platelet count of less than 20×10^9/L, and a neutrophil

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ORCID ID of the author: A.A.A. 0000-0002-4405-5826.

Address for Correspondence: Amin A. Alamin
E-mail: amakki@tu.edu.sa
ORCID ID: orcid.org/0000-0002-4405-5826

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count of less than 0.5×10^9/L.[6,7] SAA may lead to massive bleeding and infection and increase the risk of clonal disorders, such as myelodysplastic syndrome (MDS) and acute myeloid leukemia.[8] Therefore, the diagnostic results appear to play a crucial role in the effective and timely delivery of care and the achievement of good treatment outcomes. The current diagnostic approach for AA involves the evaluation of the patient's medical and physical examinations and other investigations. Among the common diagnostic procedures for the classification of bone marrow disorders are peripheral blood count, bone marrow aspiration, and trephine biopsy.[9,10] For example, differentiating between AA and other types of BMF syndromes, such as MDS, paroxysmal nocturnal hemoglobinuria (PNH), and congenital marrow failure disorders, is very challenging because they all have similar clinical and pathological features.[11]

Interleukin-2 (IL-2) is a cytokine that plays a role in the immune response, and as demonstrated in other experiments, T-cell proliferation is an important aspect of immunity.[12,13] The IL-2 receptor (IL-2R) is composed of three subunits. The IL-2R complex contains three subunits: the IL-2R alpha subunit (CD25), the IL-2R beta subunit (CD122), and the IL-2R gamma subunit (CD132).[14] Soluble CD25 (sCD25) is a bioactive molecule that is a recombinant human soluble IL-2R alpha chain that is present in serum and participates in many immunological diseases, including AA.[15] Analysis of the results revealed a correlation between AA and sCD25, and the level of sCD25 in the plasma of AA patients is elevated. Because sCD25 blocks the effect of IL-2 on T-lymphocyte proliferation, it is expected to be implicated in the pathogenesis of this disease via immune dysfunction.[16] Additionally, sCD25 has been suggested as a biomarker of AA and for disease monitoring because sCD25 levels increase at disease onset and correlate with therapy.[16]

The soluble CD25 receptor is widely used in immunologic and inflammatory diseases.[17,18] The soluble CD25 receptor is elevated in infection, autoimmunity, hematological dyscrasia, and solid neoplasms.[16,19] Additionally, the soluble CD25 receptor has been proposed as a biomarker of lymphohistiocytosis and macrophage activation syndrome, which are conditions associated with immune regulatory dysfunction and inflammation.[20,21] Under such conditions, the level of soluble CD25 receptor is often elevated, and it is used as a diagnostic criterion for this disease.[20,21]

Soluble CD117, also known as soluble c-kit, is a potential biomarker for hematological malignancies.[22] Soluble CD117 is involved in hematopoiesis and, in particular, in the maintenance of stem cells.[23] Therefore, higher sCD117 concentrations in the serum of patients with hematological malignancies are associated with disease progression.[22,24] The relationship between sCD117 and immune-mediated BMF diseases, such as SAA has not been well explained. The level of sCD117 in SAA patients and its efficacy in the diagnosis of this disease are still insufficiently understood. Thus, sCD117 can be regarded as a marker of hematopoietic activity, and its levels are usually low in SAA patients.

Nevertheless, there is a lack of sufficient information regarding which part of sCD25 is best used to differentiate between AA and other types of BMF syndrome. Therefore, the present study aimed to improve the potential of sCD25 in differentiating SAA from other marrow failure syndromes. Thus, this study aimed to determine the level of sCD25 in SAA patients and controls and the sensitivity, specificity, and predictivity of this marker for the assessment of its diagnostic potential for non-invasive SAA.

MATERIALS AND METHODS

The study protocol was approved by the Dali Referral Institutional Review Board of Hospital Ethics Committee (approval number: 88/17, date: 20.11.2017). The study data were retrospectively collected from the Hematology Department of the Referral Hospital from January 2018 to December 2022. This single-center retrospective study aimed to investigate the diagnostic potential of soluble CD25 (sCD25) in patients with BMF syndromes, including SAA, MDS, PNH, and inherited BMF syndromes.

A total of 150 patients were included in the study, representing the total number of patients aged 18 years or older with BMF who attended the hospital during the study period. Among them, 50 patients were diagnosed with SAA, and 100 patients were diagnosed with other BMF syndromes (MDS, PNH, or inherited BMF syndromes). Patients were selected from hospital records based on specific inclusion criteria: all individuals diagnosed with BMF who had complete medical records available. The exclusion criteria were applied to exclude patients who had undergone hematopoietic stem cell transplantation, received immunosuppressive therapy within the last year, or had missing or incomplete medical records.

Descriptive analysis was used to present the demographic and clinical features of the study population. The diagnosis and classification of SAA, inherited BMF syndromes, MDS, and PNH were based on standard clinical and laboratory criteria. Information on coexisting viral infections, such as hepatitis B virus, hepatitis C virus, and severe acute respiratory syndrome-coronavirus-2, was also collected from both SAA and non-SAA patients.

Statistical Analysis

The levels of soluble CD25 (sCD25) were measured using a sensitive human-soluble CD25 ELISA kit. The ROC curve was generated to evaluate the diagnostic performance of sCD25 for SAA compared with other BMF syndromes. The area under the curve (AUC) was calculated, and Youden's index was used to identify the optimal cut-off point. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the cut-off point.

To explore the relationship between sCD25 levels and disease severity, the Kruskal-Wallis test was conducted, followed by Bonferroni's post-hoc correction. Spearman's rank correlation coefficient was used to assess correlations between sCD25 levels and other continuous variables, such as laboratory findings.

A two-tailed p-value 0.05 was considered statistically significant. Data analysis was carried out using SPSS Statistics 28 (IBM Corp., Armonk, NY) and R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic and Clinical Characteristics

The present study included 150 patients, among whom 50 had SAA and 100 had other subtypes of BMF syndrome. The mean age of the SAA patients was 48 years. The mean age of patients with other syndromes was 43 years. 5±17. 2 years. The gender distribution was 1.2:1 for SAA and 1.6:1 for the other syndromes. The most common symptoms included (90% in SAA, 88% in other syndromes), easy bruising (76% in SAA, 65% in other syndromes), and recurrent infections (64% in SAA, 52% in other syndromes) as shown in Table 1.

Regarding the specific diagnoses within the other BMF syndrome groups, we observed the following distributions: MDS in 40 patients; inherited BMF syndrome in 35 patients; Fanconi anemia in 15 patients; Blackfan-Diamond anemia in 10 patients; D dyskeratosis congenita in 8 patients; and PNH in 25 patients. Laboratory findings revealed that the median soluble CD25 (sCD25) level in the SAA group was significantly greater at 3245 pg/mL [interquartile range (IQR): 2850-3620 pg/mL] compared to the other BMF syndrome group, which had a median sCD25 level of 1250 pg/mL (IQR: 980-1560 pg/mL) ($p<0.001$). The average laboratory values for neutrophils, erythrocytes, hemoglobin, platelets, C-reactive protein (CRP), and procalcitonin (PCT) in the SAA group and other groups were as follows: SAA group: neutrophils, 1.2±0.6x10^9/L; erythrocytes, 2.5±0.8x10^12/L; Hb, 8.6±1.5 g/dL; platelet (PLT), 18.4±7.2 x10^9/L; CRP, 12.4±5.3 mg/L; PCT, 0.08±0.04 ng/mL; and other group: neutrophils, 2.1±0.9x10^9/L; erythrocytes, 3.8±1.2x10^12/L; Hb, 11.2±2.5 g/dL; PLT, 120.6±45.3x10^9/L; CRP, 8.7±3.2 mg/L; and PCT, 0.05±0.02 ng/mL as shown in Table 2.

