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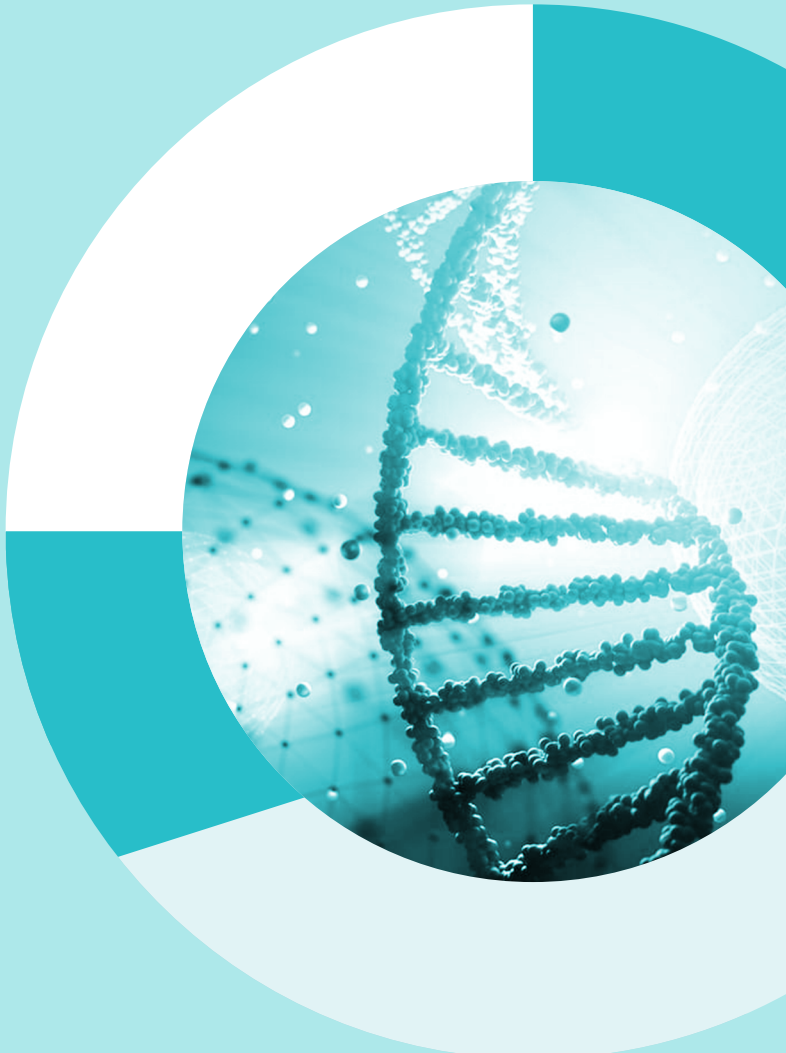

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Does Re-Reduction Improve Outcomes in Fifth Metacarpal Neck Fracture? A Matched Cohort Study

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Abstract

BACKGROUND/AIMS: To evaluate the radiological and functional effectiveness of repeated closed reduction in patients who developed early loss of reduction at the 48-hour follow-up after an initially successful closed reduction for fifth metacarpal neck fractures, and to examine its association with surgical treatment decisions.

MATERIALS AND METHODS: This retrospective matched cohort study included 200 adult patients with isolated, closed fifth metacarpal neck fractures who underwent closed reduction at a tertiary orthopedic center between January 2023 and December 2024. Patients were divided into two equal groups: the (single reduction group, n=100) and the [re-reduction group (RRG), n=100], based on whether they underwent a second closed reduction due to early loss of initially acceptable radiographic alignment detected at the 48-hour follow-up. Matching was performed 1:1 on the basis of age and sex. Radiological parameters-including dorsal angulation and metacarpal shortening-were measured at six time points during follow-up. Functional outcomes were assessed using Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) scores, grip strength, and joint range of motion. Surgical conversion rates were analyzed, and multivariate logistic regression was used to identify independent predictors of surgical intervention.

RESULTS: Initial angulation and shortening were comparable between the groups. However, the RRG exhibited significantly greater deformity at the 4th and 6th weeks, with higher angulation ($p=0.007$ and $p<0.001$, respectively) and more pronounced shortening ($p=0.001$ and $p=0.009$, respectively). At 6 weeks, QuickDASH scores were significantly worse in the RRG ($p=0.002$), though this difference was no longer statistically significant by 6 months. Flexion and extension angles were consistently more restricted in the RRG. Importantly, multivariable firth-penalized logistic regression identified initial shortening as the only independent predictor of surgical intervention, while angulation parameters did not retain statistical significance after adjustment.

CONCLUSION: Repeated closed reductions for early loss of alignment do not consistently improve outcomes and may be associated with delayed union. Longitudinal evaluation of angulation and shortening provides better clinical guidance than single-time-point assessments; however, among these parameters, initial shortening appears to be the most reliable independent predictor of eventual surgical intervention.

Keywords: Metacarpal neck fracture, closed reduction, re-reduction, treatment strategy, angulation, shortening

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INTRODUCTION

Fractures of the fifth metacarpal neck account for a substantial portion of hand injuries and represent the most common type of metacarpal fracture, particularly among young and active individuals.[1,2] These injuries usually result from direct trauma and most frequently affect the non-dominant hand.[3] Although they often present with mild angulation and shortening, they may, in some cases, lead to significant deformity, functional limitations, and cosmetic concerns.[2,4] Therefore, treatment decisions should be based not only on radiographic findings but also on patient-specific factors such as age, occupation, and functional demands.

Closed reduction followed by immobilization is often the first-line treatment option.[4-6] However, maintaining the alignment achieved after reduction can be challenging. Loss of reduction, which refers to the gradual displacement of the fracture during follow-up, has been reported in 20% to 30% of cases in the literature.[2] Studies have shown that increased angulation or shortening after reduction can negatively affect functional outcomes. In particular, angulations exceeding 30 degrees have been associated with reduced grip strength, while shortening greater than 2 millimeters may limit finger mobility.[2,7,8] This highlights the importance of ensuring the stability of the fracture position throughout the follow-up period, not just immediately after the initial reduction.

In cases of loss of reduction, repeated attempts at closed reduction are often performed to correct the deformity and avoid surgical intervention.[9-11] However, the actual functional benefit of these additional procedures and their contribution to fracture healing remain uncertain. Existing studies on this topic are limited in number and often involve small, heterogeneous patient populations.[4,6,10] Furthermore, the progression of angulation and shortening over time and their implications for clinical decision-making have not been clearly defined.[8,12] This uncertainty makes it difficult to determine whether follow-up decisions are consistently supported by objective evidence.

This study aims to evaluate the radiographic and functional effectiveness of repeated attempts at closed reduction in patients with loss of reduction following fifth metacarpal neck fractures. It also seeks to analyze the relationship between these interventions and the decision to proceed with surgical treatment.

MATERIALS AND METHODS

Study Design and Patient Selection

This retrospective, comparative cohort study was conducted at a tertiary orthopedic referral center characterized by high patient turnover and a substantial trauma workload. Approval was obtained Eskişehir City Hospital Institutional Review Board Ethics Committee (approval no: ESH/BAEK 2025/114, date: 20.02.2025). All patients aged 18 years and older who presented to the emergency department with isolated, closed fifth metacarpal neck fractures and underwent closed reduction between January 2023 and December 2024 were retrospectively reviewed using the hospital's electronic medical records. Inclusion criteria were as follows: age over 18 years, diagnosis of an isolated, closed fracture of the fifth metacarpal neck, and initial management with closed reduction in the emergency department. Exclusion criteria included age under 18, open fractures, intra-articular extension of the fracture, associated traumatic injuries in the same upper extremity, prior fractures or surgical interventions in the same hand, and insufficient clinical or radiographic data before or after the reduction. After excluding cases that met any of these criteria, 200 patients were included in the final analysis. Patients were divided into two groups based on their reduction strategy: those who underwent a single closed reduction were assigned to the "single reduction group (SRG)," while those who achieved acceptable alignment after the initial closed reduction but demonstrated early loss of reduction at the 48-hour follow-up and therefore underwent a second closed reduction were assigned to the "re-reduction group (RRG)". Each group consisted of 100 patients. One-to-one matching was performed based on age and sex to ensure comparability between groups. In cases with multiple eligible matches, the SRG patient whose reduction date was closest to that of the RRG patient was selected. This matching strategy was used to minimize the influence of potential confounders such as age and sex, thereby enhancing the internal validity of the comparative analyses. In addition to age and sex, baseline fracture characteristics, considered proxies for fracture severity and instability, were recorded for all patients. These included initial dorsal angulation, initial metacarpal shortening, rotational deformity, dominant-hand involvement, and mechanism of injury. These variables were used to assess baseline comparability between groups and to account for potential confounding by indication in subsequent analyses. Data collected retrospectively from the hospital's digital records included age, sex, duration of follow-up, time to union, hand dominance, mechanism of injury, conversion to surgical treatment, and complications.

Treatment and Follow-Up Protocol

All reduction procedures were performed in the emergency department by attending orthopedic specialists, using flexion, ulnar deviation, and dorsal pressure maneuvers.[4] Following reduction, a splint was applied to immobilize the wrist and metacarpals, with the wrist placed in slight extension and the metacarpophalangeal (MCP) joints at 90 degrees of flexion. Immediately after the initial reduction, post-reduction radiographs were obtained to confirm acceptable alignment. For clarity, radiographic time points were defined as follows: "initial" referred to the pre-reduction radiograph obtained at first presentation; "post-reduction" referred to the immediate radiograph obtained after the first closed reduction; and "48-hour" referred to the reassessment radiograph obtained approximately 48 hours after the first reduction. Post-reduction radiographs were assessed for residual angulation, metacarpal shortening, and rotational deformity at the neck of the fifth metacarpal. All patients were re-evaluated within 48 hours after the initial reduction. Radiographic and clinical findings at this time were assessed according to predefined objective criteria. Early loss of acceptable alignment at the 48-hour follow-up was defined by any of the following: dorsal angulation greater than 30° on lateral radiographs, metacarpal shortening exceeding 3 mm at the fracture site, or clinically observed rotational deformity identified by digit misalignment during fist formation.[6,10] Patients demonstrating early loss of reduction based on these criteria underwent a second closed reduction (re-reduction) within 48 hours of the initial procedure. Subsequently, all patients were followed up at the orthopedic outpatient clinic at 1, 4, and 6 weeks and at 6 months. Clinical follow-up assessed pain, swelling, range of motion (ROM), and cast tolerance, whereas radiographic follow-up monitored angulation and metacarpal length. Surgical intervention was considered if follow-up findings exceeded predefined anatomical thresholds. These included dorsal angulation over 30° on lateral radiographs, shortening greater than 3 mm, persistent rotational deformity, significant range-of-

motion limitation, or ongoing pain resulting in functional impairment.[4,6] Decisions to proceed with surgery were based on standardized criteria and were not influenced by individual physician preference. Surgical treatment options included intramedullary pin fixation or internal fixation with miniplates and screws.

Radiological and Clinical Assessment

Standard posteroanterior and lateral hand radiographs were obtained at five time points: within the first 48 hours after reduction and at follow-up visits scheduled for week 1, week 4, week 6, and month 6. On lateral radiographs, the degree of dorsal angular deformity and metacarpal shortening were measured using digital radiographic analysis software. Dorsal angulation was defined as the angle between the longitudinal axis of the fifth metacarpal shaft and the axis of the distal fracture fragment on true lateral radiographs.[1] Metacarpal shortening was measured on posteroanterior radiographs as the linear distance between the distal articular surface of the fractured fifth metacarpal and that of the adjacent fourth metacarpal, expressed in millimeters.[4] All radiological measurements were performed independently by two orthopedic surgeons who were blinded to group allocation and unaware of the study protocol. In cases of discrepancy between the two observers, the relevant images were re-evaluated by a third orthopedic specialist, whose assessment was accepted as final. Radiographs obtained after surgical fixation were not included in the longitudinal radiographic analyses of angulation and metacarpal shortening. Surgical intervention was treated as a censoring event for longitudinal radiographic outcomes; only preoperative follow-up radiographs were analyzed. Accordingly, longitudinal radiographic analyses were conducted using a per-protocol rather than an intention-to-treat approach, as postoperative imaging reflects a different treatment pathway and is not biologically comparable to non-operative follow-up.

ROM was assessed at the 6-week and 6-month follow-up visits. Measurements were based on patients' active motion and included flexion and extension angles of the fifth MCP and proximal interphalangeal (PIP) joints. All ROM measurements were performed using a standard plastic goniometer, with patients seated and hands positioned neutrally on a flat surface. Each joint angle was measured three times, and the mean value was used for analysis.

Functional outcomes were evaluated using the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) score, which was recorded at both the 6-week and 6-month follow-up visits.[13] This allowed comparison between early post-reduction function and mid- to long-term outcomes. In addition, grip strength was assessed as part of the functional evaluation at the 6-month follow-up. Measurements were obtained with patients seated, shoulders in neutral rotation, elbows at 90° flexion, forearms in neutral rotation, and wrists positioned between 0-30° of extension and 0-15° of ulnar deviation. A calibrated digital hand dynamometer (Baseline® Digital Dynamometer, Fabrication Enterprises Inc., White Plains, NY, USA) was used. Only the injured hand was evaluated; three consecutive trials were performed, and the highest value was used for analysis.

Complications that occurred during the follow-up period were assessed retrospectively through medical records and outpatient documentation. Stiffness was defined as a total active flexion arc <180° or a persistent extension deficit >20° at the MCP and/or PIP joints at the 6-month follow-up.[2,12] Malunion was defined as persistent deformity at 6 months-specifically, ≥30° of dorsal angulation or ≥3 mm of metacarpal shortening-when compared to the 6-week radiographic findings.[2] Nonunion was defined as the absence of radiographic continuity at the fracture site and persistent tenderness on palpation at 12 weeks post-injury.[2]

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY) and R software (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). Before data collection, an a priori power analysis was performed using G*Power software based on the mean and standard deviation values reported in comparable studies. This analysis demonstrated that a total sample size of 200 participants would provide sufficient statistical power to detect clinically relevant differences between study groups.

Because the distribution of continuous variables was predominantly nonparametric, between-group comparisons were conducted using the Mann-Whitney U test. At the same time, within-group paired evaluations were performed using the Wilcoxon signed-rank test. For repeated measurements involving more than two time points, the Friedman test was applied, followed by Bonferroni-corrected post-hoc pairwise comparisons. Categorical variables were assessed using chi-square or Fisher's exact tests, as appropriate. Interobserver reliability of radiological measurements was evaluated using intraclass correlation coefficients (ICCs).[14]

Following completion of the study, post hoc effect size calculations were performed for variables that showed statistically significant between-group differences. Effect sizes (r) derived from Mann-Whitney U test results averaged 0.245, corresponding to a Cohen's d value of approximately 0.52. Based on this effect size, the study's statistical power exceeded 90%, supporting the robustness of the observed differences.

Multivariable modeling was used to adjust for proxies for baseline fracture severity, alongside re-reduction status, to account for potential confounding by indication. For regression modeling, all candidate predictors were initially screened by univariable logistic regression. In accordance with established purposeful selection strategies, variables with univariable p-values <0.25 were considered for multivariable modeling, depending on the selection methods. Because the number of surgical events led to an events-per-variable below the recommended threshold of 10, conventional logistic regression was considered suboptimal because of the risk of overfitting. Therefore, a firth-penalized logistic regression model was applied using the logistf package in R to reduce small-sample bias and obtain reliable coefficient estimates. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were reported, and a p-value <0.05 was considered statistically significant.

RESULTS

Demographic and general clinical characteristics of the study groups are summarized in Table 1. The groups were statistically comparable in terms of age, sex, hand dominance, mechanism of injury, final treatment decisions, and complication rates. However, both the overall follow-up duration and time to fracture union were significantly longer in the RRG (p=0.018 and p<0.001, respectively).

Functional and clinical outcome measures are presented in Table 2. At the 6-month follow-up, there was no significant difference in grip strength between the groups. Regarding QuickDASH scores, patients in

the RRG had significantly higher values at 6 weeks (p=0.002), indicating worse function; however, the magnitude of this early difference was slightly below the distribution-based estimate of the minimal clinically important difference (Table 3) and should therefore be interpreted as having limited clinical relevance. This difference was not statistically significant at 6 months (p=0.075). In terms of joint ROM, both flexion and extension angles were significantly more restricted in the RRG at both 6 weeks and 6 months (p<0.001, p=0.023, p=0.045, and p<0.001, respectively).

Radiological assessments using conventional between-group comparisons demonstrated that initial post-traumatic and immediate post-reduction angulation values were comparable between groups (Table 4). However, during follow-up, angulation values were significantly higher in the RRG at the 4- and 6-week time points (p=0.007 and p<0.001, respectively). Similarly, metacarpal shortening measurements at weeks 1, 4, and 6 were significantly greater in the RRG (p=0.001, p<0.001, and p=0.009, respectively). At the 6-month follow-up, no significant differences were observed between groups in angulation or shortening.

Table 1. Baseline demographic and clinical characteristics of the groups

Parameters	SRG (n=100)	RRG (n=100)	p-value
Age (years)	29.02±8.23	29.71±8.31	0.541*
Follow-up duration (weeks)	10.48±3.14	11.45±2.76	0.018*
Union time (weeks)	7.55±2.13	9.19±1.91	<0.001*
Gender			0.721**
- Male, n (%)	79 (79%)	82 (82%)	
- Female, n (%)	21 (21%)	18 (18%)	
Dominant hand, n (%)	76 (76%)	71 (71%)	0.423**
Final treatment			0.491**
- Surgery, n (%)	19 (19%)	24 (24%)	
- Conservative, n (%)	81 (81%)	76 (76%)	
Mechanism of injury:			0.604***
- Fall, n (%)	23 (23%)	19 (19%)	
- Traffic accident, n (%)	9 (9%)	6 (6%)	
- Sportive activity, n (%)	10 (10%)	8 (8%)	
- Punch, n (%)	58 (58%)	67 (67%)	
Complications:			0.601***
- Stiffness, n (%)	7 (7%)	9 (9%)	
- Malunion, n (%)	7 (7%)	12 (12%)	
- Nonunion, n (%)	1 (1%)	1 (1%)	

*Mann-Whitney U test, **Chi-square test, ***Monte Carlo chi-square test.
SRG: Single reduction group, RRG: Re-reduction group.

Table 2. Functional and clinical outcomes

Parameters	SRG (n=100)	RRG (n=100)	p-value
Grip strength (kg)	44.14±8.60	43.49±7.85	0.324*
QuickDASH, 6th week	31.52±6.99	34.84±7.11	0.002*
QuickDASH, 6th month	6.83±4.65	7.73±4.28	0.075*
p-value intergroup	0.001**	0.001**	
Flexion (°), 6th week	69.05±10.07	62.60±10.16	<0.001*
Flexion (°), 6th month	86.80±6.22	85.05±5.75	0.023*
p-value intergroup	0.001**	0.001**	
Extension (°), 6th week	6.35±4.54	5.10±4.02	0.045*
Extension (°), 6th month	9.17±4.15	4.95±4.47	<0.001*
p-value intergroup	0.001**	0.001**	

*Mann-Whitney U test, **Wilcoxon test.
SRG: Single reduction group, RRG: Re-reduction group, QuickDASH: Quick Disabilities of the Arm, Shoulder and Hand.

To formally evaluate whether radiological trajectories differed between groups over time, a linear mixed-effects model (LMM) was applied. The model included group, follow-up time, and their interaction as fixed effects, with a random intercept for each patient to account for within-subject correlation across repeated measurements.

The LMM revealed a significant group×time interaction for angulation [F (5, 155.3)=3.31, p=0.007], indicating that the temporal evolution of angulation differed between the two groups. Although early post-reduction angulation values were similar, the RRG demonstrated a steeper increase during early follow-up, with the greatest divergence observed around the 4-week assessment (Figure 1a). In addition, significant main effects of group (p=0.037) and time (p<0.001) were observed.

Likewise, the LMM demonstrated a significant group×time interaction for metacarpal shortening [F(5, 21.5)=4.40, p=0.007)], indicating that shortening trajectories differed between groups. While immediate post-reduction values were comparable, the RRG exhibited greater shortening during the early follow-up period, particularly at the 1-week and 4-week time points (Figure 1b). Significant main effects of group (p=0.044) and time (p<0.001) were also identified.

Variables associated with surgical referral in the univariable analysis are presented in Table 5. Initial shortening and all angulation parameters, measured immediately after reduction and during follow-up (weeks 1, 4, and 6), showed statistically significant associations with surgical intervention in univariable models (all p<0.05). In accordance with the purposeful selection strategy, variables with a univariable p-value <0.25 were included in the multivariable model. In addition, shortening at 1 week (p=0.261) was retained because of its borderline statistical significance and clinical relevance. In the multivariable Firth-penalized logistic regression model, initial shortening was the only independent predictor of surgical intervention (OR) =1.253; 95% (CI): 1.014-1.446; p=0.036. None of the angulation parameters-including initial, post-reduction, and measurements at weeks 1, 4, or 6-remained significant after adjustment (all p>0.05). Similarly, postoperative shortening parameters (post-reduction and weeks 1, 4, and 6) did not independently predict surgical referral in the adjusted model (all p>0.05). Dominant-hand involvement approached statistical significance (OR =0.490; p=0.076), but did not reach the threshold for independent association. Overall, initial shortening emerged as the sole radiological factor independently associated with the decision to proceed with surgery.

Receiver operating characteristic analysis demonstrated that initial shortening had a modest but statistically significant ability to discriminate patients who required surgical intervention (AUC =0.645, 95% CI: 0.558-0.732, p=0.004) (Figure 2). A cutoff value of approximately 2.5 mm provided a more balanced sensitivity (65.1%) and specificity (55.4%), suggesting potential clinical utility for risk stratification rather than definitive decision-making.

Table 3. Distribution-based MCID context for QuickDASH between-group differences

Parameters	SRG (n=100)	RRG (n=100)	Between-group difference	MCID_est (0.5× SD_pooled)	Interpretation vs. MCID
6th week	31.52±6.99	34.84±7.11	+3.32	3.53	Borderline
6th month	6.83±4.65	7.73±4.28	+0.90	2.23	Below

MCID was evaluated only for the QuickDASH using a distribution-based approach (MCID_est =0.5× SD_pooled). This provides an estimate of clinical meaningfulness and should be interpreted as a supportive context rather than a definitive threshold.
SRG: Single reduction group, RRG: Re-reduction group, MCID: Minimal clinically important difference, QuickDASH: Quick Disabilities of the Arm, Shoulder and Hand, SD: Standard deviation.

Table 4. Evolution of angulation and shortening across follow-up in both groups

Parameters	SRG (n=100)	RRG (n=100)	p-value
1. Angulation (°), initial	44.83±9.00	45.03±7.86	0.773*
2. Angulation (°), post-reduction	9.42±3.62	9.39±3.22	0.813*
3. Angulation (°), 1st week	11.22±4.38	12.32±4.76	0.212*
4. Angulation (°), 4th week	13.12±5.34	15.55±5.72	0.007*
5. Angulation (°), 6th week	4.93±3.69	6.83±3.46	<0.001*
6. Angulation (°), 6th month	5.04±3.68	5.60±2.87	0.125*
Intragroup comparison in different time intervals.	**p=0.583** (5-6) p<0.05**, other comparisons**	**p<0.05** for all comparisons**	
1. Shortening (mm), initial	2.64±1.85	2.52±1.53	0.702*
2. Shortening (mm), post-reduction	1.06±0.79	1.06±0.72	0.969*
3. Shortening (mm), 1st week	1.58±1.02	2.08±0.97	<0.001*
4. Shortening (mm), 4th week	1.22±1.01	1.84±1.08	<0.001*
5. Shortening (mm), 6th week	1.35±1.12	1.71±1.05	0.009*
6. Shortening (mm), 6th month	1.30±1.19	1.54±1.11	0.101*
Intragroup comparison in different time intervals.	p=0.314** (4-5) p=0.683** (5-6) p<0.05**, other comparisons	p=0.130** (2-3) p=0.276** (4-5) p=0.219** (5-6) p<0.05**, other comparisons	

*Mann-Whitney U test, **Friedman test with post-hoc Bonferroni-corrected comparisons.
SRG: Single reduction group, RRG: Re-reduction group.