Diagnostic Performance of sCD25

sCD25 was effective in discriminating between SAA and other BMF disorders, with an receiver operating characteristic (ROC)-AUC of 0.92 (95% confidence interval: 0.89-0.95). Using a cut-off point of 2500 pg/mL, the sensitivity of the test was 84%, specificity was 88%, PPV was 72%, and NPV was 93%. Compared with patients with other syndromes, SAA patients with sCD25 levels above this threshold were significantly different ($p<0.001$).

Correlation with Disease Severity

In the context of SAA, 50 and 42 patients were treated with immunosuppressive drugs with the aim of reducing the immunological attack on hematopoietic stem cells. The treatment modality of hematopoietic stem cell transplantation was considered in patients with severe disease or relapse. In contrast, patients with other BMF syndromes received tailored therapies based on specific diagnoses. Therefore, in the group of patients with MDS (32 of 40), hypomethylating agents, including azacitidine or decitabine, were used, whereas supportive care with transfusions was mainly used for patients with inherited disorders, such as Fanconi anemia. In addition to treatment, some patients with FA receive androgens or hematopoietic growth factors to improve erythropoiesis. Out of the 25 patients with PNH, 20 were administered eculizumab, a medication that prevents the complement system from attacking red blood cells and causing thrombosis. Table 3.

Response to Immunosuppressive Therapy

This study also revealed a statistically significant relationship between sCD25 levels and the outcome of immunosuppressive treatment in SAA patients ($p=0.045$). The amount of sCD25 in the patient's blood plasma was greater in non-responders than in responders.

Comparison Between the New Diagnostic Marker and the Other Markers

Of the measured parameters in this study, sCD25 was considered superior to the reticulocyte and absolute neutrophil counts. The AUC for sCD25 was 0.92, which was significantly greater than the AUC of the reticulocyte count (0.76) and absolute neutrophil count (0.71). Thus, sCD25 had greater sensitivity and specificity than the other markers and could be useful for differentiating SAA from other types of BMF diseases. Table 4.

DISCUSSION

We aimed to establish the possibility of using sCD25 as a diagnostic marker for SAA and to compare it with that of other BMF syndromes. Finally, the data obtained in the present study strongly support the hypothesis that sCD25 can be used to enhance diagnostic strategies and therapeutic outcomes in SAA patients. Therefore, our study also

Table 1. Demographic and clinical characteristics

Characteristic	SAA group (n=50)	Other bone marrow failure syndromes group, (n=100)	Total, (n=150)
Mean age (years)	48.6 ± 12.3	43.5±17.2	45.2±15.6
Males, n (%)	28 (56%)	62 (62%)	90
Female, n (%)	22 (44%)	38 (38%)	60
Male-to-female ratio	1.2:1	1.6:1	1.2:1
Fatigue (%)	45 (90%)	88 (88%)	89
Easy bruising (%)	38 (76%)	65(65%)	69
Recurrent infections (%)	32(64%)	52 (52%)	57

SAA: Severe aplastic anemia.

Table 2. Laboratory findings

Parameter	SAA group	Other group
Neutrophils (x10^9/L)	1.2±0.6	2.1±0.9
Erythrocytes (x10^12/L)	2.5±0.8	3.8±1.2
Hemoglobin (g/dL)	8.6±1.5	11.2±2.5
Platelets (x10^9/L)	18.4±7.2	120.6±45.3
CRP (mg/L)	12.4±5.3	8.7±3.2
PCT (ng/mL)	0.08±0.04	0.05±0.02
sCD25 (pg/mL)	3245±420	1250±350

CRP: C-reactive protein, PCT: Procalcitonin.

Table 3. Correlations between sCD25 levels and disease severity

Parameter	Spearman's rho	p
Reticulocyte count	-0.56	<0.001
Absolute neutrophil count	-0.48	<0.001
Bone marrow cellularity	-0.39	0.003

Table 4. Comparison between the new diagnostic marker and the other markers

Marker	AUC	Sensitivity	Specificity
sCD25	0.92	84%	88%
Reticulocyte count	0.76	-	-
Absolute neutrophil count	0.71	-	-

AUC: Area under the curve.

reinforces the involvement of sCD25 in SAA, as patients with this disease present higher levels of this marker than those with other BMF disorders. This finding is consistent with other studies showing that sCD25 is a marker of immune dysregulation and the severity of various immunological diseases.[25,26]

The AUC of sCD25 was 0.92, indicating that it can distinguish SAA from other types of BMF syndrome. The selected cut-off criterion of 2500 pg/mL provides optimal sensitivity and specificity compared with those of other routine tests, such as reticulocyte and neutrophil counts. This is crucial from a clinical perspective because proper and early diagnosis of SAA is important for the initiation of appropriate management. The comparatively low sensitivity of sCD25 can be especially useful for excluding SAA and allowing clinicians to identify other possibilities. Consequently, this study links sCD25 to the severity of SAA in the patient group. A sCD25 level above the median is associated with a greater degree of cytopenia and lower bone marrow cellularity. In agreement with other findings, sCD25 could be used for the assessment of the disease state and the state of bone marrow.[16,27]

The association between sCD25 and the results of immunosuppressive treatment is important. These data suggest that SAA patients with elevated sCD25 levels may not require immunosuppressive treatment; thus, sCD25 can be used to predict treatment outcome and patient's need for HSCT. This finding has some therapeutic implications because it may help in the formulation of treatment plans for patients. Despite the findings of this study, further large-scale prospective studies should be conducted to determine whether sCD25 is useful for predicting patients who will benefit from immunosuppressive treatments.

Comparison with Other Markers

This study revealed that sCD25 had better diagnostic efficiency than common markers, such as reticulocyte and neutrophil counts. The higher AUC, sensitivity, and specificity of sCD25 are better than those of the others and can therefore help in the diagnosis of SAA, especially in cases where the clinical and pathological features are quite similar. The findings of this study suggest that sCD25 assessment can be useful in the diagnosis of BMF syndrome when the results are combined with other clinical and laboratory parameters.

Study Limitations

There are several limitations associated with this retrospective study that can be overcome in a prospective, large-scale multicenter study. Expanding the study of less frequent BMF subtypes may improve our knowledge of the value of sCD25 as a diagnostic marker. More studies are needed to determine the factors that increase sCD25 in patients with SAA and the effectiveness of this marker in disease progression.

CONCLUSION

Soluble CD25 (sCD25) is a non-invasive diagnostic biomarker of SAA. The good diagnostic sensitivity, association with disease severity, and possible ability to predict response to immunosuppressive treatment warrants its role in the management of SAA.

MAIN POINTS

- **Elevated sCD25 levels in SAA:** Soluble CD25 (sCD25) levels were significantly higher in patients with severe aplastic anemia (SAA) than in those with other bone marrow failure (BMF) syndromes, indicating its potential as a diagnostic marker.
- **Excellent diagnostic accuracy:** This study demonstrated that sCD25 had an excellent diagnostic accuracy for distinguishing SAA from other BMF syndromes, with an AUC of 0.92.
- **Correlation with disease severity:** Higher sCD25 levels were associated with more severe cytopenia and lower bone marrow cellularity, suggesting its role in assessing disease severity in SAA patients.
- **Predictive value for treatment outcomes:** Elevated sCD25 levels predicted non-responsiveness to immunosuppressive therapy in SAA patients, indicating its potential utility in guiding treatment decisions.
- **Superior to traditional markers:** sCD25 outperformed traditional markers like reticulocyte and neutrophil counts, in diagnosing SAA, offering a more sensitive and specific tool for clinicians.

ETHICS

Ethics Committee Approval: The study protocol was approved by the Dali Referral Institutional Review Board of Hospital Ethics Committee (approval number: 88/17, date: 20.11.2017).

Informed Consent: Retrospective study.

Footnotes

Financial Disclosure: The author declared that this study had received no financial support.

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RESEARCH ARTICLE

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The Effect of Quince Seed Mucilage on Human Foreskin Stem Cell Proliferation and Self-Renewal Potential

Betül Mammadov[1], Emil Mammadov[2], Eda Becer[3], Hafize Seda Vatansever[4,5]

[1]Department of Midwifery, Near East University Faculty of Health Sciences, Nicosia, North Cyprus
[2]Clinic of Pediatric Surgery, Dr. Burhan Nalbantoğlu State Hospital, Nicosia, North Cyprus
[3]Department of Biochemistry, Eastern Mediterranean University Faculty of Pharmacy, Famagusta, North Cyprus
[4]Department of Histology and Embryology, Near East University Faculty of Medicine, Nicosia, North Cyprus
[5]Department of Histology and Embryology, Celal Bayar University Faculty of Medicine, İstanbul, Türkiye

Abstract

BACKGROUND/AIMS: Quince seed mucilage (QSM) is used in Iranian folk medicine to treat wounds and burns. Mucilage is rich in polysaccharides and proteins. Approximately 80% of breastfeeding women experience nipple pain and soreness, often applying homemade QSM to treat nipple cracks. There are limited studies on the cytotoxic effects of QSM on fibroblast formation. The present study investigated the proliferative effects of QSM on mesenchymal stem cells isolated from newborn foreskin (hnFSSCs).

MATERIALS AND METHODS: Following a standard circumcision procedure, cells were isolated and cultured in suitable media to support growth. The quince seed gel was prepared and pulverized by drying. Foreskin stem cells were immunocytochemically characterized using CD45, CD34, and CD90 antibodies. The cytotoxic effect of quince seed gel on hnFSSCs was determined using the MTT assay. The cells were then treated with quince seed gel for 24 h, and immunohistochemical staining for Ki-67, c-Myc, OCT¾, and Sall4 was performed.

RESULTS: Immunohistochemical analysis revealed that hnFSSCs were positive for CD, CD90, and CD45 and weakly positive for CD34. The MTT results showed that quince seed gel treatment at 100 µg/mL for 24 h was the most appropriate concentration and duration compared with the positive control. QSM-treated cells showed significantly higher immunoreactivity for Ki-67 (H-score: 266.5±12.6), OCT¾ (H-score: 239±8), and Sall4 (H-score: 243.8±7.5) in comparison with the control group ($p<0.05$). In contrast, c-Myc (H-score: 226±18.8) immunoreactivity was moderate in both groups, with no significant difference ($p>0.05$).

CONCLUSION: Our results suggest that QSM can support the maintenance of self-renewal and pluripotency properties in human foreskin-derived stem cells.

Keywords: Human foreskin tissue, quince seed mucilage, stem cells, fibroblasts formation, cydonia oblonga miller

INTRODUCTION

Many natural products and plants have healing properties that are beneficial for wound healing. One such herbal product is the quince fruit (Cydonia Oblonga Miller), which belongs to the Rosaceae family. This plant, which originates in Iran, can be found in various regions across the globe. In Iranian traditional medicine, it is commonly used to treat a variety of illnesses. Upon contact with water, the seeds of this plant expand and form a gel-like substance referred to as mucilage. This substance has numerous health benefits due to its antioxidant, anti-ulcerative, antimicrobial, and wound-healing properties. Mucilage is a long-chain mucopolysaccharide. When applied to a wound, it helps

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ORCID IDs of the authors: B.M. 0000-0002-9051-0279; E.M. 0000-0001-8143-1643; E.B. 0000-0002-2378-128X; H.S.V. 0000-0002-7415-9618.

Address for Correspondence: Emil Mammadov
E-mail: dremilmammadov@gmail.com
ORCID ID: orcid.org/0000-0001-8143-1643

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to keep the wound moist and provides the necessary nutrients and environment for the cells involved in the healing process. Additionally, its antimicrobial properties help to prevent infection and promote healing. Quince cell mucilage (QSM) has been widely investigated in the last decade as a biological scaffold for tissue engineering and as a wound healing agent.[1-5]

Mesenchymal stem cells, which are versatile progenitor cells capable of self-renewal, can be extracted from various sources like adipose tissue, dental pulp, placenta, and newborn human foreskin tissue (NHF). These cells possess the remarkable capacity to transform into fat, bone, and cartilage, with only a limited number required to generate each of these tissue types.[6,7] Mesenchymal stem cells are preferred for the treatment of numerous conditions, including orthopedic injuries, autoimmune diseases, and liver problems.[8] Additionally, these cells can differentiate into different types, such as fibroblasts, which are integral components of various bodily tissues like skin, nerves, and muscles. Fibroblasts play a considerable role in the healing of skin wounds and have important implications for regenerative medicine.[9]

NHF, which is typically discarded waste, serves as a source of mesenchymal stem cells. This tissue is a skin part that develops beneath the glans penis during the third month of intrauterine life. Notably, it has the capability to proliferate without undergoing cell differentiation for an extended period after birth and can be acquired during neonatal circumcision procedure.[10] The interaction of QSM with different types of cells, such as fibroblasts, keratinocytes, and adipose-derived stem cells, has been demonstrated to be biocompatible and not cytotoxic.[5,11,12] To the best of our knowledge, the impact of QSM on foreskin-derived stem cells remains unexplored. In this study, we aimed to interpret the cytotoxic and proliferative impacts of QSM on human foreskin-isolated stem cells. In addition, human foreskin-isolated cells were characterized.