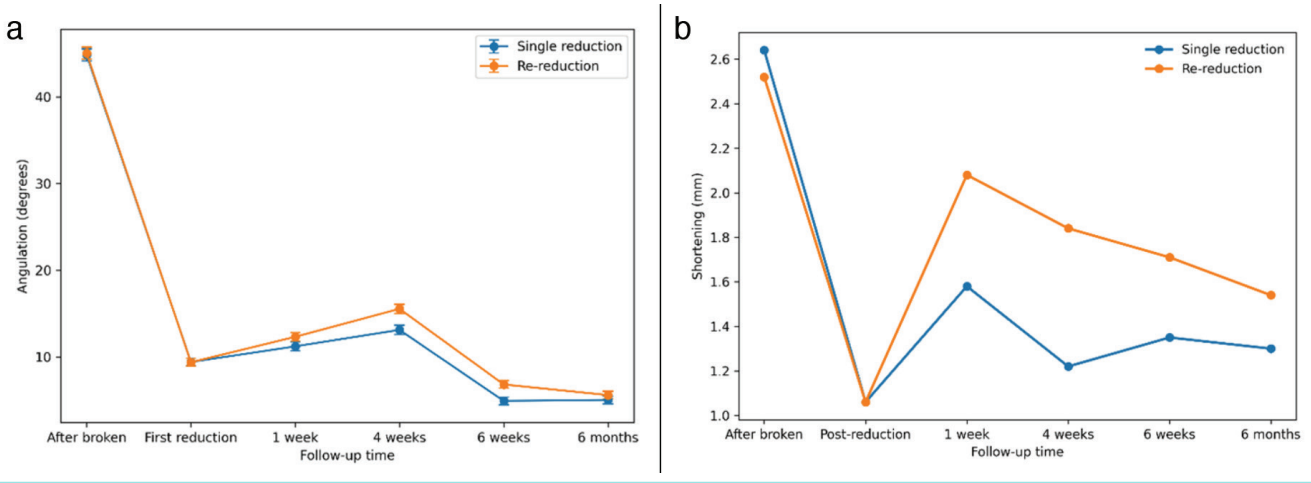

Figure 1. Estimated marginal means of radiological parameters over time according to treatment group, derived from the linear mixed-effects model. (a) Temporal changes in angulation. Although early post-reduction angulation values were comparable between groups, the re-reduction group demonstrated a greater increase during early follow-up, with the most pronounced difference observed at 4 weeks. (b) Temporal changes in metacarpal shortening. While early post-reduction shortening values were similar between groups, the re-reduction group exhibited greater shortening during the early follow-up period, particularly at the 1-week and 4-week assessments. Error bars represent standard errors.

Table 5. Univariate and firth penalized regression analysis of variables associated with surgical intervention

Predictor	OR [Exp(B)]	p-value	95% CI (lower)	95% CI (upper)
Univariable logistic regression for surgical intervention				
Group (re-reduction vs. no re-reduction)	0.743	0.390	0.377	1.464
Age (years)	0.983	0.432	0.942	1.026
Sex (male vs. female)	0.760	0.548	0.309	1.864
Dominant hand (yes vs. no)	0.596	0.162	0.288	1.232
Mechanism (1 vs. ref)	0.903	0.813	0.387	2.104
Mechanism (2 vs. ref)	0.509	0.392	0.109	2.389
Mechanism (3 vs. ref)	0.662	0.536	0.179	2.447
Initial shortening	1.380	0.003	1.117	1.704
Post-reduction shortening	1.408	0.144	0.890	2.227
Shortening at 1 week	0.825	0.261	0.591	1.153
Shortening at 4 weeks	0.794	0.166	0.573	1.100
Shortening at 6 weeks	0.778	0.126	0.564	1.073
Initial angulation	0.967	0.108	0.928	1.007
Post-reduction angulation	0.872	0.008	0.788	0.965
Angulation at 1 week	0.882	0.002	0.813	0.955
Angulation at 4 weeks	0.920	0.012	0.862	0.982
Angulation at 6 weeks	0.862	0.004	0.779	0.954
Multivariable firth penalized logistic regression				
Dominant hand (yes vs. no)	0.490	0.076	0.224	1.080
Initial shortening	1.253	0.036	1.014	1.446
Post-reduction shortening	1.321	0.311	0.772	2.296
Shortening at 1 week	0.821	0.331	0.543	1.198
Shortening at 4 weeks	0.973	0.882	0.709	1.400
Shortening at 6 weeks	0.938	0.717	0.658	1.324
Initial angulation	0.979	0.345	0.938	1.022
Post-reduction angulation	0.956	0.482	0.841	1.086
Angulation at 1 week	0.935	0.187	0.843	1.033
Angulation at 4 weeks	1.007	0.865	0.925	1.093
Angulation at 6 weeks	0.902	0.063	0.804	1.006

OR: Odds ratio, CI: Confidence intervals.

Interobserver reliability across all radiological measurements was high, with ICCs ranging from 0.772 to 0.984, indicating methodological consistency and reproducibility of the assessments.

DISCUSSION

In this study, the effectiveness of repeated closed reduction procedures was evaluated in patients who developed secondary displacement following initial closed reduction for isolated fifth metacarpal neck fractures. The analysis focused on both radiological and functional outcomes. Patients in the RRG had significantly longer follow-up and time to fracture union. Radiographic assessments revealed that angulation values at weeks 4 and 6, as well as shortening at weeks 1, 4, and 6, were significantly higher in RRG. Additionally, the rate of surgical intervention was higher in this group. Initial shortening emerged as the only independent predictor of surgical intervention in the multivariable firth penalized regression analysis. QuickDASH scores at week 6 were significantly worse in the RRG. Furthermore, flexion and extension angles were more restricted in this group at both early and late follow-up assessments, suggesting a lasting impact on joint mobility.

Fractures of the fifth metacarpal neck are frequently encountered, particularly in young males, and are often managed by closed reduction.[6,7,15-17] However, current literature indicates that the stability of closed reduction in this fracture type is limited, and significant deterioration in angulation and shortening can occur during the early post-reduction period.[18-20] For this reason, many studies have emphasized that specific radiographic thresholds, such as angulation exceeding 30 to 40 degrees or shortening exceeding 2 millimeters, serve as useful indicators for surgical decision-making.[18-23] Despite this, these thresholds are generally established based solely on initial post-traumatic radiographs, and there is insufficient data describing how fracture alignment evolves during the follow-up period. In particular, studies focusing on patients who develop secondary displacement and subsequently undergo repeat closed reductions remain scarce and lack systematic, measurement-based analyses.[4,6,10] The clinical impact and effectiveness of a second reduction attempt in this group, both radiologically and functionally, remain poorly defined. Moreover, the influence of changes in angulation and shortening, which can begin in the first weeks after reduction, has not yet been quantitatively

described in relation to treatment decisions. A distinctive aspect of the present study is its approach to angulation and shortening, treating them not as static measurements but as dynamic parameters tracked over time. Although increases in angulation at the fourth and sixth weeks were associated with repeat reduction in univariable analyses, these parameters did not remain independent predictors of surgical intervention in the multivariable model. This represents a valuable contribution to the literature, in which most studies have focused only on initial radiographs. Similarly, the significant association between the degree of initial shortening and later surgical referral supports the interpretation of early radiographs as decision-making tools, rather than passive diagnostic images.

The impact of post-reduction changes in angulation and shortening on the decision for surgical treatment has been evaluated only to a limited extent in previous studies.[18-24] In most cases, the success of reduction is determined solely by immediate post-procedure imaging, while radiological changes observed during follow-up are often overlooked in clinical decision-making. However, the findings of the present study demonstrate that increases in angulation at weeks four and six are associated with surgical intervention in univariable analysis, although these parameters did not remain independent predictors in the multivariable model. This suggests that deformity should be considered a dynamic parameter that evolves over time, rather than a fixed structural outcome. Instead of relying on static threshold values, continuous monitoring of measurements, such as angulation and shortening, throughout the follow-up period may provide more accurate guidance for timely and appropriate interventions. Nevertheless, the effectiveness of repeated closed reductions for patients who experience loss of reduction remains controversial.[25-28] In this study, patients who underwent re-reduction showed longer union times and lower functional scores. These findings indicate that a second reduction attempt may not offer equal benefit for all patients. The observation that initial shortening was a predictor of surgical intervention further supports the notion that radiographic assessment at the time of initial presentation holds not only diagnostic but also prognostic value. Therefore, decisions regarding repeat reduction should be made by integrating follow-up findings and radiographic parameters, rather than through reflexive or routine approaches. Each intervention should be clinically justified and tailored to the patient's evolving condition.

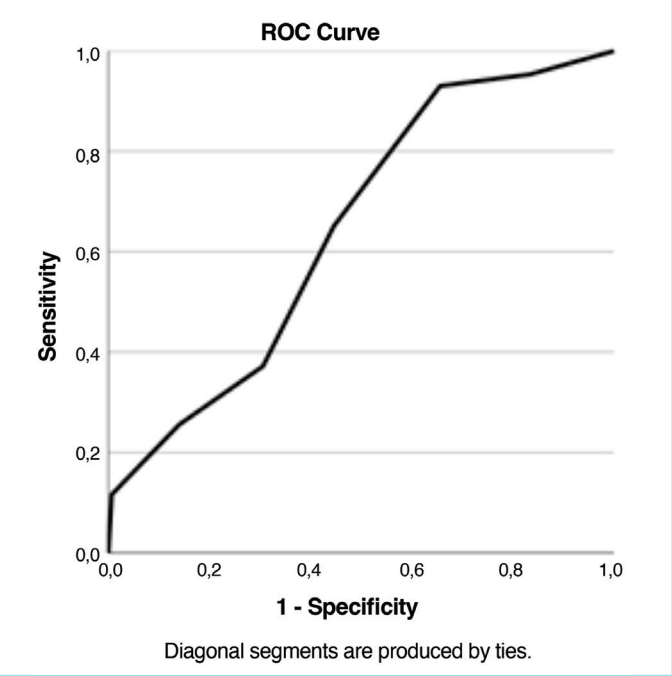

Figure 2. Receiver operating characteristic (ROC) curve of initial metacarpal shortening for predicting the need for surgical intervention.

It should also be acknowledged that patients undergoing re-reduction are likely to have fracture patterns with inherent mechanical instability. In this context, the decision to perform re-reduction may be interpreted not as an independent therapeutic intervention, but rather as a clinical marker of early instability or inadequate mechanical control. Therefore, the longer union times and inferior early functional outcomes observed in the RRG may be related primarily to the underlying fracture characteristics rather than to a direct adverse effect of the re-reduction procedure itself. Accordingly, the findings of the present study should be interpreted as associational rather than causal.

Study Limitations

One of the most significant limitations of this study is its retrospective design, which prevented standardization of treatment decisions. The choice between reduction and surgical intervention may have varied depending on individual physician preferences or institutional practices. Additionally, the technical details of repeat reductions and the quality of the reductions achieved could not be assessed uniformly. The reliability of some functional outcome measures may also be affected by their reliance on patient self-reporting and by the limited mid-term follow-up. Moreover, because the decision to perform re-reduction was not randomly assigned, patients in the RRG may have presented with fracture patterns exhibiting greater inherent mechanical instability. This selection process may have introduced confounding by indication, potentially influencing early functional outcomes and time to union, independent of the re-reduction procedure itself. In addition, the longer follow-up duration observed in the RRG does not necessarily reflect a true biological delay in fracture healing. Patients with fractures that are considered to have a higher risk of instability are more likely to undergo closer clinical surveillance and more frequent radiographic evaluations. This increased monitoring may have contributed to fracture union being documented later, thereby introducing ascertainment bias. Therefore, differences in union time between groups should not be interpreted as solely reflecting a true biological delay, rather but should be considered in the context of differential follow-up intensity. Despite these limitations, the study offers meaningful contributions by systematically evaluating the effectiveness of repeat closed reductions, analyzing time-dependent changes in radiological parameters such as angulation and shortening, and identifying their impact on clinical decision-making through multivariate analysis. The findings suggest a need to shift from rigid threshold-based decision models toward more dynamic approaches that incorporate follow-up observations. Future research using prospective designs and standardized treatment protocols may better clarify the optimal timing and selective application of repeat reduction procedures in relation to both radiological and functional outcomes. In addition, long-term follow-up data will be essential to fully understand the clinical implications of residual deformity and to establish more robust treatment algorithms for this fracture type.

CONCLUSION

This study demonstrated that radiological changes observed during follow-up after reduction of fifth metacarpal neck fractures may serve as important indicators for the treatment process. Repeated closed reductions performed in patients with secondary displacement did not yield consistent benefits across all cases and were associated with limited improvements in both functional and radiological outcomes. Continuous and dynamic evaluation of parameters such as angulation and shortening throughout the follow-up period may provide valuable guidance, particularly in determining the appropriate timing of clinical interventions. Furthermore, initial shortening emerged as an independent predictor of surgical referral, highlighting the prognostic value of early radiographic assessment.

MAIN POINTS

- Re-reduction after early loss of alignment in fifth metacarpal neck fractures does not consistently improve radiological or functional outcomes.
- Radiological parameters such as angulation and shortening should be interpreted as dynamic variables evolving over time rather than static measurements.
- Early deterioration in alignment, particularly within the first weeks, reflects underlying fracture instability rather than the effect of re-reduction itself.
- Initial metacarpal shortening emerged as the only independent predictor of subsequent surgical intervention.
- Continuous follow-up assessment provides more clinically relevant guidance than a single time-point radiographic evaluation.

ETHICS

Ethics Committee Approval: Approval was obtained Eskişehir City Hospital Institutional Review Board Ethics Committee (approval no: ESH/BAEK 2025/114, date: 20.02.2025).

Informed Consent: This retrospective, comparative cohort study.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., H.Ç.B., Concept: B.K., H.Ç.B., Design: B.K., Data Collection and/or Processing: H.Ç.B., Analysis and/or Interpretation: H.Ç.B., Literature Search: B.K., H.Ç.B., Writing: B.K.

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RESEARCH ARTICLE

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Efficacy of Tranexamic Acid in Total Knee Arthroplasty: Evaluation of Four Blood Management Protocols

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Abstract

BACKGROUND/AIMS: This paper evaluates how tourniquet use and tranexamic acid (TXA) combinations affect blood management in primary total knee arthroplasty (TKA).

MATERIALS AND METHODS: Following ethical approval, a retrospective review was conducted of 96 patients who underwent primary TKA between 2014 and 2017. Patients were divided into four groups: Group 1, no tourniquet with intravenous (IV) TXA 15 mg/kg plus intra-articular (IA) TXA 2 g; Group 2, tourniquet only (control); Group 3, tourniquet with IV TXA; and Group 4, no tourniquet with IA TXA. Demographic data, changes in perioperative hemoglobin (Hb) and hematocrit (Hct), intraoperative blood loss, postoperative drainage volume, and transfusion rates were analyzed using ANOVA and Kruskal-Wallis tests.

RESULTS: The reduction in Hb and Hct was significantly smaller in patients receiving TXA ($p<0.05$). Group 1 demonstrated the least perioperative Hb decrease (1.3±0.8 g/dL) and the lowest transfusion rate (4%), whereas the control group showed the greatest Hb decline (3.5±1.0 g/dL) and highest transfusion requirement (34%) ($p<0.05$). The mean drainage volume was 180±50 mL in Group 1, lower than in other groups ($p<0.05$). No thromboembolic or wound-related complications were observed in any TXA-treated group.

CONCLUSION: Dual-route TXA administered without a tourniquet reduces blood loss and the need for transfusions in TKA without increasing the risk of complications. Tourniquet use alone did not confer any additional hemostatic benefit and may be safely omitted when an optimized TXA protocol is implemented. These findings highlight that pharmacologic antifibrinolytic therapy offers a more effective and safer blood management strategy than mechanical occlusion methods in modern knee arthroplasty practice.

Keywords: Tranexamic acid, tourniquet, total knee arthroplasty, blood loss, transfusion, hemostasis

INTRODUCTION

Total knee arthroplasty (TKA) effectively relieves pain and improves function in patients with advanced knee osteoarthritis.[1] Despite its proven success, TKA is often associated with considerable perioperative blood loss, which may lead to increased morbidity, delayed rehabilitation, and the need for allogeneic blood transfusion.[2] Transfusion, in turn, carries potential risks, including infection, immunologic reactions, and increased healthcare costs. Therefore, minimizing blood loss remains a key component of optimizing perioperative outcomes in TKA.[3-5]

A pneumatic tourniquet is traditionally used to provide a bloodless field and to aid cement fixation during TKA.[6] Prolonged tourniquet use can cause thigh pain, delayed quadriceps recovery, wound issues, and thromboembolic events.[7,8] Consequently, the routine use of tourniquets in knee arthroplasty has become increasingly controversial.

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Tranexamic acid (TXA), an antifibrinolytic that inhibits plasminogen activation, significantly reduces blood loss in orthopedic procedures without increasing thromboembolic risk.[9-12] TXA can be administered intravenously, topically, or in combination, though the optimal route and timing of administration remain subjects of debate.

Given the uncertainty about the efficacy of TXA and tourniquet use for blood conservation, this study compared approaches that combined or omitted these techniques in patients undergoing primary TKA. The effects on perioperative blood loss, changes in hemoglobin (Hb) and hematocrit (Hct), and transfusion requirements were evaluated to determine the most effective and safe strategy for blood management during TKA.

MATERIALS AND METHODS

This retrospective study adhered to the Declaration of Helsinki and was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2018/07-47, date: 15.03.2018). We reviewed the medical records of 96 patients who underwent primary TKA and met the inclusion criteria at the Orthopedics and Traumatology Department between 2014 and 2017.

To compare different perioperative blood management strategies, patients were divided into four equal groups (n=24 each) according to tourniquet use and the method of TXA administration. All procedures were performed by a single orthopedic surgeon using the same surgical technique.

Patient Selection

Patients aged 45-80 years with primary knee osteoarthritis were included. Exclusions: secondary gonarthrosis from rheumatologic disorders, bleeding or coagulation issues, previous knee surgery, periarticular implants, hypersensitivity to TXA, or use of anticoagulants or antiplatelet drugs.

Surgical Procedure

All operations were performed by an experienced orthopedic surgeon using a medial parapatellar approach. The Vanguard® Knee System and Vanguard ROCC® prostheses were used in all cases, and no patellar resurfacing was performed. Antibiotic prophylaxis consisted of 2 g of intravenous cefazolin administered preoperatively and continued postoperatively for 24 hours in four divided doses. Patients with a cefazolin allergy received 2 g of clindamycin, following the same regimen.

In the tourniquet groups, inflation pressure was set to 300 mmHg; in the non-tourniquet groups, the cuff remained uninflated for safety purposes only. Following skin preparation and sterile draping, a standard midline incision and medial parapatellar capsulotomy were performed. Appropriate tibial and femoral bone cuts and necessary soft-tissue balancing were completed. Components were implanted using bone cement. In the tourniquet groups, the tourniquet was released after cement polymerization. After fixation, the joint was thoroughly irrigated with saline. A suction drain was inserted before capsule closure, which was performed with the knee flexed. In groups receiving intra-articular (IA) TXA, 2 g of TXA, diluted in 50 mL saline, was injected into the joint cavity via the drain after capsule closure. The study were:

Group 1: No tourniquet; 15 mg/kg intravenous TXA +2 g IA TXA

Group 2: Tourniquet used; no TXA (control group)

Group 3: Tourniquet used; 15 mg/kg intravenous TXA

Group 4: No tourniquet; 2 g IA TXA

At the end of surgery, sterile dressings were applied. Drains were opened 2 hours postoperatively and removed after 24 hours; the total drainage volume was recorded.

Postoperative Management

Hb and Hct levels were measured preoperatively and at 6, 12, 24, and 48 hours postoperatively. The differences between preoperative and postoperative values were documented for each patient.

Allogeneic blood transfusion was administered when the Hb level fell below 8 g/dL. Patients with Hb between 8 and 10 g/dL were evaluated for transfusion based on cardiovascular comorbidities or clinical symptoms, such as tachycardia, dizziness, palpitations, or fatigue. Patients with Hb levels above 10 g/dL did not receive transfusions. All transfusion events were recorded.

For deep vein thrombosis prophylaxis, a single subcutaneous dose of low-molecular-weight heparin was given at the 12th postoperative hour and was continued daily for six weeks.

Statistical Analysis

Statistical analyses were carried out using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA). Continuous variables are described as mean ± standard deviation when normally distributed, or as median (minimum-maximum) in cases where the data are not normally distributed. Categorical data are presented as counts and percentages. Group means were compared using one-way ANOVA, while medians were compared using the Kruskal-Wallis test. Group 2 served as the control group throughout the analyses. Statistical significance was defined as $p<0.05$. A sensitivity (power) analysis was performed for a one-way ANOVA with four groups, an alpha level of 0.05, and 80% power. With a sample size of 96, the study was sufficiently powered to detect an effect size of approximately Cohen's f=0.34, corresponding to a moderate effect size. Therefore, the sample size was considered adequate for detecting moderate-to-large intergroup differences, although smaller effects may have remained undetected.

RESULTS

The study included 96 patients who received primary TKA. Their average age was 66.8±7.4 years. Most of the patients, 79%, were female. There were no significant differences among the four groups in age, gender, or body mass index ($p>0.05$). The mean body mass index was 28.8±1.6 kg/m², and was similar across all groups. The right knee was operated on in 50 patients (54%), and the left knee was operated on in 42 patients (46%) (Table 1).

The demographic characteristics were similar across the four groups. Most patients were female and overweight. No notable differences were observed in preoperative Hb or packed cell volume levels.

Table 1. Comparison of baseline demographic data and preoperative laboratory parameters among the four study groups

	Group 1	Group 2	Group 3	Group 4	p-value*
Age	68±8.3	69±8.2	69±6	76 ±9.1	0.138
Sex (female/male)	22/1	20/3	21/2	20/3	0.72
BMI	28.9±1.9	28.1±1.1	28.9±1.5	29.3±1.03	0.91
Side (right/left)	13/10	15/8	10/13	12/11	0.93
Preoperative Hb	12.6±1.5	13.1±1.8	13±1.5	12.6±1.5	0.284
Preoperative PCV	38.1±3.4	40±5	39.2±3.8	38±4.6	0.365

*p<0.05.
BMI: Body mass index, Hb: Hemoglobin, PCV: Packed cell volume.

Preoperative Laboratory Parameters

Preoperative Hb was similar across groups: 13.1±1.8 g/dL in Group 1, 13.4±1.6 in Group 2, 13.0±1.5 in Group 3, and 12.6±1.5 in Group 4 (p=0.42).Preoperative Hct values were 38.1±3.4%, 40.0±5.0%, 39.2±3.8%, and 38.0±4.6%, respectively (p>0.05).

Postoperative Hemoglobin and Hematocrit Changes

Postoperative Hb and Hct values decreased in all groups compared with baseline. However, the reduction was significantly smaller in the TXA-administered groups.

At 6 hours postoperatively, mean Hb levels were 12.0±1.4 g/dL in Group 1, 11.3±1.6 g/dL in Group 2, 11.6±1.3 g/dL in Group 3, and 11.4±1.5 g/dL in Group 4 (p=0.021) (Table 2).

At 24 hours, Hb levels decreased to 11.2±1.3, 10.4±1.6, 10.7±1.2, and 10.6±1.4 g/dL, with significant intergroup difference (Kruskal-Wallis, p<0.001). A similar pattern was observed for Hct: Group 1 consistently showed the smallest postoperative decline, while Group 2 (tourniquet only) showed the greatest reduction.

Drain Output and Blood Loss

The total drainage volume in the first 24 hours differed significantly among groups (p<0.001). Mean values were: Group 1: 180±50 mL; Group 2: 250±40 mL; Group 3: 260±35 mL; Group 4: 210±30 mL (Table 2).

The lowest drainage volume was recorded in Group 1, which involved a combination of intravenous and IA TXA without the use of a tourniquet.

Blood Transfusion Requirement

Overall, 14 patients (14.5%) required allogeneic blood transfusion. The highest transfusion rate was observed in the control group (33.3%), followed by Group 4 (12.5%), Group 3 (8.3%), and Group 1 (4.2%) (p=0.018).

Complications

No thromboembolic events, wound healing problems, or allergic reactions related to TXA were observed during hospitalization or the early postoperative follow-up.