MATERIALS AND METHODS

Stem Cell Isolation and Culture from Human Foreskin Tissue

The assay was designed as an *in vitro* cell culture study. NHF tissues were obtained from two patients aged 20 and 25 days during a routine newborn circumcision procedure at the university hospital. Written informed consent was obtained from the patients' parents before surgery. The Institutional Ethics Committee granted approval for the study, ensuring adherence to ethical standards [Near East University, Ethics Committee of Health Sciences (approval number: YDU/2018/62-658, date: 18.10.2018)]. The foreskin tissue's mucosal part was separated from the specimen and digested with collagenase type 1 enzyme (Sigma, C0130) for 1.5 h at 37 °C. Thereafter, cells were centrifuged and seeded in 6-well plates. The cells were grown in DMEM-F12 medium supplemented with 1% antibiotics (penicillin-streptomycin), 10% fetal bovine serum (FBS) (Capricorn Scientific, FBS-11B), and 25 µg/mL amphotericin B (Gibco, 15290018) in a humidified incubator at 37 °C and 5% CO_2. When the cells reached an 80-85% confluent, they were passage usage trypsin-EDTA solution (0.25%, Biochrom, L 2143). The cultured cells from passage three were used in all experiments.

Human Foreskin Stem Cell Characterization

Stem cells from NHF tissues were characterized using the protocol our study group previously described.[13] Cells were fixed and incubated with primary antibodies prepared in phosphate-buffered saline (PBS). Specification of the cell characteristics, primary antibodies against CD90 (Thy-1 glycoprotein, Santa Cruz, sc-19614), CD45 (Santa Cruz, sc-1178), and CD34 (Santa Cruz, sc-74499) were used. The biotinylated secondary antibody and enzyme-labeled streptavidin (Thermo, TP-060-HL) were added and incubated. Then, cells were stained with diaminobenzidine (DAB, ScyTek Laboratories ACK125) for 4 min for immunolabeling. The following washing with water, the cells were counterstained with Mayer's hematoxylin (Bio Optica 1213) for 3 min. All staining specimens were examined under a light microscope (Olympus BX40, Tokyo, Japan).

Preparation of Quince Cell Mucilage

First, we separated the seeds from the fresh pulp. The seeds were then dried in a shaded area, maintaining a temperature of 25-30 °C. 50 grams of quince seeds were added to 1000 mL of distilled water. Heat to 50-60 °C and mix for 30 min to extract the mucilage. After allowing the beaker containing quince mucilage to sit for 30 minutes, it was allowed to reach a temperature of nearly 40 °C, ensuring that the conditions were conducive for further processing. Following this step, the mixture was delicately filtered using a clean linen cloth, allowing for the careful separation of the mucilage. The QSM was carefully heated in an oven at 40 °C to obtain a pure dry powder. From 100 g of mucilage, we successfully extracted 9.86 g of this valuable dried powder, demonstrating the efficiency of our process.

Cell Viability and Cytotoxicity Assessment

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) was used to assess the cytotoxic effects of QSM. The MTT assay was performed in accordance with the study of Becer et al.[14]. PBS was used for QSM powder dissolution. Then, it was diluted with the culture medium at five different concentrations (25, 50, 100, 200, 400 µg/mL). The cells of NHF were suspended in culture medium and seeded in 96-well culture plates at a density of 5×10^3 in each well with 100 µL of the medium. The cells were incubated with five different concentrations of QSM during both hours (24 and 48). Thereafter, 10 µL MTT solution was added to each well, and the mixture was incubated at 37 °C for 4 h. Thereafter, dimethyl sulfoxide (DMSO, Sigma, D2650-5X5ML) at a volume of 50 µL was added for dissolving the formazan salts. The absorbance values were measured at 540 nm (Versa Max, Molecular Device, Sunnyvale, USA). All MTT tests were done in 3 times.

Immunocytochemical Evaluation

The indirect immunoperoxidase method was used to evaluate Ki-67, myc, OCT¾, and Sall4 protein distributions after quince seed gel administration as previously described.[15] 5×10^3 cells/well were seeded into 24-well plates and incubated with quince seed gel for 24 h. Thereafter, cells of NHF were fixed with 4% paraformaldehyde (158,127-25G, Sigma-Aldrich) for 30 min and washed twice with PBS. In addition, cells were permeabilized using 0.1% Triton-X 100 (Merck, 108603) for 15 min. Then, 3% H_2O_2 (Sigma-Aldrich, 7722-84-1) was added for 11 min, and blocking solution was added for 10 min. Primary antibodies against Ki-67 (Thermofisher Scientific, RB-081-A1), c-Myc (Invitrogen, 14-6784-82), OCT¾ (Invitrogen, 12-5841-82), and Sall4 (Abcam, ab57577) were added and incubated overnight at +4 °C. Then, they were washed with PBS and treated with biotinylated secondary antibodies and enzyme-labeled streptavidin (TP-060-HL/Thermo) for 5 min. After washing with PBS, DAB chromogen was added, and cells were incubated for 3 min. After washing through distilled water, counterstaining was applied with Mayer's hematoxylin for 4 min. Staining intensities of Ki-67, c-Myc, OCT¾, and Sall4 were graded semi-quantitatively using H-score. The

H-score = Σл (i+1) equation was used. In addition, "i" in the equation indicates the staining intensity and is graded as 3, strong; 2, moderate; and 1, weak. The symbol "л" indicates the percentage of cells stained at various intensities, with values ranging from 0% to 100%. This metric is crucial for quantifying staining intensity.

Statistical Analysis

The data were presented as mean ± standard deviation. Additionally, the GraphPad Prism 7 program was utilized in the analysis, and group differences were analyzed using the Mann-Whitney U tests. P<0.05 was considered statistically significant.

RESULTS

MTT Evaluation

NHF cells were treated with five different concentrations (25, 50, 100, 200, and 400 µg/mL) of QSM for 24 and 48 h. We found that 100 µg/mL of QSM was more effective for cell viability protection at 48 h in cells (Figure 1). According to the cell viability results, the QSM protected the cell viability owing to its cell growth and repair-promoting effect.

Cell Morphology

Spindle shape and fibroblast-like morphology of foreskin-isolated stem cells were observed in both quince seed gel-treated and control cells (Figure 2A, B). The number and morphology of NHF cells did not differ after the application of quince seed gel.

Immunocytochemical Evaluation

The immunoreactivities of Ki-67 were strong in QSM-treated NHF cells (Figure 3A), and the staining intensity was significantly higher than that of the control group of NHF cells (Figure 3B) (p<0.05, Table 1). Moderate immunoreactivity of c-Myc was detected in both QSM-treated (Figure 3C) and control (Figure 3D) cells. However, the results showed no significant difference in c-Myc immunoreactivity compared with the control group (p>0.05, Table 1). The OCT¾ immunoreactivity was strong in QSM-treated NHF cells (Figure 3E), and the staining intensity was statistically significant compared with the control group of NHF cells (Figure 3F) (p<0.05, Table 1). Strong and weak Sall4 immunoreactivities were defined in the QSM and control groups, respectively (Figure 3G, H). The Sall4 H-score value in the NHF cells was considerably different from that in the control group (p<0.05, Table 1).

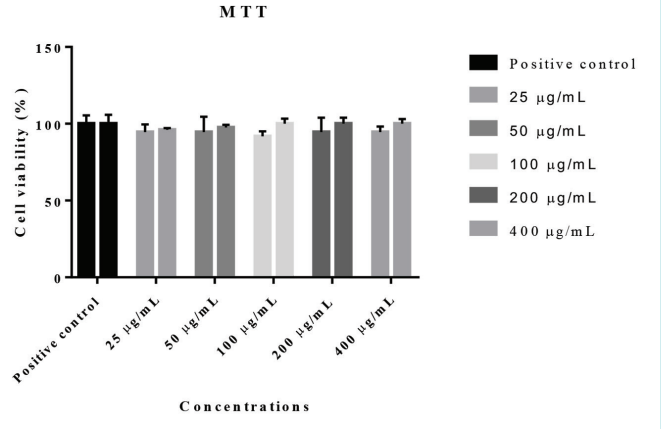

Figure 1. Effect of QSM on cell viability of cells. Cells were treated with five different concentrations of quince seed gel for both hours (24 or 48). Absorbance = 540 nm.

DISCUSSION

Quince, a fruit predominantly cultivated in Iran, Türkiye, and the Caucasus region, is well-known for its healing properties in this region. Quince seeds are used to treat diarrhea, cough, and intestinal colic as part of folk medicine practice. When seeds are placed in water, a colloidal solution, called mucilage, is formed from the seed cores. In particular, quince seed mucilage (QSM), which is abundant in healing attributes, is often used to treat nipple cracks in breastfeeding mothers in Türkiye. Extensive research has focused on QSM, and its chemical composition has revealed a structure primarily comprised of water-soluble polysaccharides such as methoxyuronic acid and cellulose. Subsequent studies identified the chief water-soluble polysaccharide within QSM as a partially O-acetylated (4-O-methyl-D-glucurono)-D-xylan containing a notable concentration of glucuronic acid residues. Moreover, acid hydrolysis showed that the mucilage consists of L-arabinose, D-xylose, and aldobiuronic acid.[3,16,17] The QSM has two applications as a tissue engineering substrate for scaffolds and wound-healing materials. A study by Jafari et al.[12] demonstrated that QSM/polyvinyl alcohol scaffolds exhibited strong fibroblast adhesion along with exceptional biocompatibility. Şimşek et al.[18] developed bioengineered three-dimensional constructs from QSM, showing strong attachment and migration of human adipose-derived mesenchymal stem cells, with no cytotoxicity observed. The researchers concluded that QSM has the potency to be a substitute for routinely utilized polysaccharides in tissue engineering and regenerative medicine studies.[18] In another application, Cetin Genc et al.[19] enriched QSM with nano-hydroxyapatite, manufactured scaffolds by freeze drying, and analyzed the osteogenic derivation of human adipose-stem cells from mesenchymal tissue. Immunohistochemical staining indicated that cells with a spherical morphology infiltrated the bioscaffold pores, whereas real-time polymerase chain reaction analyses showed an early up-regulation of osteogenic markers. The authors believe that QSM scaffolds enriched with nanohydroxyapatites have the potential for regenerative applications, especially in non-load bearing areas, such as the craniomaxillofacial region.[19]

QSM has also been researched as a material to promote wound healing. Hemmati et al.[20] investigated the impact of QSM cream on the T-2 toxin-induced dermal toxicity in rabbits and showed significant healing changes compared with the untreated and sham groups. Tamri et al.[21] demonstrated that 20% cream produced from QSM at the Eucerin base showed increased growth factors (EGF; TGF-β1; VEGF; PDGF) in the wound fluid. In addition, wound contraction was faster and the tensile strength of the wound was enhanced in the wound treated with 10% and 20% QSM cream compared with the control group. Furthermore,

Table 1. H-score values of Ki-67, c-Myc, OCT¾, and Sall4 in cells treated with QSM at 100 µg/mL QSM for 48 h and control group

	QSM group	Control group
Ki-67	266.5±12.6*	103.8±4.8
c-Myc	226±18.8	211±3.4
OCT¾	239±8*	107.5±9.5
Sall4	243.8±7.5*	105±5.8

*The data were significant compared with the control group (p<0.05). QSM: Quince seed mucilage.

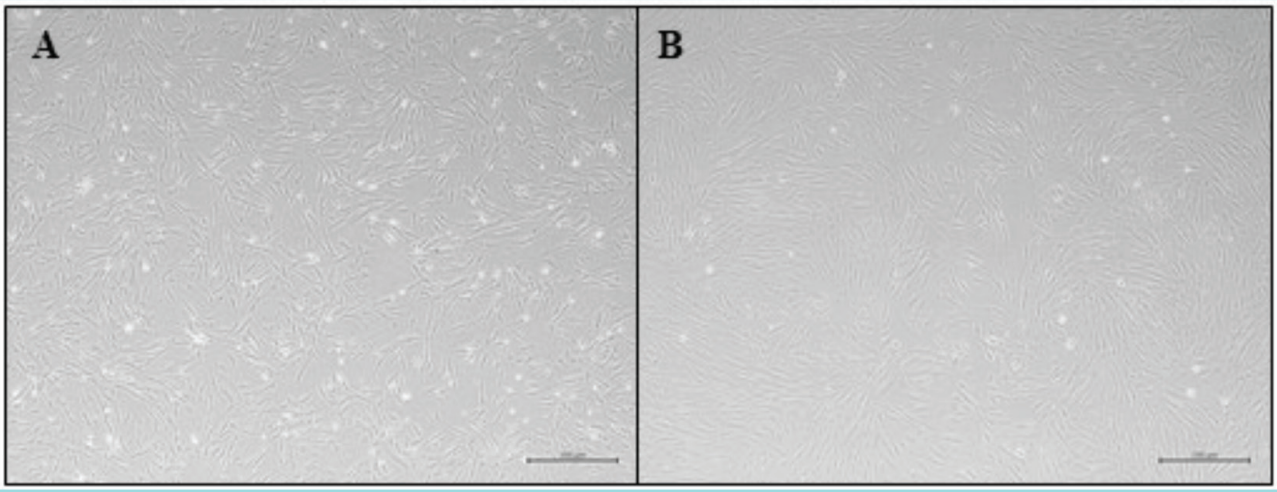

Figure 2. Cells were viewed under an inverted microscope after treatment with control (A) gel or quince seed gel (B). Scale bar = 200 µm.