DISCUSSION

This study examined how different combinations of tourniquet use and TXA affected perioperative blood loss in TKA patients. According to the results, the group that received both intravenous and IA TXA without a tourniquet showed the smallest decrease in Hb, the least drainage, and the lowest transfusion rate. On the other hand, patients operated on with a tourniquet but without TXA experienced the highest blood loss and the greatest need for transfusion. These findings show that TXA is more effective than a tourniquet in reducing perioperative bleeding, and that using two routes offers additional benefit. Jansen et al.[13] emphasized that TXA was an effective part of blood-saving strategies during arthroplasty. Konig et al.[14] showed that topical TXA administration reduced both blood loss and the need for transfusion in total hip and knee arthroplasties. López-Hualda et al.[15] also demonstrated that local TXA use was safe and effective in minimizing bleeding. Likewise, in another study, the combination of intravenous and IA TXA was superior to a single route of administration.[16] Our study confirms TXA's key role in blood conservation during TKA, regardless of the route of administration. Previous randomized studies have also

Table 2. Comparison of perioperative outcomes among groups

Parameter	Group 1 (no tourniquet, IV + IA TXA)	Group 2 (tourniquet only, control)	Group 3 (tourniquet + IV TXA)	Group 4 (no tourniquet, IA TXA)	1 vs. 2 vs. 3 vs. 4	1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Maximum Hb change (g/dL)	1.3±0.8	3.5±1.0	3.0±0.9	2.9±1.1	<0.05	<0.05	<0.05	<0.05	0.324	0.143	0.970
Transfusion rate (%)	4	34	13	18	<0.05	<0.05	0.301	0.160	0.870	0.184	0.685
Intraoperative blood loss (mL)	220±30	280±90	210±35	300±25	<0.05	<0.05	0.540	0.020	<0.05	<0.05	<0.05
Drainage volume (mL)	180±50	250±40	260±35	210±30	<0.05	<0.05	<0.05	0.200	0.540	0.310	<0.05

Pairwise p-values indicate significant differences where p<0.05; no boldface highlighting is used.
TXA: Tranexamic acid, IV: Intravenous, IA: Intra-articular, Hb: Hemoglobin.

demonstrated that TXA reduces perioperative blood loss and may be superior to tourniquet-only strategies. However, most studies have evaluated only one or two blood management protocols. In contrast, the present study simultaneously compared four perioperative blood management strategies within the same study population, providing a broader perspective on their relative effectiveness.

Tourniquets are used to reduce bleeding and improve visualization during surgery; however, these benefits were not observed in our series, and recent studies have highlighted potential adverse effects. Extensive literature reports that tourniquet use may cause postoperative thigh pain, delayed recovery, muscle ischemia, and an increased risk of thromboembolic complications.[17,18] Li et al.[19] and Huang et al.[20] further showed that tourniquet use did not reduce the total amount of bleeding; led to an increase in postoperative bleeding in some cases due to reactive hyperemia and fibrinolytic activation after the cuff was released. The study shows that tourniquet use alone offers no benefit and may increase blood loss in the absence of TXA.

The superior results in the group receiving both intravenous and IA TXA can be explained by the complementary mechanisms of the two administration routes. Intravenous TXA provides systemic antifibrinolytic activity, while IA application achieves high local concentrations and acts directly on the surgical field to stabilize clot formation. This combination likely contributed to the significantly lower postoperative Hb drop and drainage output observed in this group. Additionally, avoiding the tourniquet may have reduced tissue hypoxia and subsequent reperfusion-related fibrinolysis, further minimizing bleeding.

Both single-route TXA administrations (intravenous and IA) effectively reduced blood loss compared with the control, but were less effective than the combined approach. Similarly, Adravanti et al.[16] showed that combined use was more successful than either route alone. This supports the idea that TXA use -regardless of the administration route- is a reliable and safe means of reducing bleeding and may decrease the need for tourniquet use during TKA. Importantly, no thromboembolic or wound complications were observed in any of the TXA groups, supporting the safety of its use in this setting.

Study Limitations

The primary limitations of this study are its retrospective design and the relatively small sample size. The follow-up was limited to the early postoperative period, and routine doppler ultrasonography screening for deep vein thrombosis was not performed. Patients were clinically monitored, and doppler evaluation was performed only when clinically indicated; therefore, asymptomatic thromboembolic events may not have been detected. No cost analysis was performed for the different blood management protocols.

CONCLUSION

Our results show that administering both intravenous and IA TXA without a tourniquet is the most effective and safest approach to reduce blood loss during TKA. While tourniquets reduce intraoperative bleeding, they do not improve overall blood conservation. Avoiding tourniquet use may also reduce associated complications, thereby making TXA a safer and more effective strategy for blood management in TKA.

MAIN POINTS

- Combined intravenous and intra-articular administration of tranexamic acid (TXA) resulted in the smallest decrease in hemoglobin, drainage volume, and transfusion rate in primary total knee arthroplasty.
- Tourniquet use alone did not provide superior overall blood conservation compared with TXA-based protocols.
- The Simultaneous comparison of four perioperative blood-management protocols within a single study design is a major strength.
- Although no thromboembolic or wound complications were observed, the retrospective design and limited follow-up require cautious interpretation of safety outcomes.

ETHICS

Ethics Committee Approval: Approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval number: 2018/07-47, date: 15.03.2018).

Informed Consent: Not required due to retrospective study design.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.I., M.E., Concept: Y.I., M.E., Design: Y.I., M.E., Data Collection and/or Processing: Y.I., M.Ç., Analysis and/or Interpretation: Y.I., Y.S.K., M.Ç., Literature Search: Y.I., Y.S.K., M.Ç., Writing: Y.I., M.Ç.

DISCLOSURES

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

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Declaration on the Use of Artificial Intelligence (AI): The authors declare that artificial intelligence (AI) tools were not used, or were used solely for language editing, and had no role in data analysis, interpretation, or the formulation of conclusions. All scientific content, data interpretation, and conclusions are the sole responsibility of the authors. The authors further confirm that AI tools were not used to generate, fabricate, or “hallucinate” references, and that all references have been carefully verified for accuracy.

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RESEARCH ARTICLE

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Effects of Prenatal Gabapentin Exposure on Fetal Skeletal Development in Rats: Assessment of Bone Development and Ossification

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Abstract

BACKGROUND/AIMS: Gabapentin (GBP) is often prescribed to pregnant women to manage neuropathic pain and epilepsy. However, the impact of antiepileptic drugs on prenatal skeletal development remains controversial. The aim of this study was to investigate, using a rat model, the possible toxic effects of GBP exposure during pregnancy on fetal bone development.

MATERIALS AND METHODS: Pregnant Wistar albino rats were randomly assigned to five groups (n=4 each): a control group and four GBP-treated groups receiving 10, 30, 60, or 120 mg/kg/day throughout gestation. Fetuses were collected at term and evaluated using double staining. Ossification lengths and areas of forelimb and hindlimb long bones were quantitatively measured. Immunohistochemical (IHC) analyses were performed on femoral sections to assess the distribution and staining intensity of alkaline phosphatase (AP) and tartrate-resistant acid phosphatase (TRAP), key markers of osteoblastic and osteoclastic activity, respectively.

RESULTS: Fetuses exposed to GBP demonstrated reduced body weight and smaller morphometric measurements compared with controls. Quantitative analysis revealed a significant decrease in ossification of both forelimb and hindlimb bones across all treatment groups, with a clear dose-dependent pattern. IHC findings showed diminished AP and TRAP immunoreactivity in GBP-exposed pups, indicating impaired bone formation and resorption .

CONCLUSION: Continuous GBP exposure during pregnancy adversely affects fetal skeletal development in rats. Prenatal GBP administration led to lower birth weight, delayed and reduced ossification, and suppressed bone metabolic activity, particularly at higher doses. We believe these findings highlight the potential developmental risks associated with GBP use during pregnancy and underscore the need for caution.

Keywords: Toxicology, ossification, anatomy, immunochemistry

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INTRODUCTION

Epilepsy, a neurological disorder that is prevalent worldwide, affects millions of people and often requires continuous pharmacological treatment during pregnancy.[1] Gabapentin (GBP) is an anticonvulsant primarily indicated for partial-onset seizures and requently administered to pregnant women with epilepsy. In addition to its antiepileptic properties, GBP is used to treat chronic pain conditions (such as inflammatory pain) and psychiatric disorders.[2,3]

GBP is classified as a gamma-aminobutyric acid (GABA) analogue.[4] Due to its structural similarity to GABA, it readily crosses the placental barrier, thereby affecting the developing fetus. GBP is notable for its favourable safety profile, characterized by minimal drug-drug interactions and high tolerability.[5,6]

Antiepileptic drugs (AEDs) are commonly prescribed to women of reproductive age, but they are associated with a significant risk of teratogenicity.[7] Prenatal exposure to AEDs has been documented to cause both toxic and teratogenic effects, and the nature and severity of these outcomes depend on the stage of pregnancy during exposure.[8] In particular, AED use during pregnancy has been reported to adversely affect embryogenesis and osteogenesis.[9] Since the 1960s, research on skeletal toxicology has accelerated, and evidence has accumulated showing reductions in bone mineral density (BMD) and impairments in bone metabolism, particularly in paediatric and adolescent populations. Due to the increasing clinical use of GBP and the lack of comprehensive safety data during pregnancy, a significant gap exists in the literature regarding its effects on pregnancy-related outcomes.[10-12]

The exact effects of AEDs on skeletal integrity remain controversial, and the effects of GBP have been particularly understudied. Experimental studies have yielded inconsistent results regarding the developmental toxicity of GBP. However, evidence from rodent models suggests that prenatal GBP exposure may have toxic effects.[2,13] Additionally, Freyer[6] reported that oral GBP administration during organogenesis delayed ossification in many fetal bones. The relationship between GBP treatment and bone demineralisation has not been definitively established. However, other studies have highlighted negative correlations. These correlations exist among AED use, bone loss, and calcium metabolism disorders.[14,15] Recent findings indicate that in 50% of exposed individuals, AEDs contribute to reduced BMD, increased fracture risk, and skeletal malformations.[16]

Despite these findings, data specifically evaluating prenatal skeletal development following GBP exposure, particularly those obtained using double staining (DS) and immunohistochemical (IHC), remain limited. Therefore, this study evaluated the potential effects of prenatal GBP exposure on skeletal development in rats using DS and IHC.

MATERIALS AND METHODS

This is an experimental animal study. This study has been approved by the Erciyes University Animal Experiments Local Ethics Committee (approval no: 16/141, date: 16.11.2016).

Animals and Study Protocol

Twenty adult female Wistar albino rats (8 weeks old) were included. For mating purposes, female rats were housed overnight with male rats. The presence of spermatozoa in vaginal smears the following morning was considered gestational day (GD) 0. All animals were kept under standardized environmental conditions.

Study Groups and Drug Administration

In anticipation of an average litter size of ten-twelve fetuses per dam and considering potential fetal loss due to treatment toxicity, the animals were randomly divided into five groups of four dams each. GBP was dissolved in saline solution and administered via oral gavage once daily from GD 1 to GD 20. The groups were as follows:

- Control: received saline vehicle only
- 10 mg/kg/day GBP (low dose)
- 30 mg/kg/day GBP
- 60 mg/kg/day GBP
- 120 mg/kg/day GBP (high dose)
- The administered doses were selected based on previous studies.[13,17]

Experimental Procedure and Fetal Evaluation

On the twentieth GD, all pregnant rats were anesthetized intraperitoneally with xylazine and ketamine. After adequate anaesthesia had been achieved, a midline incision was performed, and the uterus was carefully excised with the fetuses *in situ*. Fetuses were collected and examined under a stereomicroscope for external malformations and gross skeletal deformities.

Each fetus and placenta was individually weighed. Cranio-caudal (CC) length, occipitofrontal diameter, and biparietal diameter were measured using a high-precision digital caliper. Following these assessments, fetuses were randomly allocated to either DS or IHC evaluation for further analysis of skeletal development and bone metabolism.

Double Staining Evaluation

The fetus's skeleton was stained using the DS method (Supp1). High-resolution images of the skeletal bones of the fetal fore- and hindlimbs were captured using an Olympus SZX16 stereomicroscope (Olympus Corporation, Tokyo, Japan) equipped with a digital imaging system. Specimens were placed on millimeter graph paper for spatial calibration, and the images were transferred to a computer for quantitative analysis.

Morphometric measurements were performed using ImageJ software (version 1.51r, NIH, USA). For each specimen, the total bone length, ossified zone length, total bone surface area, and ossified zone surface area were measured. Ossification ratios were calculated using these values. This analysis enabled a precise evaluation of both longitudinal and surface-based ossification in the developing limb bones, allowing for comparative assessment across experimental groups.

Immunohistochemical Evaluation

IHC evaluations were performed in a blinded manner. For IHC evaluation, fetuses from each experimental group were randomly selected and euthanized under appropriate anaesthesia. The femurs were carefully dissected and processed for histological and IHC analyses. Initially, a standard histological protocol was employed to assess the general tissue architecture of the bone. Subsequently, haematoxylin-eosin staining was performed to evaluate the histopathological features (Supp2).

In this study, the expression patterns of two key markers were investigated: alkaline phosphatase (AP), an established marker of osteoblastic activity and bone formation, and tartrate-resistant acid phosphatase (TRAP), a marker indicative of osteoclastic activity and bone resorption. IHC staining for AP and TRAP was conducted on femoral sections to assess the potential alterations in bone metabolism resulting from prenatal GBP exposure.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 28.0.1; IBM Corporation, Armonk, NY, USA). The normality of the distribution was assessed by the Shapiro-Wilk test. Intergroup comparisons were conducted using ANOVA, followed by Tukey's post-hoc test for multiple comparisons. A $p<0.05$ value was considered significant.

RESULTS

No miscarriages or stillbirths were observed. Fetal and placental weights were significantly reduced in GBP-treated groups compared to the control, with a more pronounced effect at higher doses, indicating a dose-dependent pattern. Similarly, all fetal length parameters showed significant decreases across treatment groups, suggesting impaired overall fetal growth. Despite these changes, maternal body weight gain was relatively preserved, with only slight reductions observed at higher doses. These findings indicate that GBP induces fetal growth restriction independently of overt maternal toxicity.

Morphometric Findings

The numbers, body weights, and heights of the fetuses were recorded prior to histological staining. All morphometric parameters were highest in the control group. In the GBP-administered groups, a statistically significant reduction in these parameters was observed, and this reduction correlated with dose escalation. Notably, the differences between the control group and the 120 mg/kg GBP group were statistically significant ($p<0.05$). These findings imply that GBP may adversely affect fetal growth and development in a dose-dependent manner (Figure 1).

Double Staining Findings

In DS, ossified regions were stained red, while cartilaginous structures were stained blue. Morphometric evaluations included measurements of length and surface area of the clavicle, scapula, humerus, radius, and ulna in the forelimb and of the femur, tibia, and fibula in the hindlimb (Figure 2). Changes in overall bone dimensions among the GBP-treated groups are summarized in Table 1, whereas Figure 3 presents a comparison of ossified region sizes across groups. The control group demonstrated the highest values for both total bone length and ossification percentage, while the lowest values were recorded in the 120 mg/kg GBP group. An Analysis of ossification length percentages showed significant differences between the control group and all treatment groups for the scapula, humerus, and femur. Furthermore, significant differences for the remaining bones were detected between the control group and the 120 mg/kg GBP group ($p<0.05$).

Group comparisons of ossification area percentages indicated that proportions of both total bone area and ossified area were greater in the control group (Figure 3). Statistically significant differences in ossification area percentages were identified between the control group and the 30, 60, and 120 mg groups for the scapula and radius; between the control group and the 120 mg group for the humerus and ulna; between the control group and the 60 and 120 mg groups for the tibia; and between the control group and all treatment groups for the femur ($p<0.05$) (Table 1).

Based on the DS findings, GBP administration-particularly at higher doses (60 and 120 mg/kg/day)-was associated with a general tendency toward delayed ossification and reductions in total bone length and surface area. However, these changes did not follow a consistent dose-dependent pattern across all skeletal parameters.

Immunohistochemical Findings

In the control group, IHC analysis revealed a well-preserved hyaline cartilage architecture within the quiescent zone. In the proliferative zone, chondrocytes exhibited mitotic activity, forming characteristic isogenic cell clusters. The hypertrophic zone was populated by enlarged, terminally differentiated chondrocytes. In the zone of calcification, degenerative changes in chondrocytes were evident, while in the zone of ossification, osteoprogenitor cells were observed differentiating into osteoblasts (Figure 4).

Alkaline Phosphatase Density Findings

IHC samples from all groups were evaluated by light microscopy (Table 2). The highest level of AP expression (89.94 ± 3.50) was detected in the ossified regions of the control group (Figure 4). Statistical analysis revealed significant differences between the control group and the GBP-treated groups (60 mg and 120 mg) ($p<0.05$).

Tartrate-Resistant Acid Phosphatase Density Findings

IHC evaluation of tissue specimens from all groups demonstrated TRAP expression localized to the ossification zones. The highest intensity of TRAP expression was observed in the control group (76.73 ± 5.20) (Table 2). Statistical analysis revealed a significant difference in TRAP expression between the control group and the high-dose GBP group ($p<0.05$). While the activities of osteoclasts and osteoblasts appeared to be in physiological balance under normal conditions, the findings suggest that increasing doses of GBP disrupt this homeostasis, thereby impairing the ossification process (Figure 4).

DISCUSSION

Epilepsy is one of the most prevalent neurological disorders worldwide, and it particularly affects women of reproductive age. The management of epilepsy during pregnancy is critical because seizures, inherent to the chronic nature of the disease, may adversely affect maternal physiology and, via placental transfer, fetal development.[16,18]

Given that women with epilepsy often require continued AED therapy during gestation, it is essential to evaluate the potential developmental toxicity of these medications on both the mother and fetus. The increasing use of GBP underscores the need for robust evidence to inform women of childbearing potential about the risks and benefits of GBP treatment regarding pregnancy-related outcomes. While current data suggest that the risk of major congenital malformations associated with early gestational exposure to GBP is relatively low, its toxicological profile remains insufficiently elucidated.[11,12,19]

GBP is widely utilized in the treatment of neuropathic pain, spasticity, and inflammatory conditions, such as migraine.[2] Despite its therapeutic efficacy, GBP has been associated with adverse effects

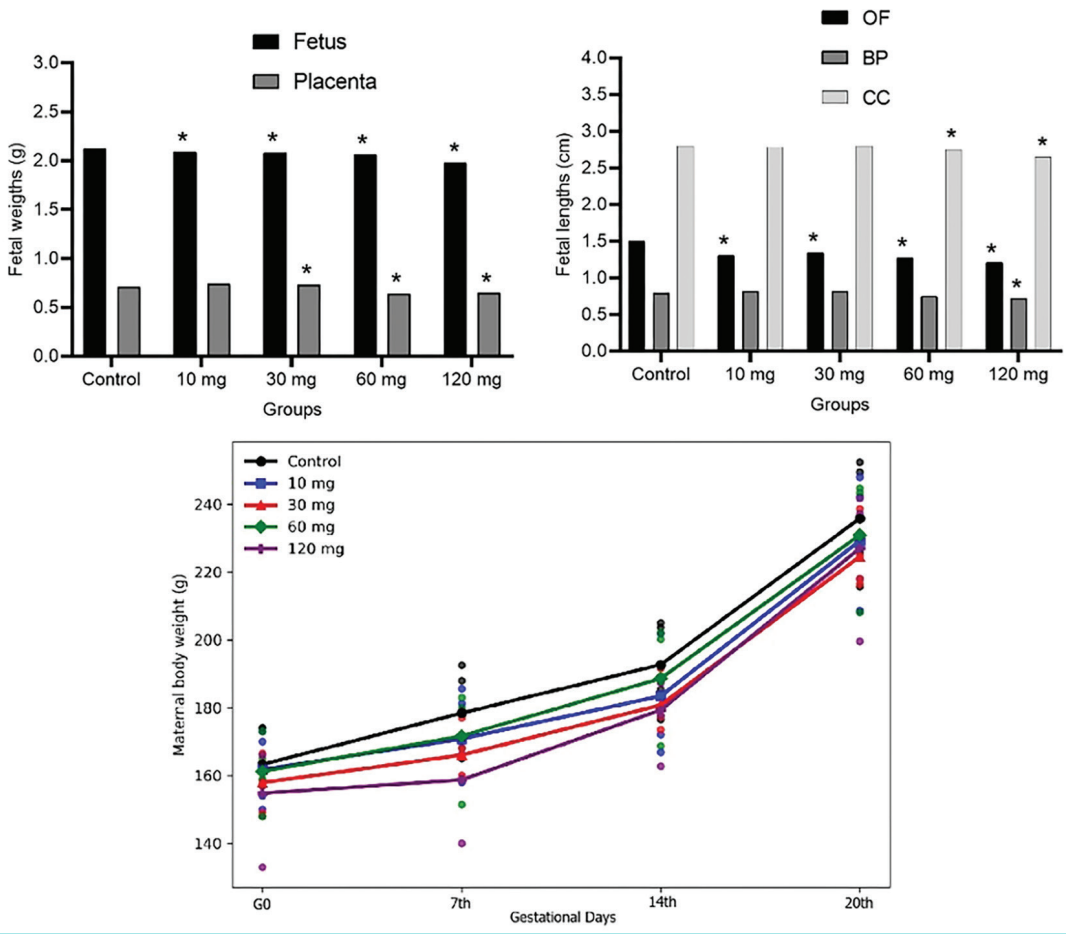

Figure 1. Effects of GBP exposure on fetal development parameters and maternal weight during gestation. Comparison of fetal and placental weights across experimental groups (Control, 10, 30, 60, and 120 mg/kg). Comparison of fetal lengths, including occipitofrontal (OF), biparietal (BP), and cranio-caudal (CC) measurements among groups. Changes in maternal body weight throughout gestation (G0, 7th, 14th, and 20th days) across all experimental groups. Data are presented as mean values. Asterisks (*) indicate statistically significant differences compared to the control group ($p<0.05$).

GBP: Gabapentin.

on bone development, including reductions in BMD and increased bone fracture risk. Moreover, it may cause mild side effects across multiple organ systems. Commonly reported adverse effects include weight gain and bone fragility.[20, 21] Although the precise impact of AEDs on bone metabolism remains controversial, accumulating evidence indicates that these drugs disrupt bone remodelling and increase fracture risk, potentially through indirect mechanisms, such as impaired calcium absorption, mediated by alterations in vitamin D metabolism.[10,22]

The analgesic effect of GBP is primarily exerted through a reduction in calcium influx. Nevertheless, sustained exposure to GBP may disrupt the normal physiological role of the α2β1 (alfa2/delta-1) subunit, which is critical for the proper development of musculoskeletal tissues. Consequently, long-term administration of GBP may adversely affect skeletal integrity.[23]

In the present study, we aimed to investigate the developmental and fetotoxic effects of GBP on prenatal bone development using DS and IHC. Both DS and IHC are reliable methods for evaluating skeletal alterations during the prenatal and postnatal periods in developmental toxicology research.[24] Previous studies conducted in both humans and animal models have demonstrated developmental toxicity associated with GBP exposure during pregnancy. Consistent with our findings, a study observed adverse effects on embryo-fetal development in rats following prenatal administration of pregabalin, a GBP AED whose effects are very similar to those of GBP.[25]

The effects of GBP on bone development may also manifest as alterations in morphometric parameters, such as fetal weight and CC length. In a study assessing these parameters, Prakash et al.[26] administered GBP at doses of 113, 226, and 452 mg/kg/day to rats during early, mid, and late gestation. The authors reported significant growth retardation, reduced litter size, and multiple gross malformations, particularly in the mid- and late-gestation groups. Similarly, Afshar et al.[13] administered GBP intraperitoneally at doses of 25 and 50 mg/kg/day during the first 15 days of gestation in mice and observed significant reductions in fetal body weight, together with skeletal and macroscopic malformations.

In our study, no major congenital anomalies were identified. However, we observed a dose-dependent decrease in fetal and placental weights, intrauterine growth restriction, and reduced litter size, particularly at higher GBP doses. These reductions were statistically significant compared with the control group.

Jetté et al.[20] conducted a retrospective study and reported a significantly increased risk of non-traumatic wrist, hip, and vertebral fractures among users of most AEDs, including GBP, with the exception of valproic acid, which showed no association with fracture risk. A related study involving 1,385 AED users found that postmenopausal women using AEDs had an increased risk of falls and fractures, emphasizing the importance of fall-prevention strategies in this population.[27] Additional studies have supported a strong association between AED use and fracture susceptibility.[28,29]

Although fracture risk was not directly evaluated in our study, we observed marked ossification delays, reductions in total bone length and area, and diminished ossification zones, particularly in the high-

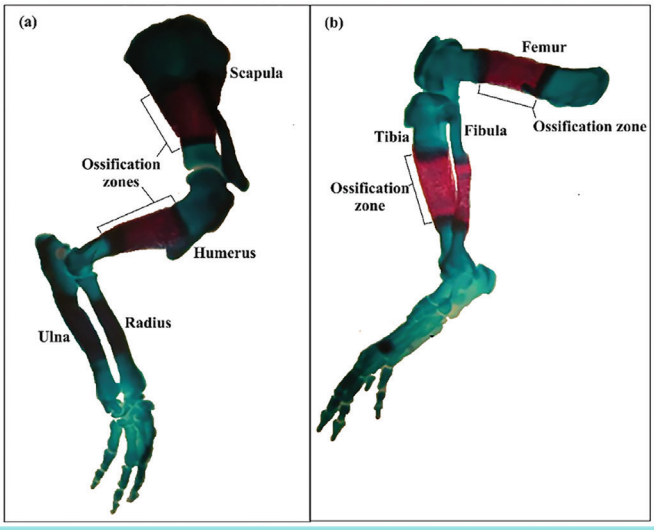

Figure 2. Images of forelimb (a) and hindlimb (b) in the control group stained with DS.