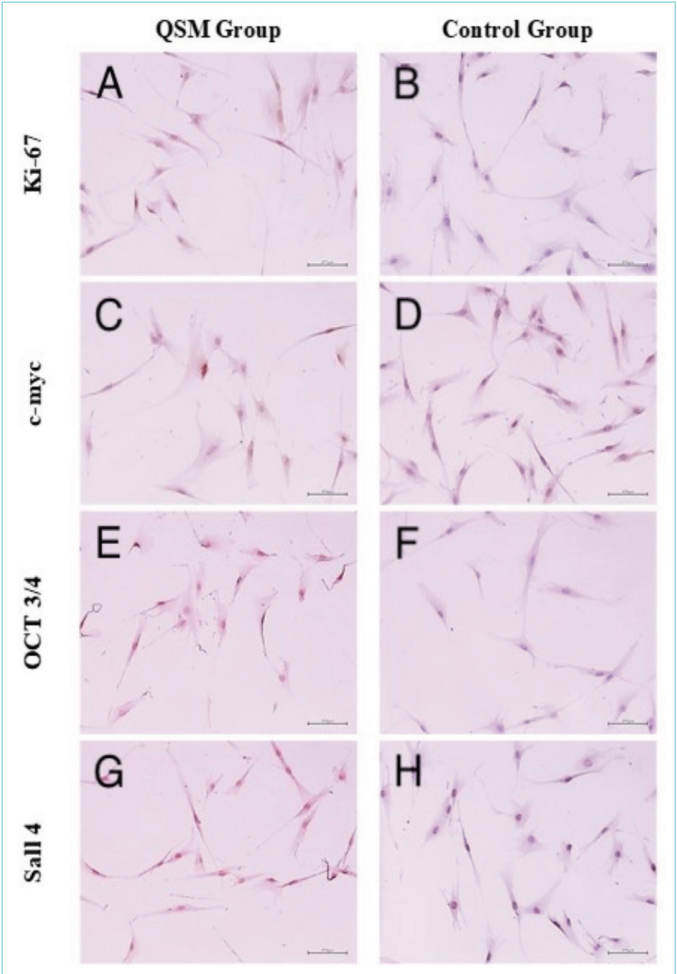

Figure 3. Immunoreactivity of Ki-67 (A, B), c-Myc (C, D), OCT¾ (E, F), and Sall4 (G, H) in cells after treatment with 100 µg/mL QSM (A-G) and control (B-H) groups. Scale bar = 200 µm.

Xin et al.[22] demonstrated that a conditioned medium derived from human foreskin-isolated cells, when combined with hyaluronic acid, promotes the regeneration of the extracellular matrix and accelerates wound healing in diabetic mice.

Recent research has revealed that cells isolated from the human foreskin exhibit fibroblast-like structures and possess stem cell properties, as well as pluripotent and multipotent abilities.[13,23] Additionally, human foreskin-isolated cells have become commercially available and are used in products like Apligraf® (Organogenesis, Inc.) and Dermagraft® (Organogenesis, Inc.).

In this study, we conducted experiments to assess the impact of QSM on human foreskin-isolated stem cells. Specifically, we investigated the influence of QSM on the proliferation and stem cell properties of these cells. Notably, our study represents the first study to examine the impacts of QSM on the proliferation and activation of stemness signaling pathways in human foreskin-isolated cells. To explore this, we exposed human foreskin-isolated cells to various concentrations of QSM (25-50-100-200-400 µg/mL) for 24 and 48 h. We evaluated cell viability using the MTT assay and found that all concentrations were non-toxic, indicating that the selected concentration and time frame enhanced cell viability. Our results showed that 100 µg/mL of QSM was particularly effective at enhancing cell viability after 48 h of exposure.

Ki-67, a nuclear protein, is used as a marker to determine proliferating cells. According to the results of our study, the immunoreactivity of Ki-67 was crucially higher in QSM-treated human foreskin-isolated cells than in the control group. Ghafourian et al.[24] reported that QSM stimulated human skin fibroblast proliferation. QSM could be used as a wound-healing agent. Quince seeds contain phenolic compounds (3,5-caffeoylquinic acids, caffeoylquinic,…), amino acids (asparagine, glutamic and aspartic acids), and organic acids (ascorbic, citric, malic, fumaric acids, ...).[25] The rich phytochemical profile of quince seeds indicates the proliferative effects and wound-healing activities of QSM.

Sall4 (Spalt-like transcription factors 4) is a transcription factor essential for the self-renewal and pluripotency maintenance of stem cells. Sall4 protein expression gradually reduces with the tissues and organs maturation.[26] It regulates transcription key stemness factors, such

as OCT¾, SOX2, and c-Myc. OCT¾ and c-Myc are especially important regulators for maintaining the self-renewal and pluripotency of stem cells.[27] Our results showed that Sall4 and OCT¾immunoreactivities were significantly higher in QSM-treated human foreskin-isolated cells compared with the control group. Moreover, c-Myc immunoreactivity was higher in QSM-treated human foreskin-isolated cells than in control cells. Although a difference was observed between the groups, the difference did not reach statistical significance.

Study Limitations

The chemical composition of QSM can vary depending on the source and preparation method. Standardizing the extraction and preparation processes will ensure consistency and reproducibility in future research. Our study was conducted *in vitro*. To confirm the applicability of our findings, additional studies must be conducted using relevant *in vivo* models and eventually human trials.

CONCLUSION

Our findings demonstrate that QSM at a concentration of 100 µg/mL significantly enhances cell viability and promotes the expression of key stemness factors, such as Sall4 and OCT¾, in human foreskin-isolated stem cells. These outcomes suggest that QSM can support the maintenance of self-renewal and pluripotency properties in these cells. Further studies are required to identify the mechanisms underlying the effects of QSM on stem cell proliferation and activation pathways to harness its therapeutic potential in regenerative medicine.

MAIN POINTS

- **Effective Concentration:** The 100 µg/mL concentration of QSM significantly enhanced cell viability after 48 h, indicating its potential for cell growth and repair.
- **Morphology Consistency:** Treatment with quince seed gel did not alter the spindle shape or fibroblast-like morphology of foreskin-isolated stem cells, maintaining the number and form of cells.
- **Immunoreactivity Increase:** QSM treatment resulted in a marked increase in Ki-67 and OCT¾ immunoreactivity, with statistically significant differences compared with the control group, whereas c-Myc showed no significant change.

ETHICS

Ethics Committee Approval: The Institutional Ethics Committee granted approval for the study, ensuring adherence to ethical standards [Near East University, Ethics Committee of Health Sciences (approval number: YDU/2018/62-658, date:18.10.2018)].

Informed Consent: Written informed consent was obtained from the patients' parents before surgery.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.M., Concept: B.M., E.M., E.B., H.S.V., Design: B.M., E.M., E.B., H.S.V., Data Collection and/or Processing: B.M., E.M., E.B., H.S.V., Analysis and/or Interpretation: E.M., H.S.V., Literature Search: B.M., E.M., E.B., H.S.V., Writing: B.M., E.M., E.B., H.S.V.

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CASE REPORT

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A Case of Primary Hypothyroidism Complicated with Pituitary Pseudo-Macroadenoma and Chronic Adnexal Torsion

Zeliha Atak[1], Behiye Oral[2], Elif Güneş[3], Sakine Rahimli Ocakoğlu[1], Feyza Bayram[4]

[1]Clinic of Obstetrics and Gynecology, University of Health Sciences Türkiye, Bursa City Hospital, Bursa, Türkiye
[2]Clinic of Radiology, University of Health Sciences Türkiye, Bursa City Hospital, Bursa, Türkiye
[3]Clinic of Endocrinology and Metabolism, University of Health Sciences Türkiye, Bursa City Hospital, Bursa, Türkiye
[4]Clinic of Obstetrics and Gynecology, University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye

Abstract

Primary hypothyroidism with extremely high thyroid-stimulating hormone levels can cause bilateral theca lutein cysts and pituitary pseudo-macroadenoma. We report a case of bilateral ovarian cysts complicated by chronic adnexal torsion. Although the size of the pituitary pseudo-macroadenoma and the right ovary decreased after successful levothyroxine treatment, it was determined that the opposite ovary was torsioned. We suggest that ovarian hyperstimulation due to severe primary hypothyroidism can be treated medically and that possible complications should be closely monitored.