DS: Double staining.

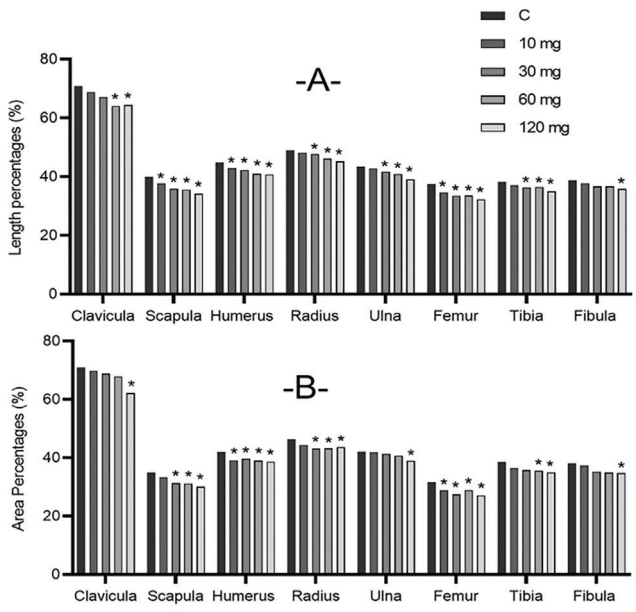

Figure 3. A comparison of the length (A) and area (B) of the ossified zones between the groups (* indicates that the difference is statistically significant compared to the control group).

Table 1. Total bone length and area values of fetuses selected for groups.

		GBP groups				
		10 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg	Control
Bones	**Parameter**	**n=27**	**n=24**	**n=27**	**n=26**	**n=22**
Clavicula	TL	3.04±0.19	3.05±0.25	3.15±0.17	3.00±0.21	3.16±0.22
	TA	0.99±0.13	1.03±0.18	1.08±0.11	0.97±0.15	1.12±0.20
Scapula	TL	4.26±0.24	4.21±0.28	4.30±0.28	4.25±0.27	4.37±0.20
	TA	6.16±0.68	6.02±0.80	6.33±0.69	6.16±0.72	6.47±0.87
Humerus	TL	4.42±0.20	4.39±0.25	4.50±0.18	4.39±0.21	4.57±0.25
	TA	4.16±0.39	4.14±0.49	4.33±0.38	4.15±0.41	4.37±0.53
Radius	TL	3.27±0.17	3.21±0.25	3.33±0.18	3.27±0.14	3.37±0.18
	TA	1.60±0.18	1.52±0.23	1.61±0.25	1.54±0.17	1.70±0.25
Ulna	TL	4.51±0.25	4.41±0.40	4.63±0.27	4.5 ±0.22	4.73±0.22
	TA	2.44±0.30	2.32±0.42	2.48±0.42	2.51±0.27	2.63±0.30
Femur	TL	3.79±0.18	3.75±0.30	3.84±0.21	3.82±0.24	3.86±0.24
	TA	2.97±0.33	2.95±0.45	3.12±0.27	3.06±0.33	3.19±0.37
Tibia	TL	3.70±0.24	3.64±0.31	3.78±0.24	3.74±0.26	3.81±0.24
	TA	2.36±0.28	2.34±0.33	2.54±0.30	2.43±0.32	2.55±0.30
Fibula	TL	3.46±0.20	3.45±0.29	3.58±0.20	3.54±0.20	3.60±0.16
	TA	1.04±0.15	1.06±0.15	1.15±0.12	1.13±0.12	1.18±0.14

GBP: Gabapentin. n: number of fetuses in the groups selected for DS.
TA: Total bone area (mm^2), TL: Total bone length (mm).

Table 2. Intensities of AP and TRAP expression in all experimental groups

	GBP groups				
	10 mg/kg	30 mg/kg	60 mg/kg	120 mg/kg	Control
	n=21	n=16	n=24	n=15	n=25
AP	86.63±4.60^{ac}	86.34±3.72^{ac}	85.09±6.90^{a}	80.95±6.80^{b}	89.94±3.50^{c}
TRAP	75.64±4.64^{a}	74.54±4.98^{ab}	73.88±5.05^{ab}	71.08±8.94^{b}	76.73±5.20^{a}

(x^{a}, y^{b}): group x is statistically different from group y.
(x^{a}, y^{b}, z^{ab}): groups x and y are statistically different, group z is similar to groups x and y.
n: number of fetuses in the groups selected for IHC analysis.
AP: Alkaline phosphatase, TRAP: Tartrate-resistant acid phosphatase.

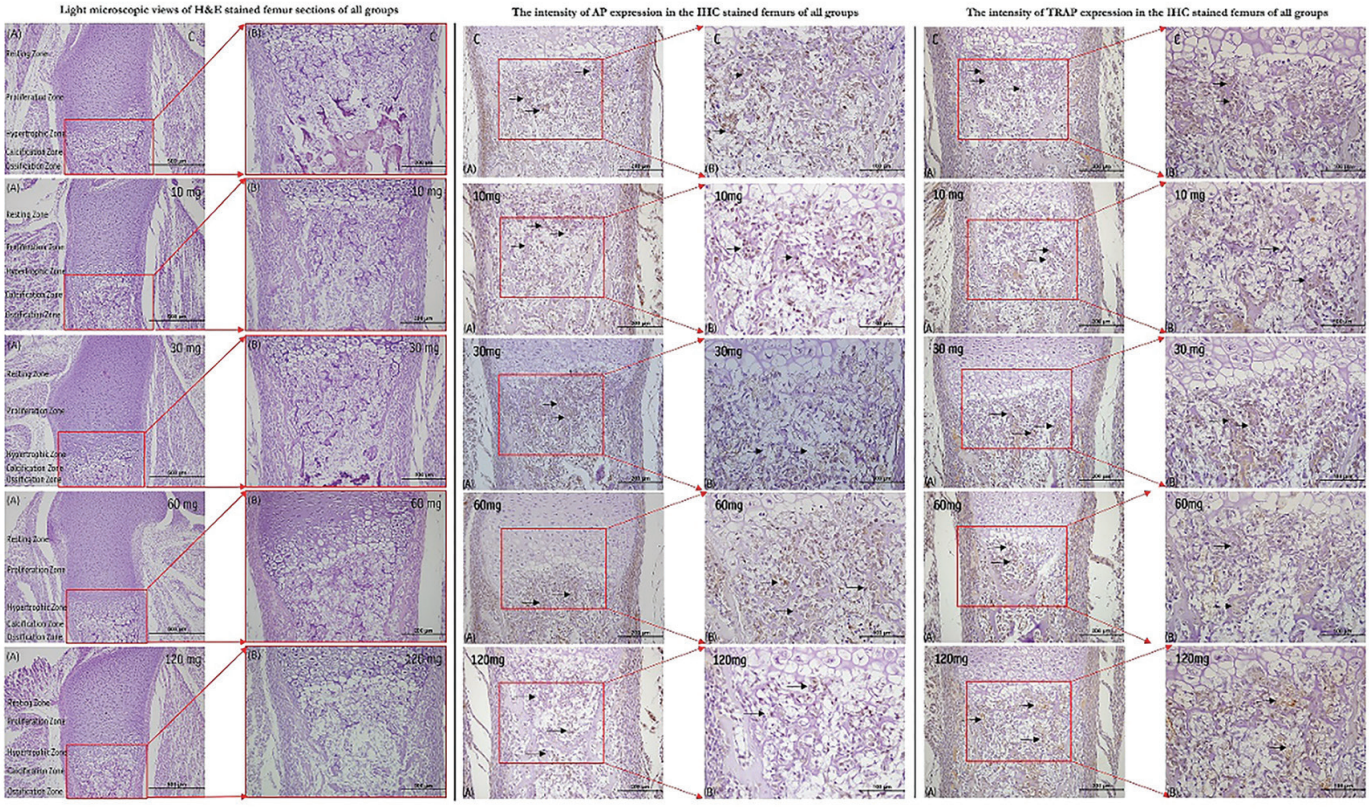

Figure 4. The zones of the femur in control group were identified using IHC. Arrows indicate the intensity of AP and TRAP expression in all groups (A) x20 and (B) x40, (C) Control group 10 mg, 30 mg, 60 mg and 120 mg GBP groups.

IHC: Immunohistochemical, AP: Alkaline phosphatase, TRAP: Tartrate-resistant acid phosphatase, GBP: Gabapentin.

dose GBP group. Moreover, IHC analysis revealed a disruption of bone homeostasis, evidenced by decreased AP and TRAP expression levels, suggesting a potential increase in fracture risk.

TRAP is a key enzyme involved in the development of the growth plate and metaphysis, and is widely used as a specific histochemical marker of osteoclastic and cartilaginous activity. Although TRAP deficiency in mice does not prevent overall development, it results in short, fragile bones due to dysfunction of the growth plate.[30] Simko et al.[29] examined the impact of sex hormone imbalance on susceptibility to AED-induced bone loss in orchiectomized Wistar rats and reported notable decreases in BMD, body weight, and bone strength. In addition, Blumer et al.[30] demonstrated that TRAP expression plays a crucial role in skeletal maturation, with its deficiency resulting in reduced ossification activity, particularly in the metaphyseal regions of long bones. Consistent with these observations, our findings showed that increasing doses of GBP were associated with reduced expression of bone turnover markers, including AP and TRAP, at ossification sites, suggesting impaired skeletal development and a potential increase in fracture risk.

Study Limitations

This study has many methodological limitations. Although the number of pregnant rats in each group was limited, this sample size is comparable to that in similar experimental toxicology studies and sufficient to demonstrate consistent, dose-dependent effects. During the experiment, the loss of some animals-particularly at higher GBP doses-may have reduced group sizes; however, the remaining samples permitted reliable morphometric, skeletal, and IHC assessments. Second, the IHC assessment of AP and TRAP expression was limited to the femur,

a long bone. This approach is commonly used to evaluate endochondral ossification. Despite these limitations, the combination of DS and IHC ensured a robust evaluation of prenatal skeletal development and bone metabolism. Third, a significant limitation of this study is that fetuses were treated as independent observational units, and the absence of maternal identifiers in the dataset prevented clear consideration of the litter effect. Since fetuses from the same mother may share biological and environmental similarities, this could lead to pseudo-replication. However, similar fetal-level analytical approaches have been reported in experimental toxicology studies.

CONCLUSION

The findings of this study demonstrate that maternal GBP exposure throughout gestation results in reductions in key morphometric parameters, including fetal and placental heights and weights, as well as delays in long bone development and ossification. Furthermore, IHC analyses revealed dose-dependent decreases and/or dysregulation in expression levels of AP and TRAP, enzymes critical for osteoblastic and osteoclastic activity, respectively. These results suggest that GBP administration during pregnancy may impair normal skeletal development by disrupting bone metabolism. The outcomes of this study provide valuable insights into the potential developmental effects of AEDs and underscore the need for further comprehensive investigations of the safety of GBP use during pregnancy.

MAIN POINTS

- Prenatal gabapentin (GBP) exposure reduced fetal and placental growth parameters.
- Long bone development and ossification were delayed in rat fetuses.
- Expression of alkaline phosphatase and tartrate-resistant acid phosphatase showed dose-dependent dysregulation, indicating altered bone turnover.
- Gestational GBP exposure may impair normal fetal skeletal development.

ETHICS

Ethics Committee Approval: This study was performed at Erciyes University Experimental Research Application Centre. Ethical approval of this study was granted by Erciyes University Animal Experiments Local Ethics Committee (approval no: 16/141, date: 16.11.2016).

Informed Consent: This is an experimental animal study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.D., İ.U., S.Y., E.B., G.Ö.Ö., Concept: M.D., E.B., E.U., Design: M.D., İ.U., S.Y., E.U., Data Collection and/or Processing: M.D., İ.U., E.B., G.Ö.Ö., Analysis and/or Interpretation: M.D., S.Y., E.B., G.Ö.Ö., Literature Search: M.D., Writing: M.D., E.U.

DISCLOSURES

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

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RESEARCH ARTICLE

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Association Between Vitamin D Levels and Clinical and Biochemical Parameters in COVID-19 Patients

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Abstract

BACKGROUND/AIMS: Both coronavirus disease 2019 (COVID-19) and vitamin D deficiency (VDD) are widespread health problems today. This study was designed to compare serum 25-hydroxyvitamin D [25(OH)D] levels among three groups: patients with COVID-19 pneumonia, patients with non-COVID-19 pneumonia, and healthy volunteers, and to investigate whether vitamin D levels correlate with laboratory findings and infection severity.

MATERIALS AND METHODS: This prospective case-control study was carried out at a single tertiary care centre over four consecutive months between May and August 2020. A total of 90 individuals were enrolled and assigned equally to three groups: 30 with COVID-19 pneumonia, 30 with non-COVID-19 pneumonia, and 30 healthy controls. Multiple linear regression modelling was applied to determine independent predictors of serum 25(OH)D levels.

RESULTS: Both pneumonia groups exhibited markedly diminished 25(OH)D concentrations relative to healthy controls, with no statistically significant difference observed between the two pneumonia cohorts. In the multivariate regression model, membership in the healthy control group emerged as the sole independent determinant of elevated 25(OH)D levels. No meaningful correlations were identified among vitamin D concentrations, laboratory indices, and illness severity.

CONCLUSION: VDD was common in both COVID-19 and non-COVID-19 related pneumonia groups but was not associated with disease severity. Our results indicate that VDD may influence susceptibility to lower respiratory tract infections rather than disease progression.

Keywords: COVID-19, pneumonia, vitamin D

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), which develops as a result of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, manifests with a broad clinical spectrum, ranging from fever, fatigue, and myalgia to cough, sputum production, and respiratory distress. Although most patients are asymptomatic or have mild symptoms, severe complications can arise in a significant number.[1,2] Poor prognostic factors include advanced age, obesity, cancer, immunodeficiency, cardiac disorder, chronic lung disease, chronic kidney failure, and smoking.[3] Furthermore, it has been reported that these factors are also related to lack of vitamin D.[4] Although the impacts of vitamin D on the skeletal system and calcium metabolism are generally known, many studies in the literature investigate its relationship with the immune system and infectious diseases.[5] Prior to the COVID-19 era, two studies reported that vitamin D administration reduced respiratory tract infections, particularly in critically ill patients.[6,7] In addition, studies have reported that vitamin D may exhibit various biological activities against COVID-19, including immune system regulation and endothelial dysfunction protection.[8] Therefore, the potential linkage between vitamin D status and COVID-19 susceptibility has increasingly been investigated in clinical research. The primary objective of this study was to analyse and compare the serum 25-hydroxyvitamin D [25(OH)D] levels in patients with COVID-19-related pneumonia (CP), in patients with non-COVID-19-related pneumonia (NCP), and in healthy individuals. Furthermore, the study aimed to establish any potential relationship between 25(OH)D levels, disease severity, and laboratory data. To the best of our knowledge, no prior prospective study has simultaneously assessed 25(OH)D levels across CP, NCP, and healthy control groups while also identifying independent predictors of vitamin D status through multivariate regression analysis.

MATERIALS AND METHODS

A prospective case-control design was employed at a tertiary referral hospital from May through August 2020. A total of 90 participants were enrolled in three groups, each consisting of 30 consecutively recruited individuals: CP patients, NCP patients, and healthy controls. The study protocol was approved by the Erciyes University Clinical Research Ethics Committee (approval number: 2020/217, date: 29.04.2020), and written informed consent was obtained from all participants before inclusion.

Group 1: Patients with CP admitted to the hospital's pandemic service were included (n=30). The diagnosis of CP was established by positive SARS-CoV-2 RNA detection in nasopharyngeal swab specimens. The biospeedy COVID-19 real-time polymerase chain reaction (PCR) kit was used to detect SARS-CoV-2 RNA. In addition, thoracic computed tomography (CT) findings were compatible with COVID-19 disease, defined as bilateral, peripheral, or multifocal ground-glass opacities or consolidation patterns, as per the expert consensus criteria of Radiological Society of North America (RSNA).[9]

Group 2: Patients who had two negative SARS-CoV-2 PCR tests on nasopharyngeal swab samples and in whom CP was ruled out were included (n=30). Thoracic CT findings were compatible with pneumonia but incompatible with typical COVID-19 radiology, as per the RSNA consensus criteria.[9] Thoracic CT scans were performed at hospital admission (day 1).

Group 3: The first 30 consecutive healthy adults who applied to our hospital's endocrinology and metabolism diseases clinic, had no known chronic diseases, and had no history of respiratory infection in the preceding three months were recruited.

Participants who were under 18 years of age, over 80 years of age, or who had taken any medication and/or supplement that may affect vitamin D metabolism in the last six months were excluded.

Socio-demographic data (age, sex), clinical symptoms (fever, headache, cough, dyspnoea, sore throat, diarrhoea), and vital signs (temperature, pulse, oxygen saturation) were recorded at hospital admission. Each participant's comorbid conditions were systematically recorded, including coronary artery disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, dyslipidemia, renal insufficiency, and malignancy. The laboratory data including complete blood count, procalcitonin, C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (eGFR), ferritin, D-dimer, albumin, and inflammatory markers including systemic immune-inflammation (SII) index, neutrophil-to-lymphocyte ratio (NLR), CRP-to-albumin ratio (CAR) and platelet-to-lymphocyte ratio (PLR) were recorded at hospital admission (day 1).[10,11] 25(OH)D levels were measured in all participants. All pneumonia patients underwent a thoracic CT scan.

The SII index was determined using the formula listed below: SII index = (neutrophil count*platelet count)/lymphocyte count.[10,11]

Serum 25(OH)D concentrations were measured in venous samples collected at admission using an electrochemiluminescence immunoassay (ECLIA) on a Cobas E601 system (Roche Diagnostics). The lowest detectable concentration of 25(OH)D was 3 ng/mL. 25(OH)D ≥30 ng/mL was considered as normal, 25(OH)D <20 ng/mL was considered as vitamin D deficiency (VDD) and 25(OH)D 20-30 ng/mL was considered as vitamin D insufficiency (VDI).[12,13]

Pneumonia severity was classified according to the national guideline of Türkiye,[14] as follows:

- Mild pneumonia: Mild clinical symptoms, ≤50% involvement on thoracic tomography, respiratory rate <24/minute, and oxygen saturation >93%.
- Moderate pneumonia: Mild clinical symptoms, ≤50% involvement on thoracic tomography, and the existence of any of the two criteria: respiratory rate 24-30/minute, and oxygen saturation 90-93%.
- Severe pneumonia: The existence of any of those criteria: respiratory rate >30/minute, oxygen saturation <90%, bilateral and common (≥50%) involvement on thoracic tomography.
- This study did not include patients with mild pneumonia since they were not hospitalized following the national guideline. Therefore, we classified patients into two groups with moderate and severe pneumonia.[14]

Statistical Analysis

Descriptive statistics are shown as median and minimum-maximum ranges or mean ± standard deviation (SD) for continuous data. Categorical data are reported as percentages and frequencies. Non-parametric comparisons of two groups were analysed using the Mann-Whitney U test, whereas differences among three or more groups were assessed with the Kruskal-Wallis test. If a difference was noted using the Kruskal-Wallis analysis, the Dunn test was conducted for multiple

comparisons. The chi-squared test was employed to identify relationships between categorical variables. The Spearman correlation analysis was employed to evaluate the relationship between numerical data. P<0.05 was considered statistically significant. Independent determinants of serum 25(OH)D concentrations were identified through multiple linear regression modelling. In the first model, all 90 participants were included, with age, sex, and group allocation as independent variables. In the second model, only the 60 pneumonia patients were included, and age, sex, CRP, albumin, lymphocyte count, NLR, CAR, and eGFR were evaluated as independent variables (biochemical parameters were not available for healthy controls). Regression outputs are reported as beta coefficients (β), accompanied by 95% confidence intervals (CI) and corresponding p-values. A post-hoc power analysis was performed based on the observed difference in serum 25(OH)D levels between the CP group and the healthy controls (mean difference: 7.0 ng/mL, pooled SD: 9.05). With 30 participants per group and a two-tailed alpha of 0.05, the achieved statistical power was 85%, which is considered adequate for the primary comparison of this study. SPSS 26.0 (IBM Corporation, NY, US) was used to perform all statistical analyses.

RESULTS

The study enrolled 90 participants with a mean age of 45.5±13.9 years (range 20-79), of whom 57.8% were male. Participants were allocated to three equal groups of 30 participants each: those with SARS-CoV-2 PCR-confirmed pneumonia, those with PCR-negative pneumonia, and those who were healthy controls. Half of the patients with pneumonia (27/60) had at least one comorbidity. The two most common comorbidities were type 2 diabetes mellitus (23.3%) and hypertension (23.3%). The main demographic and clinical features of the three groups are detailed in Table 1.

Fever (51.7%), cough (45%), and arthralgia (31.7%) were the most common symptoms. Although arthralgia was more commonly observed in CP patients, this difference was not statistically significant (p=0.052). Dyspnea was more frequent in NCP patients (p=0.006). When the vital signs of the patients at the admission were evaluated, the median fever was 36.3 (36-39.1) °C, the mean pulse was 102±18 rate/minute, and the median oxygen saturation was 96% (75-100%). Patients with NCP had significantly higher values of neutrophils, white blood cells, CRP, procalcitonin, D-dimer, ferritin, troponin, creatinine, NLR, SII index, and CAR, and lower values of eGFR and albumin than CP patients. CP patients had a longer hospital stay (Table 2).

Circulating 25(OH)D values averaged 11.9±6.7 ng/mL in CP patients, 11.3±6.2 ng/mL in NCP patients, and 18.9±10.9 ng/mL in healthy individuals. Statistical analysis revealed that 25(OH)D levels in CP and NCP patients were lower than those in healthy controls (p=0.004 and p=0.002, respectively). Additionally, we found that 86.7% of patients with CP had VDD, compared with 56.7% of controls. Vitamin D status and 25(OH)D levels of all participants are shown in Table 3.

No significant relationship was detected between 25(OH)D levels and any inflammatory parameters, including CRP, procalcitonin, ferritin, D-dimer, troponin, white blood cell, neutrophil, and lymphocyte counts (all p-values >0.050). Additionally, derived inflammatory indices such as PLR, NLR, CAR, and SII index did not exhibit correlations with serum 25(OH)D levels (all p>0.050).

Multivariate linear regression analysis revealed that membership in the healthy control group was the only independent predictor of higher serum 25(OH)D levels compared with the CP group (β=6.278, 95% CI: 1.94-10.62, p=0.005). Age and sex were not independent predictors of 25(OH)D levels. In the second model, including only pneumonia patients, none of the biochemical or inflammatory parameters were independently associated with serum 25(OH)D levels (all p>0.05, Adjusted R^2=-0.022) (Table 4).

DISCUSSION

In this study, VDD was found in 90% of NCP patients and 86.7% of CP patients, compared with only 56.7% of healthy controls. When the groups were compared, pneumonia patients demonstrated markedly reduced 25(OH)D concentrations relative to age- and sex-matched healthy individuals. The 25(OH)D levels were similar between the CP and NCP groups. Consistent with our univariate findings, multivariate linear regression analysis confirmed that group allocation, specifically membership in the healthy control group, was the only independent predictor of higher serum 25(OH)D levels (β=6.278, 95% CI: 1.94-10.62, p=0.005). Neither demographic variables (age, sex) nor inflammatory and biochemical parameters (CRP, albumin, NLR, CAR, eGFR, lymphocyte count) were independently associated with 25(OH)D levels. These findings suggest that pre-existing VDD may contribute to

Table 1. Main demographic and clinical characteristics of all participants

Variables	COVID-19 patients (n=30)	Non-COVID-19 patients (n=30)	Healthy controls (n=30)	p-value
Age (years), median (min-max)	40.5 (20-76)	51 (20-79)	41 (25-61)	0.074
Sex (male), n (%)	14 (46.7%)	22 (73.3%)	16 (53.3%)	0.094
Current smoker, n (%)	5 (16.7%)	8 (26.7%)	5 (16.7%)	0.535
Comorbidities	10 (33.3%)	17 (56.6%)	N/A	0.069
Diabetes mellitus	10 (33.3%)	4 (13.3%)	N/A	0.67
Hypertension	7 (23.3%)	7 (23.3%)	N/A	1
Coronary artery disease	5 (16.7%)	4 (13.3%)	N/A	0.71
Chronic obstructive pulmonary disease	0	5 (16.7%)	N/A	0.062
Dyslipidemia	1 (3.3%)	1 (3.3%)	N/A	1
Chronic renal disease	3 (10%)	6 (20%)	N/A	0.472
Malignancy	1 (3.3%)	3 (10%)	N/A	0.61

N/A: not applicable, COVID-19: Coronavirus disease 2019.

Table 2. Clinical characteristics and laboratory data of all cases with pneumonia

Variables	Total (n=60)	COVID-19 patients (n=30)	Non-COVID-19 patients (n=30)	p-value
Onset symptoms				
Fever	31 (51.7%)	16 (53.3%)	15 (50%)	0.796
Cough	27 (45%)	12 (40%)	15 (50%)	0.436
Dyspnea	14 (23.3%)	2 (6.7%)	12 (40%)	**0.006**
Sore throat	14 (23.3%)	7 (23.3%)	7 (23.3%)	1
Headache	9 (15%)	5 (16.6%)	4 (13.3%)	0.718
Arthralgia	19 (31.7%)	13 (43.3%)	6 (20%)	0.052
Nausea-vomiting	3 (5%)	3 (10%)	0	0.237
Diarrhoea	4 (6.7%)	3 (10%)	1 (3.3%)	0.612
Vital signs				
Fever	36.3 (36-39.1)	36.2 (36-38.8)	36.6 (36-39.1)	0.224
Pulse	102±18	101.8±16.6	101.5±19.8	0.800
Oxygen saturation	96 (75-100)	96 (88-100)	94.5 (75-99)	0.056
Laboratory data				
White blood cell count (mm^3)	6485 (630-18960)	5130 (3180-11100)	9580 (630-18960)	**<0.0001**
Neutrophil count (mm^3)	4175 (140-15200)	2985 (1780-8700)	6865 (140-15200)	**<0.0001**
Lymphocyte count (mm^3)	1504±808	1503±607	1505±980	0.992
Platelet count ($x10^3/mm^3$)	226,5 (99-548)	226 (103-548)	231 (99-454)	0.953
Haemoglobin (g/dL)	14 (7.2-17)	13 (10-17)	14.3 (7.2-16.7)	0.320
Creatinine (mg/dL)	0.88 (0.43-5.22)	0.80 (0.43-1.35)	1.04 (0.53-5.22)	**<0.0001**
eGFR (mL/min)	93.5 (13-132.4)	97.1 (49.1-132.4)	84.8 (13-122)	**0.002**
CRP (mg/L)	18.7 (0.2-316)	5.4 (0.2-144.7)	48.2 (2.6-316)	**<0,0001**
Procalcitonin (ng/mL)	0.07 (0-16)	0.05 (0-0.21)	0.12 (0.03-16)	**<0.0001**
D-dimer (µgram/L)	530 (189-11160)	385 (189-1520)	740 (189-11160)	**<0.0001**
Ferritin(ng/mL)	173.5 (6.6-989)	132 (6.6-989)	222 (18.5-620)	**0.039**
Troponin (ng/mL)	0.006 (0.002-0.770)	0.004 (0.002-0.026)	0.01 (0.002-0.770)	**<0.0001**
Albumin (g/dL)	4.4 (2.8-5.2)	4.5 (3.7-5.2)	4.2 (2.8-5)	**0.011**
Clinical severity scores				
NLR	3.1 (0.4- 62)	1.8 (1.1-11.3)	4.65 (0.4-62)	**0.001**
PLR	175.9 (58.5-1655)	175.9 (58.5-473.5)	183.2 (80-1655)	0.626
SII index	720.8 (82.4-20522)	500.1 (146.3-3402.6)	953 (82.4-20522)	**0.003**
CAR	4.3 (0-83.4)	1.1 (0-35.4)	12.1 (0.5-83.4)	**<0.0001**
Outcome				
Length of hospital stay (days)	6 (2-14)	8 (3-14)	5 (2-14)	**0.001**
Oxygen need	16 (26.6%)	5 (16.7%)	11 (36.7%)	0.072
ICU admission	2 (3.3%)	0	2 (6.6)	0.246
Mechanical ventilation	2 (3.3%)	0	2 (6.6)	0.246
Death	2 (3.3%)	0	2 (6.6)	0.246
Disease severity				
Moderate pneumonia	53 (88.3%)	25 (83.3%)	28 (93.3%)	0.424
Severe pneumonia	7 (11.7%)	5 (16.7%)	2 (6.7%)	

Values are expressed as n (%), mean ± SD or median (min-max).
COVID-19: Coronavirus disease 2019, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune-inflammation, CAR: CRP to albumin ratio, ICU: Intensive care unit, SD: Standard deviation.

Table 3. 25(OH)D levels and vitamin D status of all participants

25(OH)D level and status	COVID-19 patients (n=30)	Non-COVID-19 patients (n=30)	Healthy controls (n=30)	p^a-value	p^b-value	p^c-value
25(OH)D (ng/mL) (mean ± SD)	11.9±6.7	11.3±6.2	18.9±10.9	0.958	0.004	0.002
Vitamin D status				**0.002**		
Vitamin D deficiency	26 (86.7%)	27 (90%)	17 (56.7%)			
Vitamin D insufficiency	4 (13.3%)	3 (10%)	7 (23.3%)			
Vitamin D sufficiency	0	0	6 (20%)			

p^aCOVID-19 vs. non-COVID-19 patients, p^bCOVID-19 patients vs. controls, p^cNon-COVID-19 patients vs. controls according to vitamin D status (<20 vs. ≥20 ng/mL).
COVID-19: Coronavirus disease 2019, SD: Standard deviation.

Table 4. Multivariate linear regression analysis for independent predictors of serum 25(OH)D levels

Variable	β	SE	95% CI	p-value
Model 1: All participants (n=90) - Dependent variable: 25(OH)D; R^2=0.157, Adjusted R^2=0.118				
Non-COVID-19 pneumonia (vs. COVID-19)	**-1.977**	**2.321**	**-6.59 to 2.64**	**0.397**
Healthy controls (vs COVID-19)	**6.278**	**2.183**	**1.94 to 10.62**	**0.005**
Age	**0.115**	**0.067**	**-0.02 to 0.25**	**0.089**
Sex	**-1.543**	**1.876**	**-5.27 to 2.19**	**0.413**
Model 2: Pneumonia patients only (n=60) - Dependent variable: 25(OH)D; R^2=0.116, Adjusted R^2=-0.022				
Age	0.112	0.075	-0.04 to 0.26	0.142
Sex	0.227	1.870	-3.53 to 3.98	0.904
CRP	0.132	0.158	-0.19 to 0.45	0.408
Albumin	3.224	2.877	-2.55 to 9.00	0.268
Lymphocyte count	1.278	1.214	-1.16 to 3.72	0.298
NLR	0.121	0.118	-0.12 to 0.36	0.313
CAR	-0.530	0.635	-1.81 to 0.75	0.408
eGFR	0.025	0.046	-0.07 to 0.12	0.582

Reference category for group comparison: COVID-19 pneumonia.
β: Unstandardized beta coefficient, SE: Standard error, CI: Confidence interval, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, CAR: CRP-to-albumin ratio, eGFR: Estimated glomerular filtration rate, COVID-19: Coronavirus disease 2019, 25(OH)D: 25-hydroxyvitamin D.

susceptibility to lower respiratory tract infections, independent of the acute inflammatory response.

In a retrospective study in Switzerland, D'Avolio et al.[15] found that 25(OH)D concentrations were considerably lower in SARS-CoV-2 PCR positive patients than in SARS-CoV-2 PCR negative patients and healthy controls. The control group consisted of people with 25(OH)D levels measured one year ago, and the clinical severity of the patients was not mentioned. Unlike that study, our investigation was conducted prospectively; all included patients had pneumonia; and the control group consisted of healthy individuals evaluated during the same period. Similarly, the healthy control group had higher 25(OH)D levels, but no difference was observed between the SARS-CoV-2 PCR-positive and PCR-negative groups. These findings suggest that reduced vitamin D levels may represent a risk factor not only for COVID-19 but also for lower respiratory tract infections.

In another retrospective cohort, COVID-19 cases exhibited mean 25(OH) D levels of 13.8±7.2 ng/mL, substantially below the 20.9±7.4 ng/mL observed in the healthy comparators. VDD was found in 82.2% of COVID-19 patients and 47.2% of control subjects.[16] Similarly, 25(OH) D levels were 11.9±6.7 ng/mL in CP patients and 18.9±10.9 ng/mL in healthy controls, and the 25(OH)D levels of control groups were higher than in CP patients in our study. VDD was detected in 86.7% of CP patients and 56.7% of controls. These findings indicate that VDD may be associated with increased susceptibility to pneumonia. In the previous study, 19 of 216 COVID-19 patients received vitamin D supplements. However, the researchers reported that these 19 patients were analysed as a separate group. Because vitamin D supplementation may bias the results, patients who had taken a vitamin D supplement for at least 6 months were excluded from our study.

Ye et al.[17] conducted a study in China including 62 COVID-19 patients and 80 healthy controls. Similarly, they found that VDD in COVID-19 patients was considerably greater than in controls. In addition, they compared 25(OH)D concentrations between mild/moderate and severe/critical groups, and reported that these concentrations were lowest in the severe/critical groups. In our study, patients who met the hospitalization criteria of the Ministry of Health Guide were included and therefore mainly belonged to the moderate and severe disease groups. Contrary to the study of Ye et al.,[17] vitamin D levels and VDD status were similar in the two disease groups (p=0.748, p=0.188, respectively).

A few studies have been conducted on the association between COVID-19 infection and vitamin D levels in Türkiye. In a study, the mean 25(OH)D

level was 15±10.3 ng/mL. VDD and VDI were found in 69.1% and 22.8%, respectively.[18] In our study, the mean 25(OH)D level was lower, and no COVID-19 patient had a sufficient level of 25(OH)D. Despite higher vitamin D levels in that cohort, their reported mortality rate (46.3% vs. 0%) was substantially higher than ours. This may be explained by other confounding factors, such as comorbidities, gender, smoking status, and by a higher proportion of severe/critical disease in their population (68.5% vs. 16.7%).

While the association between circulating 25(OH)D concentrations and COVID-19 has been widely investigated, the present study is, to the best of our knowledge, the first prospective investigation to compare vitamin D status across CP, NCP, and healthy control groups simultaneously. This study analysed laboratory parameters, clinical outcomes, and pneumonia severity. We found that vitamin D levels and clinical outcomes were similar between the two groups, except for hospital stays. However, biochemical parameters, especially inflammation-related markers, were higher in NCP patients. This observation suggests that although the clinical outcomes of COVID-19 and other lower respiratory tract infections may be comparable, systemic inflammation may be more pronounced in NCP. This difference may be attributable to the distinct pathophysiological mechanisms underlying bacterial and viral pneumonia. NCP is more commonly caused by bacterial pathogens, which typically elicit a more robust innate immune response characterized by marked elevations of CRP, procalcitonin, and neutrophil-predominant inflammation.[19,20] In contrast, SARS-CoV-2 has been shown to actively evade innate immune defenses through suppression of interferon responses and is often associated with relatively lower early inflammatory biomarker levels despite substantial lung involvement.[21,22]

Several studies have documented an association between lower 25(OH)D levels and worse COVID-19 outcomes. In a retrospective study of 88 hospitalized patients using LC-MS/MS methodology, Nguyen et al.[23] found that VDD was independently associated with longer hospital stay and higher adjusted odds of in-hospital mortality and mechanical ventilation. Similar associations between low 25(OH)D levels and greater disease severity or adverse clinical outcomes have also been reported in other COVID-19 cohorts.[24,25] In our cohort, however, no meaningful association was identified between 25(OH)D concentrations and either disease severity or clinical outcomes. This discrepancy may be attributable to several factors. First, our cohort included only moderate and severe cases of pneumonia, which may have limited the detectable gradient in vitamin D levels across severity groups. Second, whereas Nguyen et al.[23] measured 25(OH)D using LC-MS/MS, we used an ECLIA immunoassay, which may underestimate vitamin D levels in certain patients. Finally, the modest sample size may have reduced the ability to detect statistically significant associations with clinical outcomes.

Despite the absence of a supplementation intervention in our study, markedly reduced 25(OH)D concentrations were consistently observed in both pneumonia groups relative to healthy controls. Supporting a potential preventive role of vitamin D against respiratory infections, Jolliffe et al.[26] conducted a comprehensive meta-analysis of 43 randomized controlled trials and reported a modest but statistically significant protective effect of vitamin D supplementation against acute respiratory tract infections (odds ratio 0.92, 95% CI: 0.86-0.99).[26] However, this meta-analysis focused on acute respiratory tract infections in general, and the evidence remains heterogeneous and not specific to pneumonia or COVID-19. Therefore, further targeted randomized controlled trials are required to determine whether correction of VDD through supplementation can reduce the risk of pneumonia in high-risk populations.

We found that serum 25(OH)D concentrations were significantly diminished in pneumonia patients, irrespective of COVID-19 status, compared with healthy individuals. Nevertheless, the absence of any correlation with laboratory parameters or disease severity points to VDD as a predisposing condition rather than a driver of clinical deterioration. Larger multicenter studies are warranted to confirm these findings and to improve generalizability to different populations.

Study Limitations

The present study is subject to a number of limitations. First, the modest sample size of 30 participants per group may have constrained the statistical power of our analyses and increased the likelihood of a type II error, thereby reducing the capacity to identify genuine associations between 25(OH)D levels and clinical or disease severity parameters. Second, the study was conducted between May and August 2020, during the summer months in Türkiye, when sun exposure is typically highest. This seasonal factor may have elevated baseline 25(OH)D levels across all groups, thereby masking differences that might be observed during winter months. Third, the single-center nature of this study, conducted at a tertiary institution in Türkiye, may limit the applicability of our findings to broader populations and diverse clinical settings. Fourth, only hospitalized patients with moderate or severe pneumonia were included; findings cannot be extrapolated to patients with mild or asymptomatic COVID-19. Fifth, serum 25(OH)D levels were measured only at hospital admission, and no longitudinal follow-up measurements were performed. In addition, acute illness may influence vitamin D-binding protein levels and, consequently affect 25(OH)D concentrations, possibly affecting measured vitamin D levels at admission. Finally, key determinants known to affect vitamin D status, including nutritional habits, duration of sun exposure, physical activity level, and socioeconomic background, were not systematically collected and may constitute unmeasured sources of confounding.

CONCLUSION

Patients with pneumonia had substantially lower serum 25(OH)D concentrations than age- and sex-matched healthy individuals. No meaningful difference in vitamin D levels was observed between the CP and NCP groups, and a multivariate regression analysis identified group allocation as the sole independent predictor of serum 25(OH)D levels. No association was identified among vitamin D levels, the severity of infection, and laboratory parameters. These findings suggest that VDD may be more relevant as a predisposing factor for lower respiratory tract infections rather than a determinant of disease severity once pneumonia develops. Although a causal relationship cannot be established from this observational study, vitamin D supplementation and food fortification strategies may represent preventive approaches in high-risk populations. Future large-scale randomized controlled trials are warranted to better clarify the interplay between vitamin D status, supplementation strategies, and clinical outcomes in COVID-19.

MAIN POINTS

- Circulating 25-hydroxyvitamin D [25(OH)D] concentrations were markedly lower in patients with pneumonia, irrespective of severe acute respiratory syndrome-coronavirus-2 status, compared with healthy individuals.
- Vitamin D levels did not differ significantly between patients with coronavirus disease 2019 (COVID-19)-related pneumonia and patients with non-COVID-19-related pneumonia.
- No meaningful relationship was identified between 25(OH) D concentrations and inflammatory biomarkers, biochemical parameters, or clinical severity.
- Vitamin D may be associated with susceptibility to lower respiratory tract infections, including COVID-19, but does not appear to influence clinical severity once pneumonia develops.
- Multivariate regression analysis identified healthy control status as the only independent predictor of higher 25(OH)D levels, suggesting that VDD in pneumonia patients likely reflects a pre-existing condition rather than a consequence of acute illness.

ETHICS

Ethics Committee Approval: This study was approved by the Erciyes University Clinical Research Ethics Committee (approval number: 2020/217, date: 29.04.2020).

Informed Consent: All participants provided informed consent prior to their inclusion in the study.

Footnotes

Authorship Contributions

Concept: C.Ş.K., F.B., Design: C.Ş.K., H.A., F.B., Data Collection and/or Processing: C.Ş.K., B.B.K., Z.T., Analysis and/or Interpretation: C.Ş.K., B.B.K., H.A., Z.T., Literature Search: C.Ş.K., C.Y., Ö.K., Writing: C.Ş.K., B.B.K., Z.T., C.Y., Ö.K., F.B.

DISCLOSURES

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RESEARCH ARTICLE

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The Role of the Triglyceride-Glucose Index in Predicting Gestational Diabetes Mellitus

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Abstract

BACKGROUND/AIMS: The present study investigated whether the triglyceride-glucose (TyG) index could serve as a predictive marker for gestational diabetes mellitus (GDM).

MATERIALS AND METHODS: This retrospective case-control analysis included pregnant women who were followed and delivered at our institution between April 2018 and April 2024. Among 1,360 evaluated pregnancies, 64 women diagnosed with GDM were assigned to the study group, while 132 uncomplicated singleton pregnancies were assigned to the control group. Clinical characteristics, obstetric outcomes, and metabolic parameters were compared between groups. First-trimester laboratory measurements, including fasting glucose, triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, body mass index (BMI), TyG index, and TyG-BMI, were obtained from medical records.

RESULTS: Women with GDM demonstrated significantly higher BMI values than controls (p=0.021) and delivered at an earlier gestational age (p<0.001). In addition, TG levels, fasting glucose, TG/HDL-C ratio, TyG index, and TyG-BMI index were significantly elevated in the GDM group (p<0.05 for all comparisons). Multivariable logistic regression analysis, adjusted for maternal age, BMI, smoking status, and parity, revealed that the TyG index was independently associated with GDM [adjusted odds ratio: 1.85, 95% confidence interval (CI): 1.14-3.02, p=0.013]. Effect size estimates and CIs supported the clinical relevance of these findings.

CONCLUSION: The TyG index may represent a practical and cost-effective marker for identifying women at increased risk of GDM. Incorporating this index into routine antenatal evaluation could support earlier risk stratification and improve preventive care strategies.

Keywords: Triglyceride-glucose index, gestational diabetes mellitus, pregnancy, insulin resistance

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INTRODUCTION

Gestational diabetes mellitus (GDM) is impaired glucose regulation first recognized during pregnancy and typically resolves after delivery. Its development is mainly driven by progressive insulin resistance, accompanied by an inadequate compensatory response by pancreatic β-cells. Maternal hyperglycemia can negatively influence placental function, resulting in increased fetal glucose exposure and subsequent fetal hyperinsulinemia.[1-3] These metabolic disturbances are associated with adverse outcomes, including excessive fetal growth, neonatal hypoglycemia, and an increased risk of long-term metabolic disease. Therefore, early detection and appropriate management of GDM are crucial to reducing both maternal and neonatal morbidity.[4]

Various professional organizations, such as the World Health Organization, the International Association of Diabetes and Pregnancy Study Groups, the American College of Obstetricians and Gynecologists, and the National Institute for Health and Care Excellence, have proposed different screening and diagnostic strategies. Both one-step and two-step oral glucose tolerance test protocols are widely used in clinical practice.[5]

Pregnancy is also characterized by substantial alterations in lipid metabolism, particularly a gradual increase in circulating triglyceride (TG) levels.[6] These changes become more pronounced in later trimesters and are largely driven by hormonal influences and increased energy requirements. Elevated estrogen levels promote hepatic lipoprotein production, while pregnancy-related insulin resistance contributes to reduced lipid clearance and enhanced lipolysis, leading to increased release of free fatty acids.[7]

Although these metabolic adaptations are essential for fetal development, excessive lipid accumulation has been associated with adverse pregnancy outcomes, including GDM, preeclampsia, and fetal macrosomia. In recent years, there has been growing interest in simple biochemical markers and composite indices for early disease prediction.[8,9] Among these, the TG-glucose (TyG) index has been proposed as a practical and economical surrogate marker of insulin resistance.[10,11] Since it is derived from routinely measured fasting glucose and TG levels, it may provide valuable insight into early metabolic alterations.

Accordingly, this study aimed to evaluate the potential role of the TyG index in predicting the development of GDM.

MATERIALS AND METHODS

This retrospective case-control study was performed in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion. Ethical approval was granted by the institutional review board of our hospital Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 2024/372, date: 25.12.2024).

A total of 1,360 pregnant women who were followed and who delivered at our center between April 2018 and April 2024 were evaluated retrospectively. The study group included 64 women aged between 18 and 45 years with singleton pregnancies who were diagnosed with GDM. The control group consisted of 132 women in the same age range who had uncomplicated singleton pregnancies and no diagnosis of GDM.

Women without pre-existing diabetes were screened for GDM between 24 and 28 weeks of gestation using a 75-g oral glucose tolerance test. All tests were performed in the morning following a fasting period of at least 8 hours. Plasma glucose concentrations were measured at baseline (fasting) and at 1 and 2 hours after glucose intake. GDM was diagnosed when at least one of these values met or exceeded the established diagnostic thresholds, based on internationally accepted criteria.[12]

Participants were excluded if they had a history of assisted reproductive techniques, a body mass index (BMI) greater than 30 kg/m^2 at the time of pregnancy diagnosis, multiple gestations, known chromosomal abnormalities, a previous preterm delivery, a prior complicated obstetric history, a chronic systemic disease, or use of immunosuppressive therapy.

Demographic features, obstetric parameters, and biochemical parameters were compared between the two groups. Laboratory data obtained during the first trimester were retrospectively retrieved from hospital records. The evaluated parameters included BMI, total cholesterol (TC), TGs, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), TyG index, and TyG-BMI.

The TyG index was calculated as the natural logarithm of fasting TG and glucose levels [ln (TG × glucose/2)]. The TyG-BMI index was derived by multiplying the TyG index by BMI. Additionally, lipid ratios were calculated as TG/HDL-C and TC/HDL-C (mg/dL).

Statistical Analysis

A total of 1,360 pregnant women who were monitored and delivered at our center between April 2018 and April 2024 were retrospectively reviewed. Sixty-four women aged 18-45 years who had singleton pregnancies and were diagnosed with GDM constituted the study group. The control group consisted of 132 women of similar age who had uncomplicated singleton pregnancies and no evidence of GDM.

Participants without previously diagnosed diabetes were screened for GDM between 24 and 28 weeks of gestation using a standard 75-g oral glucose tolerance test. All measurements were obtained in the morning after fasting for at least 8 hours. Plasma glucose levels were recorded during fasting and at 1 and 2 hours after glucose administration. A diagnosis of GDM was established if one or more values met the accepted diagnostic thresholds.[12]

Exclusion criteria included conception via assisted reproductive techniques; a BMI above 30 kg/m^2 at initial evaluation; multiple pregnancies; known fetal chromosomal abnormalities; a history of preterm birth; previous complicated obstetric outcomes; chronic systemic disorders; and the use of immunosuppressive medications.

Clinical characteristics, obstetric outcomes, and biochemical parameters were compared between the groups. First-trimester laboratory results were obtained from hospital records. The variables analyzed included BMI, TC, TG, HDL-C, LDL-C, FBG, and the TyG and TyG-BMI indices.

The TyG index was calculated as the natural logarithm of the product of fasting TG and glucose levels [ln (TG × glucose/2)]. The TyG-BMI index was calculated as the product of the TyG value and the BMI. In addition, lipid ratios were determined as TG/HDL-C and TC/HDL-C (mg/dL).

RESULTS

BMI was higher in the GDM group compared with control group (p=0.021). Gestational age at delivery was lower in the GDM group than in the controls (p<0.001) (Table 1).

Biochemical parameters of the study groups are presented in Table 2. TG levels and FBG levels were higher in women with GDM than in controls (p=0.032 and p=0.018, respectively). Similarly, the TG/HDL-C ratio was elevated in the GDM group (p=0.012). In addition, both the TyG index and the TyG-BMI index were higher in women diagnosed with GDM (p=0.028 and p=0.034, respectively) (Table 2).