Keywords: Chronic ovarian torsion, pituitary pseudo-macroadenoma, primary hypothyroidism, theca lutein cysts

INTRODUCTION

Hypothyroidism is a serious metabolic disorder with multisystem effects. Ovarian cyst formation mimicking ovarian hyperstimulation syndrome is a rare complication of untreated primary hypothyroidism. The pathophysiology of this phenomenon is intriguing and involves several hormonal interactions. Hypotheses of structural similarity between thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG) or between TSH and follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have been proposed. However, the exact mechanism underlying ovarian cyst formation in patients with primary hypothyroidism remains unclear.[1,2]

Cases of multicystic ovarian appearance associated with primary hypothyroidism other than pregnancy are limited in the literature.[3,4] The most important complication potentially limiting fertility in enlarged ovaries is ovarian torsion. Herein, we present a case of ovarian enlargement complicated by chronic ovarian torsion and pituitary pseudo-macroadenoma associated with severe primary hypothyroidism.

CASE PRESENTATION

A 27-year-old gravida 2, parity 2 woman was admitted to the gynecology emergency clinic with lower abdominal pain and abnormal uterine bleeding. The patient's medical history revealed that she had autoimmune hypothyroidism since 2017. At the time of the patient's first diagnosis of hypothyroidism (2017), her TSH was 111.22 mIU/L, free triiodothyronine (FT3): 2.46 ng/L, and free thyroxine (FT4): 0.77 ng/dL. In May 2018, her anti-thyroid peroxidase (anti-TPO) antibody level was >1300 IU/mL (normal range; 0-57 IU/mL).

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ORCID IDs of the authors: Z.A. 0000-0002-4876-0573; B.O. 0000-0002-9952-4140; E.G. 0000-0002-5441-2604; S.R.O. 0000-0001-8159-9489; F.B. 0000-0003-1735-6997.

Address for Correspondence: Zeliha Atak
E-mail: zeliha.atak@hotmail.com
ORCID ID: orcid.org/0000-0002-4876-0573

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The patient was prescribed levothyroxine, but she did not take her medication regularly. Hospital records showed that the patient gave birth in 2018, but she did not attend any of her follow-up visits after the postpartum period. She presented to a local hospital in February 2022 due to fatigue; treatment for anemia with a hemoglobin level of 9.3 g/dL and antidepressant medication were prescribed for her depressive mood disorders. The results of thyroid function tests at a local hospital in March 2022 were; TSH >100.00 mIU/L (0.35-5.5), FT3: 1.51 pg/mL (2.3-4.2), FT4: 0.40 pg/mL (0.8-1.76), anti-TPO: 937.63 IU/mL (0-60), antithyroglobulin antibodies: 1.65 IU/mL (0-4.5). It was found that the patient did not start receiving the recommended treatment with levothyroxine. The first application of the patient to our hospital was on April 2, 2022. The body mass index of our patient was 25.2 kg/m^2. Physical examination revealed widespread abdominal tenderness and a mass extending above the umbilicus. Ultrasound scan showed that the endometrial thickness was 6.6 mm, the right ovary was 124x102x55 mm, and the left ovary was 135x139x80 mm in size, with mild ascites. A multicystic appearance was observed in both ovaries, mimicking ovarian hyperstimulation (Figure 1). The patient did not have a recent history of any medication. There were no signs of bradycardia or myxedema on physical examination. Until the last 2 months, the patient's menstrual history was unremarkable. She emphasized that she had heavy menstrual bleeding for the past 10 days. The laboratory findings at admission and during follow-up are summarized in Table 1. Liver and renal function tests were within the normal range during the follow-up period. Magnetic resonance imaging (MRI) of the pituitary gland revealed an 18 mm macroadenoma. Although compression of the optic chiasm was noted due to macroadenoma, no visual field defects.

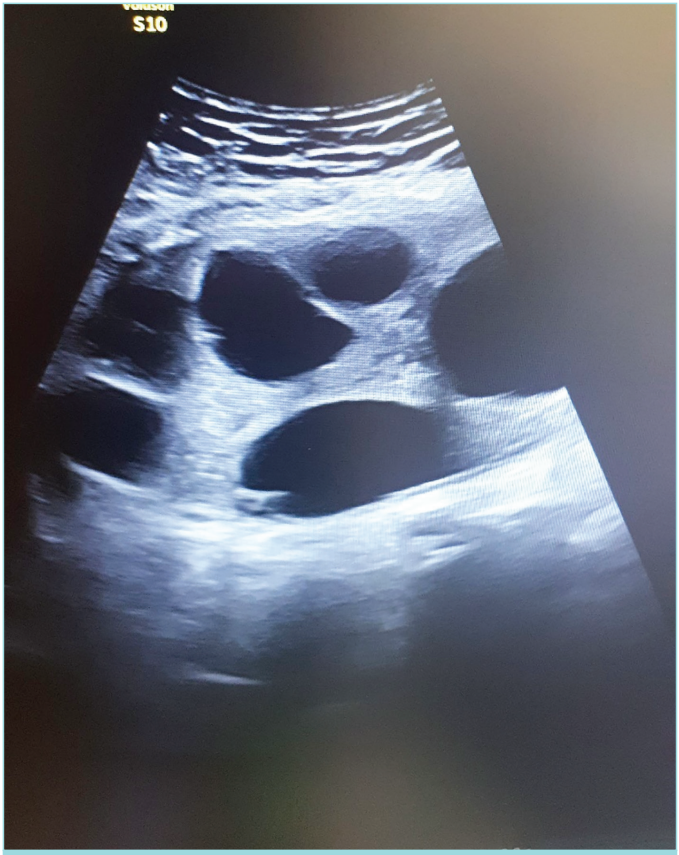

Figure 1. Ultrasonographic appearance of theca lutein cysts.

At follow-up, the hemoglobin value of the patient who experienced heavy menstrual bleeding decreased to 7.2 g/dL. For the treatment of heavy menstrual bleeding, both norethisterone acetate and tranexamic acid tablets were administered three times daily. Intravenous iron carboxymaltose was administered to the patient to treat chronic iron deficiency anemia after transfusion with erythrocyte suspension.

Levothyroxine 1x125 mg was started to treat primary hypothyroidism. At the end of 7th month of thyroxine replacement therapy, pituitary MRI revealed regression of the pseudo-macroadenoma (Figure 2).

The patient responded to treatment, and her menstrual cycle and bleeding returned to the normal range with the normalization of the thyroid function tests. Radiological assessment at the end of the 7-month follow-up period showed that the right ovary had returned to normal size. However, it was noted that the decrease in the size of the left ovary was not as significant as that of the right ovary. Additionally, due to occasional complaints of left groin pain and diminished left ovarian vascularity, the patient was scheduled for surgery with a preliminary diagnosis of ovarian torsion. However, the patient refused the surgery because of the intermittent self-resolving pain. The patient did not undergo surgery after clinical suspicion of ovarian torsion and underwent laparoscopic left oophorectomy at another medical center approximately 18 months after the primary hospital admission. The perioperative surgical note noted an adnexal mass of approximately 8,5 cm in size, in which normal ovarian tissue could not be clearly distinguished. The mass was in torsion for two complete rotations. Foci of necrosis, microcalcification, and hemorrhage were observed on histopathological examination of the oophorectomy material.