All biochemical variables included in Table 2 showed an approximately normal distribution; therefore, parametric tests were used for comparisons.

After adjusting for potential confounders, including maternal age, BMI, smoking status, and parity, the TyG index remained significantly associated with GDM [adjusted odds ratio (OR): 1.85, 95% confidence interval (CI):1.14-3.02, p=0.013]. In a separate model, the TyG-BMI index also showed an independent association with GDM (adjusted OR: 1.02, 95% CI: 1.01-1.04, p=0.008).

Table 1. Comparison of demographic and obstetric data according to the presence of GDM

	GDM n=64	Controls n=132	p-value
	Mean ± SD		
Age (years)	29.7±4.1s	29.2±3.9	0.78
BMI (kg/m²)	24.4±3.9	23.5±3.7	0.021
Smoking, n (%)	7 (10.9%)	14 (10.6%)	0.88
Gravidity	3 (1-4)	3 (1-5)	0.82
Parity	2 (1-4)	2 (1-3)	0.88
Birth weight (g)	3370±380	3310±410	0.56
Gestational week	36.2±1.1	38.6±1.2	<0.001

BMI: Body mass index, GDM: Gestational diabetes mellitus, SD: Standard deviation.

DISCUSSION

This study evaluated the relationship between the TyG index and GDM and demonstrated that several metabolic parameters differed between women with and without GDM. Specifically, BMI, TG levels, fasting glucose, and TyG-related indices were higher in the GDM group. Because GDM is typically diagnosed in the late second trimester, identifying reliable markers earlier in pregnancy remains a clinical priority.

The underlying mechanism of GDM is primarily associated with progressive insulin resistance combined with an inadequate compensatory response of pancreatic β-cells.[13] Although homeostasis model assessment of insulin resistance is commonly used to estimate insulin resistance, its routine clinical use is limited by cost and the absence of universally accepted cut-off values. In contrast, the TyG index has emerged as a practical alternative based on routinely available laboratory parameters,[14] making it more feasible for integration into standard antenatal care.

Elevated TyG levels have previously been associated with a range of metabolic and cardiovascular disorders, including metabolic syndrome and type 2 diabetes.[15-18] Consistent with these findings, our results showed higher TyG and TyG-BMI values in women with GDM, suggesting that these indices may reflect underlying metabolic disturbances during pregnancy.

In the present cohort, BMI was significantly greater in the GDM group, supporting the known link between increased adiposity and impaired glucose metabolism. Higher BMI contributes to insulin resistance and may predispose individuals to GDM. Additionally, an earlier gestational age at delivery observed in this group may indicate a higher burden of obstetric complications. Previous reports have shown that GDM is associated with conditions such as preeclampsia, fetal macrosomia, and polyhydramnios, which can lead to earlier delivery.[19] Moreover, maintaining adequate glycemic control is essential, as maternal hyperglycemia is closely associated with adverse perinatal outcomes, including preterm birth.[20]

Table 2. Comparison of biochemical parameters according to the presence of GDM

	GDM n=64	Controls n=132	p-value	Mean difference (95% CI)	Effect size (Cohen's d)	Adjusted p (FDR p-value)
	Mean ± SD					
TC (mg/dL)	204.2±36.52	199.68±33.8	0.26	4.52 (-6.24 to 15.28)	0.13	0.416
TG (mg/dL)	135.68±58.64	112.52±48.82	0.032	23.16 (6.36 to 39.96)	0.44	0.035
FBG (mg/dL)	98.18±18.72	87.26±10.24	0.018	10.92 (5.94 to 15.90)	0.80	0.042
TC/HDL-C	4.19±1.36	4.06±1.26	0.18	0.13 (-0.27 to 0.53)	0.10	0.360
TG/HDL-C	2.81±1.12	2.28±1.12	0.012	0.53 (0.19 to 0.87)	0.47	0.032
HDL-C (mg/dL)	48.62±16.66	49.12±15.76	0.68	-0.50 (-5.44 to 4.44)	-0.03	0.760
LDL-C (mg/dL)	128.36±25.8	129.12±20.64	0.76	-0.76 (-8.08 to 6.56)	-0.03	0.760
LDL-C/HDL-C	2.66±1.02	2.63±1.04	0.46	0.03 (-0.28 to 0.34)	0.03	0.613
TyG-	8.43±0.42	8.28±0.38	0.028	0.15 (0.03 to 0.27)	0.38	Not applicable (primary outcome)
TyG-BMI-	205.69±42.1	194.18±41.8	0.034	11.51 (0.92 to 22.10)	0.27	Not applicable (primary outcome)

All biochemical parameters in this table were compared using Independent Samples t-tests and are presented as mean ± SD. Effect sizes* are reported as Cohen's* d. Secondary biochemical comparisons were adjusted using the Benjamini-Hochberg FDR procedure (p=0.05). Since TyG and TyG-BMI were pre-specified as primary outcomes, FDR-adjusted p-values are not reported for these variables.
GDM: Gestational diabetes mellitus, TC: Total cholesterol, TG: Triglyceride, FBG: Fasting bloodxglucose, HDL-C: high-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TyG: Triglyceride glucose, BMI: Body mass index, SD: Standard deviation.

Analysis of lipid parameters revealed increased TG levels in the GDM group, which may indicate an underlying metabolic imbalance and heightened insulin resistance. Consistent with earlier studies, elevated TG appear more frequently in women with GDM and may play a role in its development.[21] Furthermore, maternal lipid concentrations have been shown to influence fetal growth, with higher TG levels being linked to adverse fetal outcomes.[22] The increased TG/HDL-C ratio observed in our study further supports the presence of an unfavorable metabolic profile in these patients.

Fasting glucose levels were also higher among women with GDM, reflecting impaired glucose regulation. The simultaneous elevation of the TyG and TyG-BMI indices highlights their potential as composite markers that integrate lipid and glucose metabolism. Since these parameters are routinely measured in early pregnancy, the TyG index represents a simple, non-invasive, and cost-effective tool for risk assessment in clinical practice.

A key strength of this study is the combined evaluation of multiple metabolic parameters using a comprehensive statistical approach. In addition to standard hypothesis testing, effect sizes and CIs were reported to clarify the findings' clinical significance. Furthermore, predefining primary outcomes and using false discovery rate correction helped reduce the likelihood of type I error.

Importantly, the association between the TyG index and GDM persisted after adjustment for potential confounding variables, suggesting that TyG may serve as an independent predictor. Our findings are consistent with previous studies reporting a link between higher TyG levels and increased risk of GDM. For example, Pazhohan et al.,[10] reported associations between GDM and metabolic parameters such as fasting glucose, TG, TG/HDL-C ratio, and TyG index. Similarly, Sánchez-García et al.,[11,23] demonstrated that second-trimester TyG measurements may have high sensitivity for GDM screening. Kim et al.,[24] also identified a relationship between pre-pregnancy TyG values and GDM risk, particularly in primiparous women. In addition, a meta-analysis by Song et al.,[25] confirmed that elevated TyG levels are independently associated with GDM.

Overall, these results emphasize the importance of early recognition of metabolic risk factors during pregnancy. Early identification and appropriate management strategies are essential to improving both maternal and neonatal outcomes. The inclusion of multiple biochemical indicators further enhances the clinical applicability of our findings.

Study Limitations

Several limitations of this study should be acknowledged. First, the retrospective nature of the design restricts the ability to draw definitive causal inferences and may result in incomplete or biased data collection. Second, the relatively small sample size may have reduced the statistical power of the analyses, particularly for subgroup analyses.

Furthermore, potentially influential factors, such as dietary habits, physical activity, and lifestyle characteristics were not assessed, which may limit interpretation of the findings. The single-center setting reduces external validity and may limit generalizability to broader populations.

Although adjustments were made using multivariable regression models, the possibility of residual confounding cannot be entirely ruled out. Unmeasured variables, including socioeconomic status, nutritional patterns, physical activity levels, and family history of diabetes, may still have influenced the observed associations.

CONCLUSION

This study highlights the potential utility of the TyG index as a predictor of GDM. Given its reliance on routinely obtained laboratory parameters, the TyG index may serve as a practical and accessible tool for early risk assessment during pregnancy and may be incorporated into standard obstetric care. Early identification of high-risk individuals may enable timely preventive strategies and improved clinical management. Nevertheless, larger-scale prospective studies are needed to further validate these findings and clarify the clinical applicability of the TyG index.

MAIN POINTS

- The TG/HDL-C ratio, triglyceride-glucose (TyG), and TyG-body mass index (BMI) values were higher in the gestational diabetes mellitus (GDM) group, demonstrating the role of metabolic disorders in GDM development.
- High TyG and TyG-BMI indices can be considered potential early biomarkers for GDM, thus offering a practical and easily applicable screening tool in addition to the classic oral glucose tolerance test.
- The gestational age at delivery was significantly earlier in the GDM group, highlighting the importance of early diagnosis and close follow-up to prevent pregnancy complications.

ETHICS

Ethics Committee Approval: This retrospective case-control study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Ethical approval was obtained from the institutional Buca Seyfi Demirsoy Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 2024/372, date: 25.12.2024).

Informed Consent: Written informed consent was obtained from all participants prior to inclusion.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.A., M.E.P., Concept: U.A., M.E.P., Design: O.Y., T.B.B., Data Collection and/or Processing: H.A.A., M.E.P., Analysis and/or Interpretation: O.Y., M.E.P., S.E., Literature Search: O.Y., T.B.B., Writing: C.A., A.İ.

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RESEARCH ARTICLE

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Relationships Among Clinical, Biomechanical, and Psychological Parameters in Individuals with Subacromial Impingement Syndrome

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Abstract

BACKGROUND/AIMS: This study aimed to investigate the relationships among acromio-humeral distance (AHD), ultrasonographic tendon thicknesses, pain intensity, kinesiophobia, functional status, and postural parameters in individuals with subacromial impingement syndrome (SAPS).

MATERIALS AND METHODS: Forty-four individuals diagnosed with SAPS were included in this cross-sectional study. AHD and rotator cuff tendon thicknesses were assessed using ultrasonography. Pain intensity was evaluated using the visual analog scale and the McGill Pain Questionnaire. Upper extremity disability was assessed using the Disabilities of the Arm, Shoulder and Hand (DASH) scale, while kinesiophobia levels were evaluated using the Fear-Avoidance Beliefs Questionnaire (FABQ). Postural alignment was analyzed with the AI-based Posture Evaluation and Correction System® (APECS®) system. Associations among the study variables were analysed using Pearson correlation analysis.

RESULTS: No significant relationships were found between AHD and pain intensity, disability, or tendon thickness ($p>0.05$). However, a weak negative correlation was observed between AHD and the kyphotic posture parameter [APECS- lateral body alignment (LBA)]. Pain intensity and higher FABQ scores were positively associated with greater upper extremity disability (DASH). FABQ showed a moderate-to-strong positive correlation with DASH scores. Among postural parameters, LBA was associated with AHD and with the thicknesses of supraspinatus tendon, infraspinatus tendon, and long head of biceps tendon. Additionally, anterior knee alignment and head tilt were positively correlated with tendon thickness measurements.

CONCLUSION: Our findings suggest that postural deviations may be associated with tendon characteristics and subacromial space parameters in individuals with SAPS. Additionally, the observed relationships between kinesiophobia, pain, and disability may highlight the importance of psychosocial factors. However, these findings should be interpreted with caution due to the cross-sectional design, and further longitudinal studies are needed.

Keywords: Subacromial impingement syndrome, posture, ultrasonography, acromio-humeral distance, rotator cuff tendon thickness

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INTRODUCTION

Shoulder pathologies are a common complaint in musculoskeletal injuries, with subacromial impingement syndrome (SAPS) accounting for a significant proportion of these pathologies.[1] SAPS is characterised by increased mechanical stress, impingement, and inflammation of the rotator cuff structures located between the acromion and the humeral head during arm elevation.[1,2]

Both internal and external causes related to the shoulder complex are assumed to play a role in the emergence of this pathology by causing narrowing of the acromio-humeral distance (AHD).[3] Additionally, disorders affecting upper-extremity posture, such as shoulder protraction, anterior head tilt (ANHT), and thoracic kyphosis, may adversely impair the biomechanics of the shoulder complex.[3] Impaired shoulder architecture may increase the risk of impingement by affecting scapular movement and the subacromial space.[4] Ultrasonographic (US) studies have shown that during shoulder elevation, the AHD narrows within normal physiological limits.[4,5] Kalra et al. [5] demonstrated in their study that upright posture preserves the AHD by approximately 1.2 mm more than kyphotic posture during 45°C shoulder elevation. This finding is important in explaining the effect of postural changes on the AHD.

Although various studies exist on pain, shoulder function, disability, and kinesiophobia in patients with SAPS,[6-8] evidence regarding the effects of posture on AHD and tendon loading is both limited and inconsistent. Therefore, a comprehensive clinical examination of the relationships among posture, AHD, tendon thickness, pain, kinesiophobia, and disability parameters will contribute to a better understanding of SAPS pathomechanics and the development of appropriate treatment strategies. In particular, the examination of the relationship among postural factors, AHD, and tendon thickness may enable clinical assessments to provide simple, non-imaging-based information about these parameters. Furthermore, to our knowledge, few studies have investigated the combined relationships among tendon thickness, AHD, and the aforementioned clinical and postural factors. This study was designed to examine the effects of posture on SAPS development and to assess the relationship between function, disability, kinesiophobia, and tendon thickness, as a complementary component of a previously published investigation.

Therefore, the aim of this study was to investigate the relationships among AHD, US tendon thicknesses, pain intensity, kinesiophobia, functional status, and postural parameters in individuals with SAPS. It was hypothesized that postural alignment and psychosocial factors would be associated with both structural and clinical parameters.

MATERIALS AND METHODS

Participants

Though this cross-sectional study was conducted as part of a doctoral thesis project, it included all 44 eligible individuals aged 18-65 years who presented with shoulder pain between June 2023 and September 2023 and were diagnosed with SAPS based on clinical, radiological, and US examinations. Although derived from the same research framework, the present study differs from previous work in terms of its specific research objectives, an expanded sample, and the inclusion of additional postural assessments. Volunteers who had a shoulder pain complaint lasting more than one month, who had limited passive movement compared to the opposite shoulder, who had positive Neer, Hawkins, and Jobe supraspinatus (SSp) tests for impingement, and who were able to communicate were eligible for inclusion. Individuals presenting with a neurological condition affecting the upper extremity or with neurological findings related to cervical disc herniation were excluded. Patients with complete rupture of one of the rotator cuff tendons, evidence of calcific tendinitis, previous shoulder surgery, or prior receipt of physical therapy, rehabilitation, or corticosteroid injections for the same complaints within the last 6 months were excluded from the study. Based on the study by Emadi et al.,[8] the sample size required for an effect size of 0.894 and $\alpha=0.05$ at a 95% ($1-\beta=0.95$) power level was calculated to be 38 individuals using the G*Power 3.1.9.2 software. This effect size was selected due to methodological similarities with the present study, particularly in terms of population characteristics and US assessment. Given the exploratory nature of the present study, the sample size was considered adequate for detecting moderate to large associations. To account for potential data losses, 44 individuals were enrolled in the study. The protocol for this study was approved by the Near East University Ethics Committee (approval no: YDU/2023/115-1751, date: 21.06.2023). All procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Assessment Methods

Acromio-humeral distance

US is a non-invasive, portable imaging method that does not involve ionising radiation and is based on the interaction of high-frequency sound waves with biological tissues.[9] In this study, all measurements were performed using a GE LogiqP6 Pro with a linear transducer. Participants were evaluated in a seated position according to standard shoulder scanning protocols.[9] AHD was measured as the perpendicular distance from the most lateral edge of the acromion to the superior aspect of the humeral head. Rotator cuff tendons, including the SSp, infraspinatus (ISp), and subscapularis (SSc), as well as the long head of biceps tendon (LHBT), were assessed and tendon thicknesses were recorded according to standard anatomical landmarks. All US measurements were performed by the same experienced examiner using standardized procedures.

Pain

The visual analogue scale (VAS) was used to quantify pain intensity, with scores ranging from 0 (no pain) to 10 (worst imaginable pain). Participants indicated their pain levels for rest, activity, and night pain by marking the scale, and the corresponding values were measured in centimetres.[10]

The McGill Melzack Pain Questionnaire provides a multidimensional evaluation of pain by examining sensory qualities, pain characteristics, intensity, and temporal aspects. For quantitative scoring, the total number of descriptors selected in the second section ranges from 0 to 78. The actual pain intensity score in the fourth section ranges from 1 (mild) to 5 (unbearable). The Turkish version of the McGill Pain Questionnaire has demonstrated acceptable validity and reliability.[11]

Kinesiophobia

We assessed kinesiophobia using the Fear-Avoidance Beliefs Questionnaire (FABQ). It includes 16 items divided into two subscales: physical activity and work. The physical activity subscale comprises

five items, whereas the work-related subscale includes eleven items. All items are being scored on a 7-point Likert scale where 0 denotes "strongly disagree" and 6 indicates "strongly agree". Each subscale can be evaluated separately. The physical activity section is scored between 0 and 20 points, and the work section is scored between 0 and 42 points. It is assumed that, as the total score approaches 0, fear-avoidance behaviour within the section decreases, whereas it increases as the score approaches the maximum. The validity and reliability of the scale in Turkish have been established.[12] All questionnaires were administered by a physiotherapist face-to-face.

Function and disability

The DASH-T questionnaire was used to assess physical impairments and symptoms in order to evaluate upper extremity disability. It consists of 30 questions.[13] The first 21 questions assess the patient's difficulty with daily living activities; five questions assess symptoms (pain, activity-related pain, tingling, stiffness, weakness); and the remaining four questions each assess social function, work, sleep, and the patient's self-confidence. A total score ranging from 0 to 100 is obtained. High scores indicate severe disability (0 points: no disability; 100 points: maximum disability). The validity and reliability of the questionnaire in Turkish have been established.[14]

Postural Assessment

Postural assessment was performed using an artificial intelligence-based posture analysis system capable of quantitatively evaluating body posture, spinal alignment, joint alignment and angular relationships, as well as overall postural symmetry.[15,16] In this context, postural deviations in individuals diagnosed with SAPS were assessed using the AI-based Posture Evaluation and Correction System® (APECS®) mobile application. All measurements were conducted by the same physiotherapist to ensure consistency. For clarity, APECS variables used in the analysis were defined according to their anatomical representations, including ANHT, anterior knee alignment (ANKA), and lateral body alignment (LBA).

Statistical Analysis

All statistical analyses were performed using SPSS 26.0 software. The distributional characteristics of the variables were assessed using the Shapiro-Wilk test, which showed that the data were normally distributed. Therefore, Pearson correlation analysis was used to evaluate the relationships among US tendon thickness measurements, AHD, pain intensity, kinesiophobia, posture parameters, and functional status because the data were normally distributed. Correlation coefficients were interpreted as very weak (0.00-0.20), weak (0.21-0.40), moderate (0.41-0.60), strong (0.61-0.80), and very strong (0.81-1.00). A significance level of $p<0.05$ was accepted for all statistical analyses. Data were screened for outliers prior to analysis. Given the exploratory nature of the study, more than ten correlations were examined to identify potential relationships among variables. No formal correction for multiple comparisons was applied; therefore, the findings should be interpreted with caution.

RESULTS

Table 1 shows the socio-demographic characteristics of the 44 participants included in the study. The average age of the participants was 42.84±11.97 years, with 54.5% being female. The mean body mass index was 28.41±0.83 kg/m², where 40.9% classified as normal weight, 36.4% as overweight, and 22.7% as obese. The right arm was dominant in 70.5% of cases. Secondary disease was reported in 11.4% of participants. 81.8% worked in light or medium jobs, and 18.2% worked in heavy jobs. The smoking and regular alcohol consumption rates were 31.8% and 11.4%, respectively.

Table 2 presents the results of Pearson correlation analysis between the ultrasound tendon measurements, AHD, pain intensity, kinesiophobia, posture parameters (APECS sub-dimensions), function disability.

No statistically significant correlations were found between most examined clinical and functional variables and participants' AHD values ($p>0.05$). However, a weak-to-moderate negative correlation was observed between AHD and APECS-LBA ($p<0.05$). An increase in lateral posture was associated with a significant decrease in AHD ($r=-0.338$, $p<0.05$) (Figure 1).

Measurements obtained in the US are significantly and positively correlated ($p<0.05$). Accordingly, a positive relationship was found between supraspinatus tendon thickness (SSp-US) and the tendon thicknesses of the ISp-US, SSc-US, and long head of the biceps brachii (LHBT-US), as well as the overall rotator cuff tendon thickness (RC-US), which is calculated as the combined US thickness of the SSp, ISp, and SSc tendons. Furthermore, significant positive correlations were observed between ISp-US and SSc-US, between ISp-US and LHBT-US, between ISp-US and RC-US, between SSc-US and LHBT-US, between SSc-US and RC-US, and between LHBT-US and RC-US ($p<0.05$).

Participants' total FABQ scores showed statistically significant positive correlations with both VAS activity scores ($r=0.491$, $p<0.05$) and McGill total pain scores ($r=0.400$, $p<0.05$). Furthermore, a strong positive correlation was observed between participants' FABQ and DASH scores ($r=0.677$, $p<0.001$) (Figure 2).

The study revealed positive correlations between the APECS subscales and ultrasound measurements among participants ($p<0.05$). The APECS subscales were positively correlated with ANHT scores, SSp, and SSc, while APECS-ANKA scores were positively correlated with SSc and LHBT. Increases in APECS-ANKA scores paralleled increases in LHBT tendon thickness, and a positive, moderately significant relationship was observed between them ($r=0.445$, $p<0.01$). This significant relationship between APECS-ANKA and LHBT-US is shown in Figure 3. In contrast, negative correlations were found between APECS-LBA scores and SSp-US, ISp-US, and LHBT-US ($p<0.05$).

Table 1. Participants' demographic and clinical characteristics

Variable	n	%	Mean ± SD
Gender			
Female	24	54.5	
Male	20	45.5	
Age (years)			42.84±11.97
BMI (kg/m²)			28.40±0.83
Normal (18.5-24.9)	18	40.9	
Overweight (25-29.9)	16	36.4	
Obese (≥30)	10	22.7	
Dominant arm			
Right	31	70.5	
Left	13	29.5	

BMI: Body mass index, SD: Standard deviation.

Table 2. Correlations between clinical, postural, and ultrasonographic measurements

		AHD	SSp-US	ISp-US	SSc-US	LHBT-US	RC-US	VAS-actv	MCGILL total	FABQ total	APECS-ANHT	APECS-ANKA	APECS-LBA	DASH total
AHD	r	1												
SSp-US	r	0.005	1											
ISp-US	r	0.062	0.510**	1										
SSc-US	r	-0.137	0.582**	0.495**	1									
LHBT-US	r	-0.123	0.340*	0.317*	0.547**	1								
RC-US	r	0.08	0.555**	0.497**	0.554**	0.454**	1							
Vas-actv	r	-0.059	0.19	0.18	0.17	0.246	0.261	1						
MCGILL total	r	-0.065	0.174	0.348*	0.119	-0.026	0.15	0.621**	1					
FABQ total	r	-0.266	-0.018	0.046	0.128	0.12	0.087	0.491**	0.400**	1				
APECS-ANHT	r	0.23	0.508**	0.148	0.422**	0.231	0.314*	0.116	0.233	-0.014	1			
APECS-ANKA	r	0.151	-0.096	0.131	0.271	0.445**	0.208	-0.106	-0.21	-0.222	0.271	1		
APECS-LBA	r	-0.338*	-0.410**	-0.377*	-0.246	-0.192	-0.252	0.027	0.209	0.105	-0.126	-0.11	1	
DASH total	r	-0.149	0.057	0.287	0.226	0.069	0.139	0.592**	0.0642**	0.677**	0.021	-0.156	0.275	1

*p<0.05.
**p<0.01.
US: Ultrasonographic, AHD: Acromio-humeral distance, SSp: Supraspinatus tendon, ISp: Infraspinatus tendon, SSc: Subscapularis tendon, LHBT: Long head of biceps tendon, RC: Rotator cuff; FABQ: Fear-Avoidance Beliefs Questionnaire, DASH: Disabilities of the arm, shoulder and hand, APECS: Posture Evaluation and Correction System, Vas-actv: Activity visual analog scale.

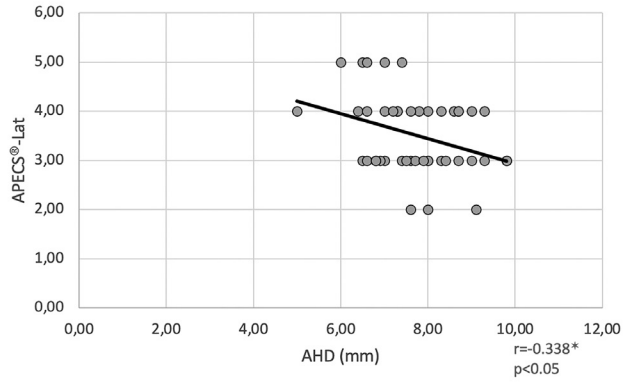

Figure 1. Distribution graph of the relationship between the acromio-humeral distance (AHD) and lateral postural alignment (APECS-LBA). *Indicates statistical significance (p<0.05).

APECS-LBA: Posture Evaluation and Correction System-lateral body alignment.

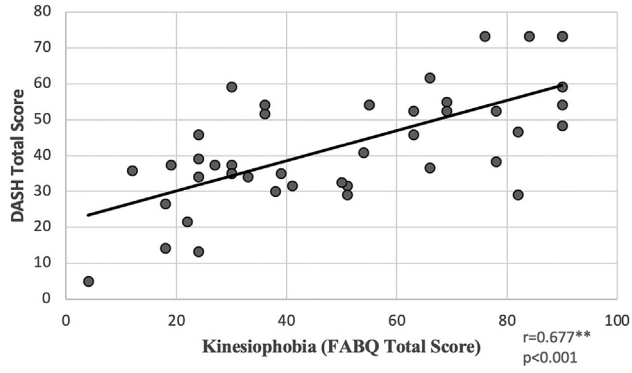

Figure 2. Distribution graph of the relationship between kinesiophobia (FABQ) and upper extremity functional impairment (DASH). **Indicates statistical significance (p<0.001).

FABQ: Fear-Avoidance Beliefs Questionnaire, DASH: Disabilities of the arm, shoulder and hand.

DISCUSSION

The relationship between the musculoskeletal system and body posture plays a fundamental role in both static alignment and functional biomechanics. Previous studies have suggested that thoracic kyphosis and altered scapulothoracic alignment may contribute to the pathomechanics of SAPS, although these relationships have not always been consistently confirmed through clinical assessments.[3,5] The main finding of the present study indicates that AHD was negatively associated with kyphotic posture in individuals with SAPS, while positive associations were observed between postural assessment parameters, such as head tilt, shoulder equality, and knee equality, and the thicknesses of the SSp, SSc, and biceps tendons. These findings may suggest that the pathomechanics of SAPS cannot be explained solely by local tendon structure or subacromial space narrowing; rather, they may reflect a multidimensional interaction among postural alignment, tendon loading, and clinical presentation. From a clinical perspective, this may indicate that, in addition to structural imaging findings, a comprehensive evaluation of the postural chain extending from the lower extremities, through the scapula, to the upper extremities may provide clinically relevant complementary information for decision-making in individuals with SAPS.

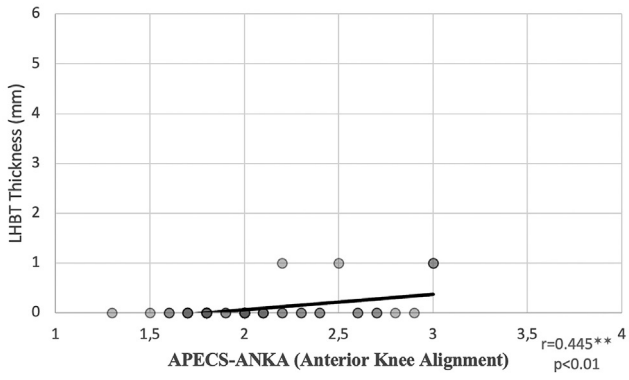

Figure 3. Scatter plot of the relationship between anterior knee alignment (APECS-ANKA) and long head of the biceps tendon thickness measured by ultrasonography (LHBT-US). A positive, statistically significant correlation was observed between APECS-ANKA and LHBT-US (r=0.445, p<0.01).

LHBT: Long head of biceps tendon, US: Ultrasonographic, APECS: Posture Evaluation and Correction System, ANKA: Anterior knee alignment, VAS: Visual analogue scale.

Studies on shoulder pathologies have reported increase in kinesiophobia, pain levels, functional loss, disability and anxiety scores, along with decrease in shoulder range of motion (ROM).[6,7] However, the relationship between these clinical parameters and AHD or tendon thickness remains unclear. Recent studies have reported no consistent association between AHD and clinical findings.[17-20] Consistent with this literature, our study found no significant relationships between AHD and tendon thickness, pain, kinesiophobia, function, or disability. AHD was negatively correlated only with the lateral postural parameter assessed using APECS®, which may suggest that AHD is more sensitive to postural alignment and scapulothoracic biomechanics than to clinical symptoms. A hunched back, characterised by increased thoracic kyphosis, anterior positioning of the head and neck, and scapular protraction, may be associated with alterations in humeral head positioning, potentially contributing to superior translation and reduced AHD. Ito and Kawakami[21] demonstrated that the supine position significantly reduces AHD due to anterosuperior humeral head shift associated with scapular anterior tilt and internal rotation. Kim et al.[22] reported that posterior and upward scapular rotation achieved through muscle training increased AHD. These findings suggest the potential role of scapular position and scapulothoracic rhythm in AHD variation.[22] Supporting this biomechanical framework, Harput et al.[23] showed that reduced scapular upward rotation was associated with superior humeral head displacement, while Bdaiwi et al.[24] reported improvements in AHD following activation of the both lower trapezius and serratus anterior muscle couple force. Eraslan et al.[25] further suggested that AHD is more closely related to muscle strength, scapulothoracic control, and biomechanical balance than to clinical symptoms. Taken together, these findings may indicate that kyphotic posture is associated with reduced AHD, potentially through changes in scapular positioning and humeral head translation. From an interpretative perspective, the lack of association between AHD and clinical parameters in our study, together with its relationship with postural alignment, may support the concept of a structural-functional mismatch in SAPS. The absence of a linear association between AHD and clinical outcomes such as pain and disability may suggest that structural narrowing of the subacromial space alone does not adequately reflect clinical severity. Instead, functional impairment in SAPS may be better understood as a multifactorial interaction among biomechanical alignment, postural adaptations, neuromuscular control, and psychosocial factors rather than by isolated anatomical measurements.

Our study also found that the total thicknesses of the SSp, ISp, SSc, LHBT, and RC tendons were interrelated. These findings suggest that the RC within the shoulder complex may function anatomically and biomechanically as an integrated unit, consistent with current literature. Arrillaga et al.[26] reported that, due to their anatomical proximity, degenerative changes may affect the structure of more than one tendon. Similarly, Kim et al.[27] demonstrated that, the SSp, ISp, and SSc tendons run parallel to each other in healthy adults and may respond collectively to loads while aging. Relatedly, studies in symptomatic population revealed the association of clinical parameters with SSp tendon thickness.[27] For example, Dede et al.[28] reported that SSp thickness may be associated with clinical functional scores. Favoring this finding, Hunter et al.[29] reported that the SSp tendons of patients with SAPS were thicker than those of the healthy individuals and were associated with AHD. Taken together, these findings suggest that RC tendons respond as a functional unit during degeneration, mechanical loading, and compression, potentially due to their anatomical proximity and the continuity of their tendon fibers. When evaluated by thickness, this may reflect a complex and integrated structural organisation rather than independent tendon behaviour.

Numerous studies have examined the relationships among pain, function, kinesiophobia, and shoulder joint ROM in shoulder pathologies. Previous research has consistently demonstrated that reductions in shoulder ROM are associated with increased pain and functional impairment. Anwer et al.[30] reported moderate negative correlations between shoulder flexion, abduction, rotation ROM and pain and functional scores in individuals with shoulder dysfunction. Similarly, Sahinoglu[31] reported that glenohumeral ROM provided limited contribution to functional level, whereas muscle strength and pain intensity were stronger predictors of disability. However, shoulder ROM measurements were not included in the correlation analysis in the present study; therefore, no direct inferences regarding ROM can be drawn from the current findings. Functional outcomes were assessed using the DASH scale. Our findings suggest that increased pain intensity and kinesiophobia were associated with greater functional disability. In line with these findings, higher levels of kinesiophobia were associated with increased pain intensity and disability, which may support the role of fear-avoidance beliefs in symptom severity. These findings suggest that psychological factors, particularly fear-avoidance behaviour, may be stronger determinants of functional disability than isolated biomechanical markers such as tendon thickness or AHD. This structural-functional mismatch may add to the growing body of evidence that clinical severity in SAPS cannot be explained solely by anatomical measurements. Instead, a biopsychosocial framework that integrates psychological and perceptual factors alongside biomechanical assessment may be essential for understanding functional outcomes in individuals with SAPS. These results suggest that functional limitations in SAPS should not be interpreted solely as a consequence of biomechanical factors, but as encompassing an additional interaction between pain intensity and psychosocial factors. Luque-Suarez et al.[6] demonstrated that higher kinesiophobia levels in chronic shoulder pain

were significantly associated with both pain intensity and disability and were linked to poorer clinical outcomes. This relationship was further supported by Martinez-Calderon et al.,[32] who emphasized the role of negative pain beliefs and activity avoidance in perpetuating disability. The significant association observed in this study between DASH scores, pain intensity, and kinesiophobia supports the notion that pain, kinesiophobia, and functional impairment constitute an interrelated clinical framework in SAPS, while their lack of association with structural parameters such as AHD and tendon thickness may highlight the multidimensional nature of clinical symptoms.

In this study, significant correlations were observed between anterior and lateral posture measurements assessed with APECS®, RC tendon thicknesses and AHD, which may support the biomechanical role of postural factors in SAPS. Positive associations between anterior postural parameters (head tilt, shoulder equality, and knee equality) and SSp, SSc, and biceps tendon thicknesses are consistent with evidence that forward head posture and shoulder protraction may adversely affect scapular biomechanics, potentially contributing to increased mechanical stress within the shoulder complex. Weon et al.[33] reported that forward head posture limits serratus anterior muscle activity and scapular upward rotation; Fathollahnejad et al.[34] demonstrated increased stress on shoulder structures associated with forward head and rounded shoulder posture. Khosravi et al.[35] further showed that head posture alterations combined with serratus anterior weakness may negatively affect scapular stabilisation. Additionally, the observed relationship between knee-level equality and the thickness of the LHBT may highlight the influence of the kinetic chain extending from the lower extremity to the shoulder. Previous studies have demonstrated that impairments in the alignment of the knee, pelvis, and thorax can disrupt scapular kinematics and increase loading of the shoulder. Optimal upper extremity movement requires coordinated interaction between the lower extremities, lumbopelvic complex, and the thoracic region,[36] and it has been shown that lumbopelvic stability influences scapular muscle activity.[36,37] Collectively, these findings may support the concept that disruptions along the postural chain may be associated with increased mechanical load on the shoulder complex, consistent with reports linking trunk and lower extremity factors to shoulder pathologies.[38,39] Importantly, the combined use of the APECS® digital posture analysis system and high-frequency US represents a methodological strength of this study, providing an objective and quantitative assessment of postural alignment and tendon structures while minimising observer-related bias. The moderate but significant association between lateral posture and AHD may further support the influence of global postural alignment on local shoulder biomechanics. However, given the cross-sectional design of the present study, causal relationships between the investigated variables cannot be established, and these findings should therefore be interpreted as hypothesis-generating rather than confirmatory. Additionally, given the number of correlations tested, the possibility of a type I error should be considered. Therefore, some of the observed associations may represent false-positive findings and should be interpreted as exploratory.

Study Limitations

Although the sample size of this study is acceptable for clinical research, studies in larger populations may more accurately reveal the strength of these relationships. Furthermore, the study population included individuals with both acute and chronic presentations and did not exclude physically active participants, including athletes; however, subgroup analyses were not performed. Therefore, the findings should be interpreted with caution when generalising them to specific subpopulations, particularly to post-surgical shoulder conditions, which were not represented in the present sample. Finally, posture assessments were performed using the APECS® system, which is based on two-dimensional measurements; as scapular and scapulothoracic motion is inherently three-dimensional and dynamic, this approach may not fully reflect the complex movement characteristics of the scapula during functional upper-extremity activities.

Additionally, because more than 10 correlation analyses were performed, the risk of type I error due to alpha inflation may have increased. Due to the exploratory nature of the study, no post-hoc correction was applied, and the findings should be interpreted with caution. Future studies using multivariable regression models are needed to identify independent predictors.

CONCLUSION

A clinically relevant finding of our study is that kyphotic posture may be associated with AHD and with disputable variations in the thickness of certain tendons. These findings suggest that specific postural parameters may be associated with tendon loading and subacromial space characteristics, and may provide clinically relevant complementary information, particularly in settings with limited assessment tools. Furthermore, the significant association between kinesiophobia and pain intensity, function, and disability may indicate that, in addition to biomechanical approaches in SAPS management, patient education and behavioural strategies targeting psychosocial components could contribute to improved treatment outcomes. Taken together, the consideration of postural factors, tendon structure, and psychosocial components may offer a comprehensive framework for the clinical assessment and management of SAPS; however, these findings should be interpreted with caution because of the study's cross-sectional design. Future longitudinal studies with larger sample sizes and advanced measurement methods, such as three-dimensional motion analysis, are needed to further clarify these relationships.

MAIN POINTS

- Postural parameters, particularly kyphotic posture, showed a significant relationship with acromio-humeral distance (AHD) in individuals with subacromial impingement syndrome (SAPS).
- AHD was not associated with pain intensity, functional disability, or kinesiophobia, suggesting limited clinical value when evaluated in isolation.
- RC tendon thicknesses were interrelated, indicating a collective biomechanical response rather than isolated tendon involvement.
- Kinesiophobia and pain intensity were strongly associated with functional disability, highlighting the importance of psychosocial factors in SAPS.
- Comprehensive postural assessment may provide clinically relevant biomechanical insight beyond conventional imaging-based evaluations.

ETHICS

Ethics Committee Approval: The protocol for this study was approved by the Near East University Ethics Committee (approval no: YDU/2023/115-1751, date: 21.06.2023).

Informed Consent: Written informed consent was obtained from all participants prior to participation in the study.

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Footnotes

Authorship Contributions

Concept: U.K., T.Y., A.Ö., Design: U.K., T.Y., A.Ö., Data Collection and/or Processing: U.K., T.Y., A.Ö., Analysis and/or Interpretation: U.K., T.Y., A.Ö., Literature Search: U.K., Writing: U.K., T.Y., A.Ö.

DISCLOSURES

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CASE REPORT

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Rupture of a Basilar Aneurysm Secondary to Wyburn-Mason Syndrome: A Case Report

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Abstract

Wyburn-Mason syndrome (WMS) is an extremely rare, non-hereditary congenital disorder characterized by arteriovenous malformations (AVMs) that primarily affect the retina and central nervous system and, less commonly, other structures. Its clinical presentation is highly variable, and management is often challenging due to the high risk of morbidity and mortality, particularly in deep lesions that are not amenable to surgical, endovascular, or radiosurgical treatment. We present the case of a young woman with relevant neurologic and ophthalmologic history who developed a massive subarachnoid hemorrhage secondary to rupture of a basilar artery aneurysm associated with a prepontine AVM, a complication that is poorly documented in the literature. The clinical course and fatal outcome are described. This case highlights the severe neurological complications associated with WMS and underscores the importance of early recognition and long-term monitoring in patients with high-risk vascular malformations.

Keywords: Wyburn-Mason syndrome, arteriovenous malformations, subarachnoid hemorrhage, basilar aneurysm, cerebrovascular malformations, neurocutaneous syndromes

INTRODUCTION

Wyburn-Mason Syndrome (WMS), also known as Bonnet-Dechaume-Blanc Syndrome, is a rare non-hereditary neurocutaneous disorder classified among the phakomatoses. It results from abnormal embryological development of the primitive vascular mesoderm shared by the optic vesicle and anterior neural tube, leading to the formation of arteriovenous malformations (AVMs).[1]

These malformations may involve the retina, optic pathway, and central nervous system, resulting in potentially severe ophthalmologic and neurologic complications.

Approximately 30% of patients with retinal involvement also present intracranial AVMs, whereas only 8% of patients with cerebral AVMs demonstrate retinal involvement.[2] Fewer than 100 cases have been reported worldwide over the past six decades, most presenting with

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ophthalmologic manifestations and only a minority presenting with severe neurological complications.

Cerebrofacial arteriovenous metameric syndromes (CAMS) represent a group of congenital vascular disorders characterized by AVMs affecting embryologically related regions of the brain and face. WMS is typically classified as CAMS type II due to the involvement of the optic nerve, optic chiasm, diencephalon, and retina. However, recent literature suggests it may present with overlapping characteristics of other CAMS subtypes.[3,4]

Clinical manifestations depend on the anatomical location and size of the vascular malformations. Ophthalmologic findings may include retinal racemose hemangioma, decreased visual acuity, afferent pupillary defects, and proptosis.[5-7] Neurological manifestations include intracranial hemorrhage, seizures, headache, and progressive neurological deficits.[1] Among these, subarachnoid hemorrhage (SAH) secondary to aneurysm rupture represents one of the most severe and life-threatening complications.

CASE REPORT

A 27-year-old woman presented to a private hospital with progressive loss of consciousness, dysarthria, vomiting, and two generalized tonic-clonic seizures following an episode of intense emotional stress. Her condition was accompanied by quadriparesis, rapid neurological deterioration, pallor, and diaphoresis.

Her medical history included congenital aniridia and left ocular proptosis, which ultimately required enucleation during the neonatal period, as well as epilepsy diagnosed at six years of age.

She had a prepontine AVM associated with WMS, diagnosed 20 years earlier by cerebral angiography, and classified as unsuitable for surgical, endovascular, or radiosurgical treatment because of its anatomical location. Although the original angiographic images were unavailable, computed tomography angiography performed one year earlier confirmed the vascular malformation (Figure 1).

Neuroimaging revealed Fisher grade IV SAH with intraventricular extension and acute hydrocephalus (Figure 2).[8] Imaging findings were consistent with rupture of a basilar artery aneurysm associated with the prepontine AVM, which was determined to be the primary source of the hemorrhage.

The patient developed severe neurological deterioration requiring endotracheal intubation, deep sedation, and ventriculoperitoneal shunt placement. She was transferred to a secondary-level public hospital for comprehensive management.

During her ICU stay, she developed severe hypernatremia, acute renal failure with anuria, hemodynamic instability requiring vasopressors, and respiratory failure requiring mechanical ventilation.

Despite aggressive supportive care, her condition progressed to refractory bradycardia and ultimately to asystole. Advanced cardiopulmonary resuscitation was unsuccessful, and death was declared.

Patient consent was provided by a family member due to the patient's neurological state, it was signed on the 7th of January, 2026 and kept by the main author, a copy has also been provided to the publisher.

DISCUSSION

In this case, the prepontine AVM represented a significant therapeutic challenge due to its deep location and complex vascular anatomy, rendering surgical or endovascular treatment not feasible.[9] Although embolization and radiosurgery are therapeutic alternatives, not all

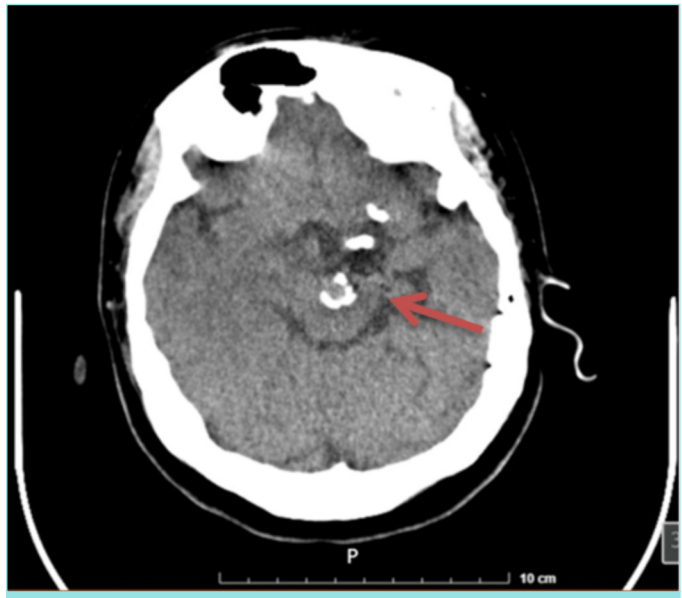

Figure 1. Brain computed tomography angiography demonstrating a prepontine and suprasellar arteriovenous malformation characterized by dilated serpiginous vascular structures arising from the basilar artery (red arrow), with associated calcifications and a nidus measuring 27×25 mm.

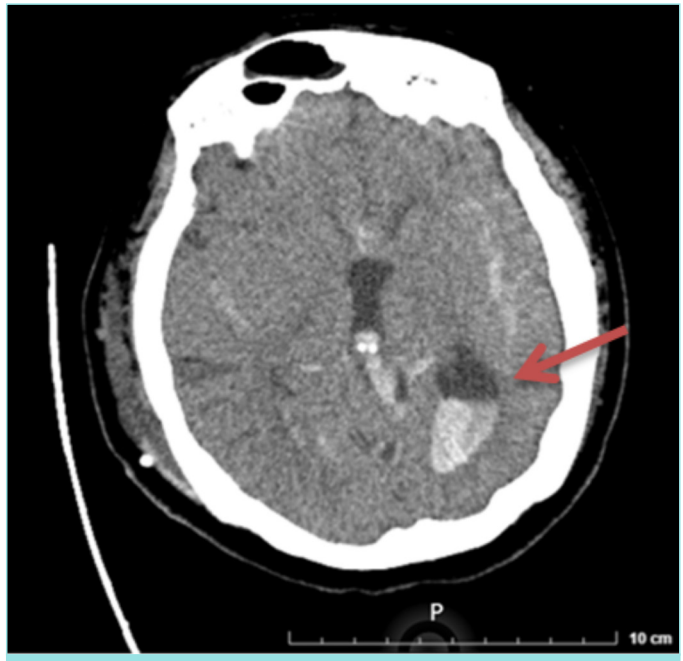

Figure 2. Non-contrast brain computed tomography demonstrates extensive subarachnoid hemorrhage with intraventricular extension (red arrow), ventriculomegaly, and erosion of the left clivus, suggestive of chronic structural changes.

AVMs are amenable to these interventions due to their size, anatomical location, or associated risk of neurological injury. SAH accounts for approximately 3% of all strokes but is associated with disproportionately high mortality and morbidity.[10,11]

The development of aneurysmal rupture associated with WMS represents a rare but devastating complication. Hemodynamic stress and abnormal vascular architecture likely contribute to aneurysm formation and rupture.

This case highlights the importance of long-term monitoring of patients with WMS, as vascular lesions may remain clinically stable for years before catastrophic deterioration.

CONCLUSION

This case report describes a rare, fatal complication of WMS: rupture of a basilar aneurysm associated with a prepontine AVM. WMS remains a poorly understood condition due to its rarity. Early recognition and long-term follow-up are essential to identify high-risk vascular malformations and prevent catastrophic neurological events. Further research is needed to better understand the natural history and optimal management of this condition.

MAIN POINTS

- Wyburn-Mason syndrome (WMS) can cause arteriovenous malformations (AVMs) primarily affecting the retina and central nervous system.
- Sometimes the complexity of their location makes this disease inoperable, turning it into a major therapeutic challenge.
- These AVMs can be asymptomatic throughout much of a patient's life and may present with aneurysmal rupture.
- As far as is known, WMS is a disease with a poor prognosis, and the medical community has not yet established a management protocol, making it a promising area for future research.

ETHICS

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.A.M.G., J.E.V.A., M.P.C.A., Concept: N.A.M.G., L.A.C.S., E.F.R.B., Design: N.A.M.G., J.E.V.A., L.A.C.S., M.P.C.A., E.F.R.B., Data Collection and/or Processing: J.E.V.A., L.A.C.S., M.P.C.A., Analysis and/or Interpretation: N.A.M.G., E.F.R.B., Literature Search: J.E.V.A., L.A.C.S., M.P.C.A., Writing: N.A.M.G., E.F.R.B.