DISCUSSION

Theca lutein cysts are physiological bilateral ovarian cysts that can cause a serious increase in ovaries' size. The pathophysiology of this condition has not been clarified. In the presence of increased ovarian sensitivity, theca lutein cysts may develop as a result of prolonged or high-concentration hCG exposure. Another hypothesis is that high levels of TSH, due to their similar glycoprotein structure, may cause cyst formation in the ovaries with an FSH- and LH-like effect.[4] Although it usually accompanyes molar or multiple pregnancies, it can rarely be observed in uncomplicated singleton pregnancies.[5] Multiple ovarian cyst cases associated with primary hypothyroidism have been reported in the literature, even in the prepubertal and pubertal period.[2,6-9]

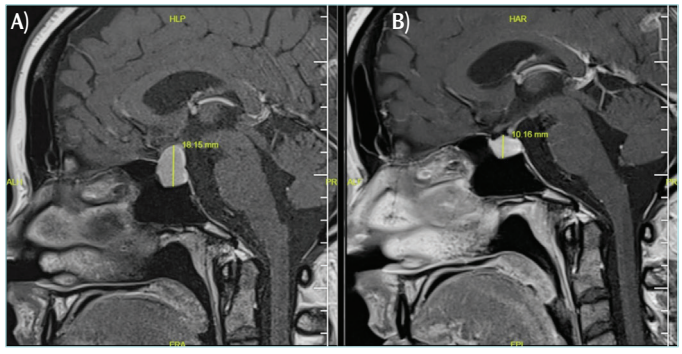

Figure 2. Contrast-enhanced magnetic resonance imaging; (A) T1A sagittal section at admission. (B) T1A sagittal section 7 months after initiating levothyroxine treatment.

Table 1. Laboratory features of the patient

	Admission	1st month	8th month	15th month	Reference range
TSH (mIU/L)	729	3.65	2.48	0.95	0.27-4.20
Free-T3 (ng/L)	1.44	5.22	3.28	3.28	2.04-4.44
Free-T4 (ng/dL)	0.59	2.59	1.6	1.81	0.93-1.71
Anti thyroglobuline antibody (IU/mL)	Normal range		Normal range		0-4.5
Anti-thyroid peroxidise antibody (IU/mL)	937.63		301		Cut-off: 60 IU/mL
FSH (IU/L)	7.8		5.2		3.5-12.5
LH (IU/L)	0.5		14		2.4-12.6
Estradiol (ng/L)	6.8		65.3		30.9-80.4
Prolaktin (µg/L)	165	91.60	45.1		4.79-23.3
GH (µg/L)	1.43		0.06		0.126-9.88
ACTH (ng/L)	34.5		48.3		7.2-63.3
Cortisol (µg/dL)	19.4	15.9	13.5		6.02-18.4
IGF-1 (ng/mL)	69.90		136		118-303
Total testosterone (µg/L)	<0.025				0.084-0.481
DHEA-SO_4 (µg/dL)	72	63			98.8-340
Total cholesterol (mg/dL)	293	190	196	239	3-200
LDL (mg/dL)	220	144	135	168	0-130
HDL (mg/dL)	40	27	46	40	45-65
Triglyceride(mg/dL)	166	95	74	155	0-200
Hemoglobin (g/dL)	8.6	10.2	9.6	9.7	11.9-14.6
CA-125 (IU/mL)	15.6	15.2	10.9	7.7	0-35
CA-19-9 (IU/mL)	4.9	5.3	6.7	3.66	0-39
CEA (IU/mL)	2.2	0.9	1.4	1.11	-
LDH (IU/L)	212	188		173	135-214
AFP (µg/L)	3.44	1.79	1.63	1.82	0-8.3

TSH: Thyroid-stimulating hormone, Free-T3: Free-triiodothyronine, Free-T4: Free-thyroxine, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, GH: Growth hormone, ACTH: Adrenocorticotropic hormone, IGF-1: Insulin-like growth factor 1, DHEA-SO4: Dehydroepiandrosterone sulphate, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CA-125: Cancer antigen-125, CA-19-9: Carbohydrate antigen-19-9, CEA: Carcinoembryonic antigen, LDH: Lactate dehydrogenase, AFP: Alpha-fetoprotein.

Ovarian masses associated with primary hypothyroidism are rarely observed in non-pregnant adult women.[10]

Thyroid function tests should be considered, especially in the presence of bilateral multiple ovarian cysts that mimic ovarian hyperstimulation syndrome. Cases in which the TSH value increased to 4191.5 mIU/L (normal, 0.47-5.01) have also been reported in the literature.[1] Our patient's TSH level upon admission was 729 mIU/L, which decreased to its normal level in the 1st month of thyroxine replacement therapy. As in our case, pituitary pseudo-macroadenoma can also be observed in these patients.[11]

Despite advances in imaging, it is still challenging to distinguish pituitary hyperplasia from pituitary adenomas. In patients with primary hypothyroidism, reactive pituitary hyperplasia can cause hyperprolactinemia, but prolactin secretion usually normalizes after the initiation of levothyroxine therapy. In the present case, prolactin levels returned to normal with levothyroxine replacement without any dopamine agonist therapy, and the appearance of macroadenoma in the pituitary gland regressed. In our case, while the laboratory parameters improved rapidly, it took seven months for the pituitary pseudo-macroadenoma to regress. Our clinical case highlights the importance of hormonal evaluation in the context of pituitary mass to reach a correct diagnosis and prevent unnecessary intervention.

There are also cases of chronic adnexal torsion reported previously.[12] If the time from diagnosis of ovarian torsion to surgery is longer than three days, it is defined as chronic adnexal torsion. Cases lasting up to 210 days between the onset of pain and diagnosis have been reported in the literature.[13] Elevated white blood cell counts and C-reactive protein levels, which are usually observed in ovarian torsion, were not observed during our patient's follow-up. In our case, the intraoperative appearance of the left adnexa and histopathological findings also supported chronic torsion.

In conclusion, knowledge that ovarian and pituitary enlargement may result from severe hypothyroidism can help avoid unnecessary medical or surgical procedures. While improvement in laboratory parameters is observed in a short period, improvement via imaging may take longer. If there is no regression in ovarian size during follow-up, ovarian torsion should be suspected.

MAIN POINTS

- In this study, we present a case of ovarian enlargement complicated with chronic ovarian torsion and pituitary pseudo-macroadenoma associated with severe primary hypothyroidism.

- Multidisciplinary approach protects the patient from unnecessary surgery and medical treatment.
- In cases of primary hypothyroidism, levothroxine treatment alone is sufficient for the regression of pituitary macroadenoma and ovarian theca luterine cysts.

ETHICS

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A., E.G., F.B., Concept: Z.A., Design: Z.A., B.O., Data Collection and/or Processing: Z.A., S.R.O., B.O., Analysis and/or Interpretation: S.R.O., B.O., Literature Search: Z.A., E.G., S.R.O., F.B., Writing: Z.A., E.G., F.B.

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

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