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CASE REPORT

CYPRUS
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Multidisciplinary Surgical Management of a Giant Presacral Schwannoma Involving the Internal Iliac Artery: A Case Report

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Abstract

Presacral (retrorectal) schwannomas are rare, benign tumors originating from the Schwann cells of the sacral nerve roots. Their deep pelvic location and proximity to major neurovascular structures make surgical management challenging. We report a case of a 57-year-old postmenopausal woman who presented with postmenopausal bleeding, an incidental finding that led to the discovery of the pelvic mass, and who was found to have a giant presacral mass involving the left internal iliac artery. Magnetic resonance imaging revealed a 12×8×12 cm lesion, consistent with a Klimo type III schwannoma arising from the presacral region. The tumor was completely excised through an anterior multidisciplinary surgical approach with intraoperative neuromonitoring, followed by total hysterectomy and bilateral salpingo-oophorectomy. The postoperative course was uneventful, and the patient remained disease-free at 39 months of follow-up. This case highlights the importance of meticulous preoperative imaging, multidisciplinary surgical planning, and intraoperative neuromonitoring for the safe management of large presacral schwannomas with major vascular involvement.

Keywords: Presacral schwannoma, klimo classification, pelvic tumor, internal iliac artery, multidisciplinary surgery

INTRODUCTION

Schwannomas, also referred to as neurilemmomas, are benign tumors originating from well-differentiated Schwann cells of the peripheral nerve sheath. They represent the most common benign tumors of the peripheral nervous system and typically exhibit slow growth and an indolent clinical course. Because of their gradual enlargement, many patients remain asymptomatic for long periods, and tumors are often detected incidentally during imaging performed for unrelated reasons. Malignant transformation is extremely rare and is most commonly associated with neurofibromatosis type 1 or prior radiation exposure.[1,2]

Schwannomas arising from the sacral nerve roots and extending into the presacral or retrorectal space are particularly rare.[3] Their deep pelvic location and close anatomical relationship with major neurovascular structures and pelvic organs often complicate both diagnosis and surgical management. The Klimo classification system categorizes sacral schwannomas into three types based on their anatomical location: type I (confined within the sacrum), type II (extending beyond the sacral bone margins), and type III (located entirely in the presacral space).[4] Because type III schwannomas are located within the presacral space, they are often in close proximity to major pelvic vessels, thereby increasing the risk of vascular involvement and significant intraoperative bleeding.

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Preoperative imaging, particularly magnetic resonance imaging (MRI), plays a crucial role in defining tumor size, anatomical relationships, and potential involvement of surrounding structures, thereby facilitating appropriate surgical planning.[5,6]

We report a rare case of a giant presacral schwannoma involving the internal iliac artery, which was successfully managed through a multidisciplinary surgical approach at our tertiary referral center. This case highlights the importance of detailed preoperative imaging and coordinated surgical planning in the safe management of giant presacral tumors.

CASE REPORT

A 57-year-old postmenopausal woman was referred to our tertiary referral center in November 2022 with postmenopausal bleeding and a pelvic mass detected on abdominal computed tomography. Pelvic examination revealed a heterogeneous mass with both solid and cystic components extending into the abdomen; the patient had no neurological symptoms such as radicular pain. Transvaginal ultrasonography demonstrated a myomatous uterus, normal-appearing ovaries, and a solid, hyperechoic mass with cystic components extending into the upper abdomen. Tumor markers and other laboratory findings were within normal limits.

Pelvic MRI, performed for further evaluation, demonstrated a 12×8×12 cm lesion arising from the presacral region (Figure 1). The patient's medical and family histories were unremarkable. Based on radiological findings, the lesion was classified as a Klimo type III presacral schwannoma. Preoperative cervical cytology and endometrial sampling (pipelle biopsy) were normal. Because the patient had a myomatous uterus associated with abnormal bleeding , a concomitant hysterectomy was planned. The case was discussed at a multidisciplinary team meeting involving neurosurgeons and radiologists, and it was decided to proceed with a combined surgical procedure via an anterior approach.

At exploratory laparotomy, a well-circumscribed presacral mass measuring approximately 12×12 cm and arising from the sacral region was identified, occupying a large portion of the pelvic cavity. A myomatous uterus and normal adnexal structures were also observed. Bilateral retroperitoneal dissection was performed, and both ureters were identified and suspended for protection. The retrorectal space was entered, dissection planes were developed, and the rectosigmoid colon was mobilized laterally. To minimize the risk of hemorrhage, major pelvic arterial and venous structures were carefully identified and controlled (Figure 2). Tumor dissection resulted in approximately 1200 mL of intraoperative blood loss, attributable to tumor invasion of the left internal iliac artery and diffuse bleeding from the presacral venous plexus. Blood loss was estimated by the anesthesia team based on the volume collected in the suction reservoir. Three units of packed red blood cells were transfused intraoperatively. Intraoperative neuromonitoring was performed at the neurosurgical team's request because of the tumor's close proximity to the sacral nerve roots. Neural signals from the first and second sacral nerve roots nerve roots were detected during dissection, allowing complete tumor excision without neurological complications.

Following tumor resection, total hysterectomy with bilateral salpingo-oophorectomy was performed. The postoperative course was uneventful, and the patient was discharged on postoperative day 4 without neurological deficits. Histopathological examination revealed spindle cell proliferation with nuclear palisading and verocay body formation, consistent with schwannoma. Immunohistochemical staining demonstrated diffuse, strong S100 positivity in tumor cells. No evidence of atypia or necrosis was identified (Figure 3). At the 39-month follow-up, the patient remained asymptomatic, and a follow-up MRI demonstrated no evidence of residual or recurrent disease. Written informed consent for publication of this case report and the accompanying images was obtained from the patient.

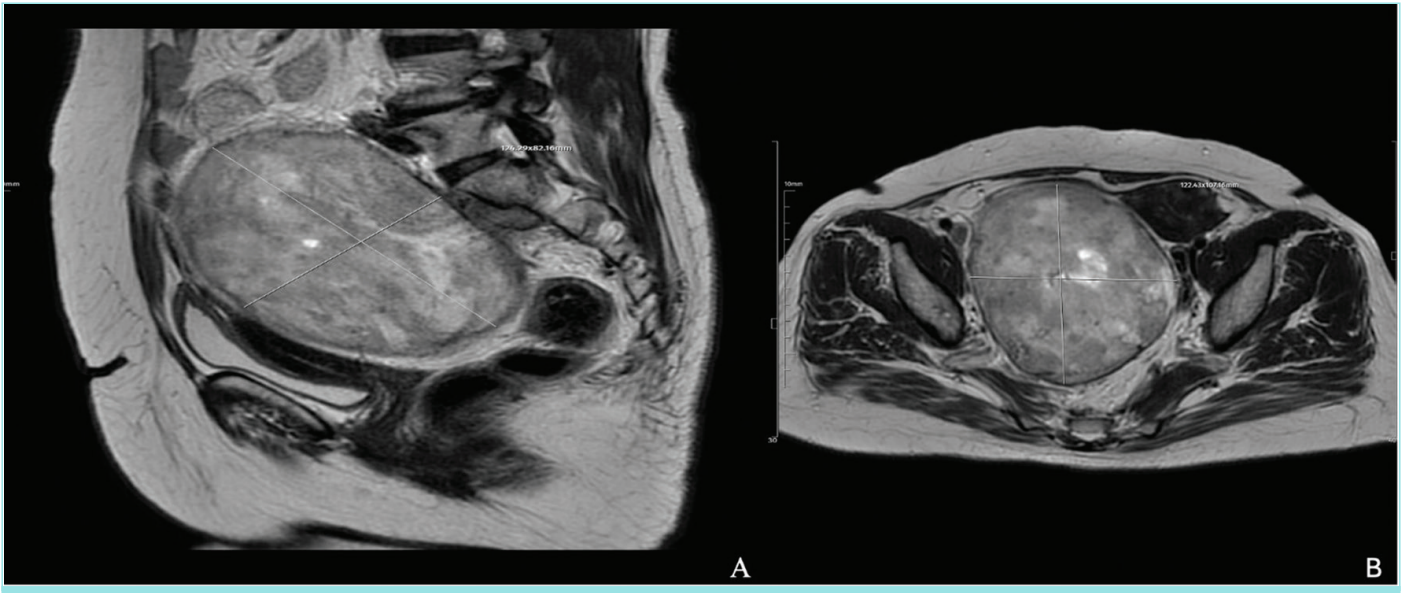

Figure 1. Pelvic magnetic resonance imaging. **A)** Sagittal view demonstrating a large presacral mass measuring approximately 128×82×122 mm. **B)** Axial view showing the lesion with a prominent solid component and cystic areas.

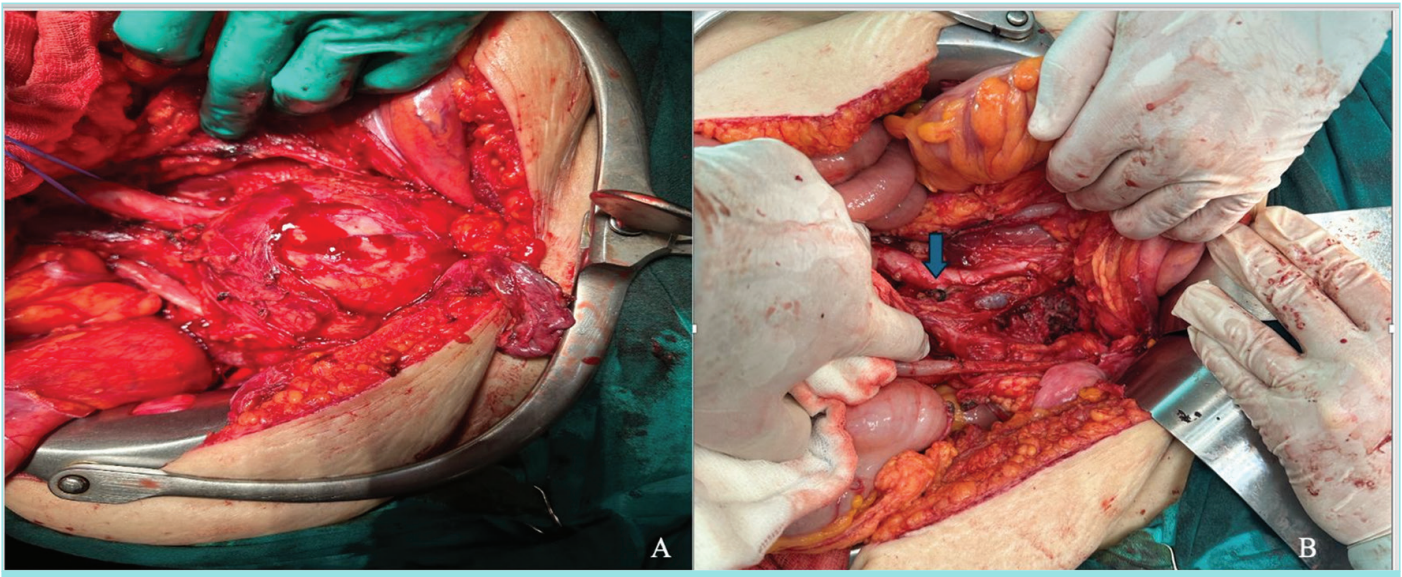

Figure 2. A) Intraoperative view of the giant presacral schwannoma. **B)** Postoperative view after tumor resection. The blue arrow indicates the ligated left internal iliac artery.

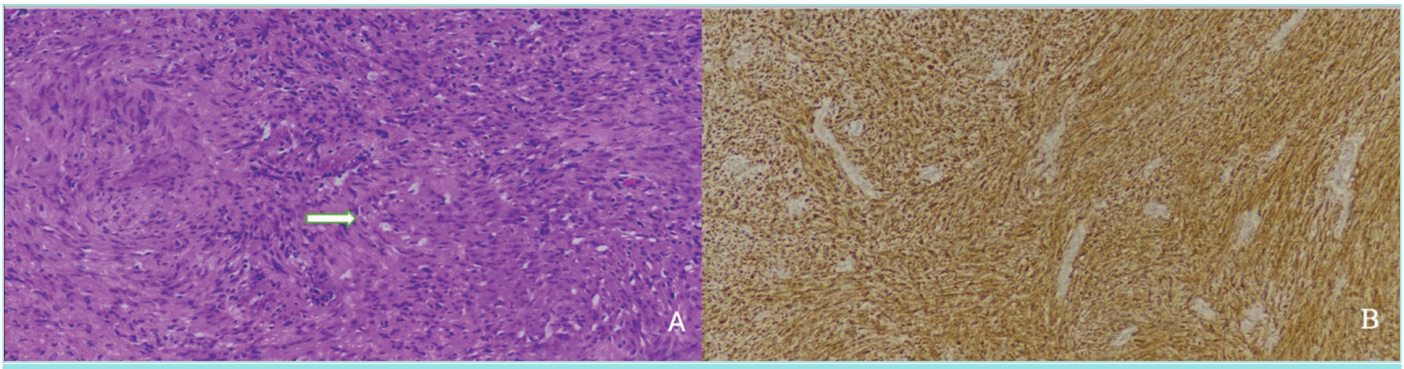

Figure 3. A) Histopathological examination showing spindle cell proliferation with nuclear palisading and Verocay bodies, consistent with schwannoma. **B)** Immunohistochemical staining demonstrated diffuse, strong S100 positivity.

DISCUSSION

Presacral schwannomas are rare benign tumors that arise from Schwann cells and represent a small proportion of all schwannomas. Their occurrence in the sacral or retrorectal region is particularly uncommon. Although schwannomas are typically benign, their deep pelvic location can make diagnosis and surgical management challenging because of their close relationship with major neurovascular structures and pelvic organs.[7] For this reason, careful preoperative imaging and multidisciplinary evaluation involving specialties such as neurosurgery and radiology are essential for optimal surgical planning. To our knowledge, a schwannoma with direct invasion of a major pelvic artery is exceedingly rare in the literature. While vascular involvement has been sporadically reported in iliac vessel schwannomas,[8] complete surgical resection of a Klimo type III presacral schwannoma with internal iliac artery invasion, managed through a multidisciplinary approach with intraoperative neuromonitoring and a 39-month disease-free follow-up, has not been previously described. This represents the primary novelty of the present case.

Complete surgical excision is considered the treatment of choice for pelvic schwannomas.[9] However, in cases of large presacral tumors, achieving complete resection may be technically demanding because these tumors are often located near major vessels and neural structures. A multidisciplinary surgical approach is therefore crucial, involving gynecologic oncologists familiar with retroperitoneal anatomy, radiologists who can accurately evaluate the tumor's relationship with major vascular structures, and neurosurgeons experienced in the management of nerve sheath tumors. Subtotal resection may be necessary to reduce the risk of major bleeding or irreversible neurological damage.[10] Although minimally invasive laparoscopic approaches have been increasingly reported for presacral schwannomas,[11] open anterior laparotomy was preferred in our case due to the tumor's large size (12 cm) and major vascular involvement of the left internal iliac artery, which carried a significant risk of intraoperative hemorrhage. The anterior approach was selected over posterior or combined approaches, as it provided direct access to major pelvic vessels, enabling rapid vascular control, a critical consideration given the internal iliac artery involvement.[3,10] Pennington et al.[3,10] and Sarhan et al.[7] reported that

complete resection is achievable in the majority of Klimo Type III schwannomas; however, subtotal resection may be considered when complete excision poses unacceptable neurological risk. In our case, complete resection was achieved without neurological deficit and was supported by intraoperative neuromonitoring; this outcome is consistent with the best results reported in the literature. Several reports have noted that the close anatomical relationship between presacral schwannomas and major pelvic vessels can increase the risk of bleeding during surgical dissection.[11,12] In our case, approximately 1200 mL of intraoperative blood loss occurred because of tumor involvement of the left internal iliac artery, necessitating arterial ligation to achieve hemostasis. This finding underscores the importance of careful preoperative vascular assessment and multidisciplinary surgical planning. Ligation of the left internal iliac artery was well-tolerated, and no postoperative complications, such as gluteal ischemia or impaired pelvic organ perfusion, were observed. Follow-up MRI performed during the 39-month postoperative period demonstrated no ischemic changes in the pelvic region, consistent with the well-established safety profile of unilateral internal iliac artery ligation due to the rich collateral pelvic circulation.

Preoperative imaging is essential in the evaluation of presacral schwannomas. MRI provides important information about tumor size, anatomical location, and its relationship to surrounding structures. MRI also helps differentiate schwannomas from other presacral or retrorectal tumors. In our patient, MRI demonstrated a large presacral mass measuring 12×8×12 cm and allowed classification of the lesion as a Klimo type III schwannoma.[4] The imaging findings also suggested involvement of adjacent vascular structures. Because of the tumor's large size and deep presacral location, a multidisciplinary surgical approach involving both gynecologic oncology and neurosurgical teams was adopted. The tumor was approached through an anterior laparotomy, which provided adequate exposure of the pelvic cavity and surrounding structures. In large presacral tumors, dense adhesions and bleeding from the presacral venous plexus are frequently encountered.

Therefore, critical anatomical structures, including the ureters and major pelvic vessels, should be carefully identified and protected before tumor resection. Despite significant intraoperative bleeding in our case, coordinated management by an experienced multidisciplinary team enabled effective hemostasis and complete tumor removal. The involvement of multiple specialties facilitated safe dissection around the sacral nerve roots and major vascular structures, thereby minimizing surgical complications. Intraoperative neuromonitoring played an additional role in preserving neural integrity during tumor dissection. Real-time monitoring of neural signals allowed the surgical team to identify and protect sacral nerve roots, thereby reducing the risk of postoperative neurological deficits. Previous studies have similarly demonstrated that neuromonitoring can be useful in complex nerve sheath tumor surgeries to preserve neural function.[13,14]

Although schwannomas are predominantly benign tumors, malignant transformation into malignant peripheral nerve sheath tumors is extremely rare and occurs in less than 1% of sporadic cases.[15] Certain histopathological features, including increased mitotic activity, nuclear pleomorphism, necrosis, loss of encapsulation, and infiltrative growth patterns, may suggest malignant potential. Therefore, careful histopathological evaluation remains essential following tumor excision. No histopathological features suggesting malignancy were identified. Complete surgical excision remains the primary treatment for schwannomas. Adjuvant therapies are generally not required for benign lesions but may be considered in cases of malignant transformation, positive margins, or recurrent disease.[16] Long-term follow-up is recommended even after complete resection because recurrence may occur, albeit rarely.

CONCLUSION

This case highlights the importance of multidisciplinary surgical management in giant presacral schwannomas with major vascular involvement. To our knowledge, this is one of the few reported cases of a Klimo type III presacral schwannoma with direct internal iliac artery invasion that were managed via an open anterior approach with intraoperative neuromonitoring, demonstrating that complete resection is achievable even with major vascular involvement. Long-term follow-up remains essential.

MAIN POINTS

- Presacral schwannomas are rare benign tumors that may present as large pelvic masses and mimic other retrorectal lesions.
- Preoperative imaging is essential to evaluate tumor size, anatomical relationships, and potential vascular involvement.
- Multidisciplinary surgical management with intraoperative neuromonitoring can facilitate safe resection of large presacral schwannomas.
- Careful surgical planning is crucial in cases of major vascular involvement to minimize intraoperative complications.

ETHICS

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.H., İ.U., Concept: C.H., F.Ş.D., Design: C.H., N.Ö., B.T., Data Collection and/or Processing: C.H., N.Ö., İ.U., Analysis and/or Interpretation: C.H., B.T., Literature Search: C.H., F.Ş.D., Writing: C.H.

DISCLOSURES

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CASE REPORT

CYPRUS
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Cyprus J Med Sci 2026;11(3):239-242

Facilitating Transfemoral Transcatheter Aortic Valve Implantation in Severe Peripheral Artery Disease Using Iliac Stenting and Radiopaque Contrast Lubrication: A Case Report

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Abstract

In this case report we aimed to explain how a severe aortic stenosis patient whom has severe stenosis in the peripherial artery was successfully treated after implanting greft stent to peripherial artery stenosis. After implanting greft stent, transcatheter aortic valve implantation (TAVI) valve can pass easily through the stent by lubricating valve with opaq material and propofol. During challenging anatomy and severe stenosis of iliac artery, predilatation and stenting is very important for successfull TAVI procedure.

Keywords: Aortic stenosis, cardiovascular disease, peripherial arterial disease, TAVI

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an alternative to surgery for patients with severe symptomatic aortic stenosis and is increasingly being performed.[1]

When TAVI was first performed, it was limited to high-risk patients; however, recent studies indicate that it can be performed safely in low-risk patients.[2,3]

Current guidelines and studies indicate that 1-year mortality among patients with symptomatic advanced aortic stenosis is significantly increased and that valve replacement is recommended for these patients.[4]

The decision for transcatheter aortic valve replacement or TAVI is determined after the heart team meeting.[5]

At this point, Euroscore is an important parameter in determining the patient's surgical risk and is decisive for the TAVI indication.[5]

TAVI is generally preferred, especially in patients with a history of previous thoracotomy and coronary bypass graft operation, because of the high risk of reoperative heart surgery.[6,7]

However, TAVI can be difficult in patients with severe atherosclerosis and peripheral artery disease. TAVI valves are implanted through a 14-16 Fr. sheath; therefore, the procedure cannot be performed when the lumen gap is less than 5 mm.[8-10]

Severe peripheral arterial disease is a major limitation to transfemoral TAVI. An inadequate iliac artery lumen diameter may prevent the advancement of large-caliber delivery systems, often necessitating alternative access routes. We present a 76-year-old male with severe

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calcific aortic stenosis and bilateral aortoiliac stenosis (minimum lumen diameters: 4.1 mm right, 2.9 mm left), (Figures 1 and 2), who was successfully treated via transfemoral TAVI. Initial balloon predilatation of the right iliac artery was insufficient to allow passage of the valve (Figure 3). A peripheral stent was subsequently implanted (Figure 4). Despite this, device development remained challenging. Lubrication of the TAVI delivery system with radiopaque contrast material facilitated successful crossing of the stented segment. A 29-mm self-expandable valve was implanted without complications (Figure 5). In patients with complex vascular anatomy, stepwise peripheral artery optimization-including balloon dilatation, stenting, and, in selected cases, radiopaque lubrication-may enable successful transfemoral TAVI and avoid alternative access strategies.

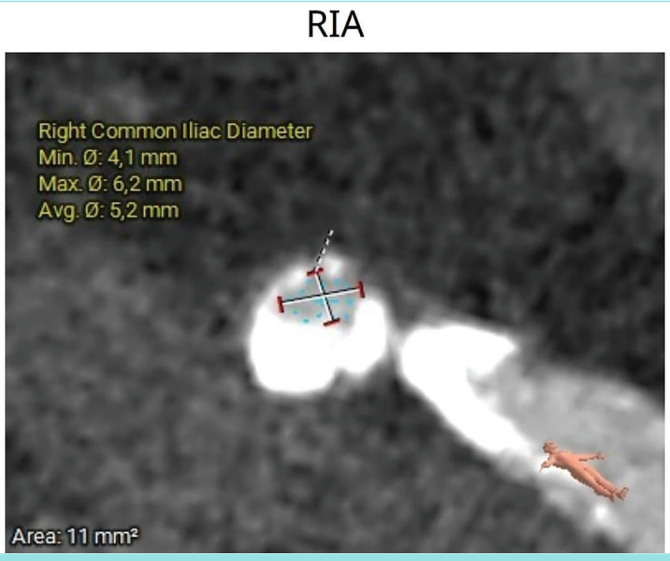

Figure 1. Right common iliac artery stenosis with mean lumen area 11 mm 2.

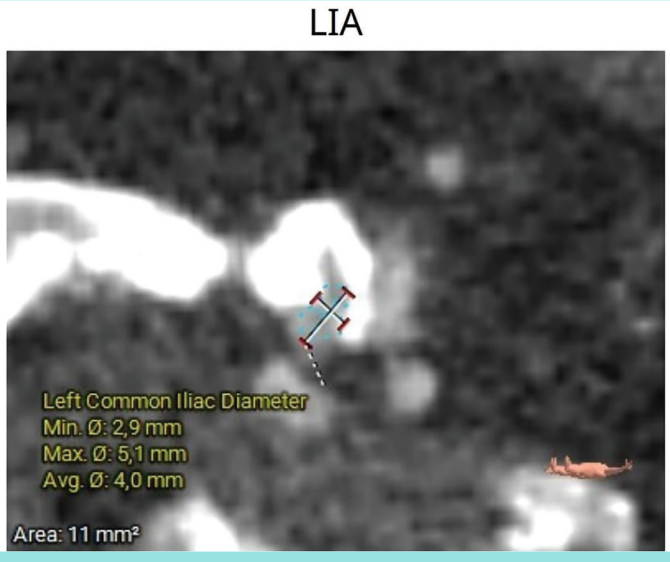

Figure 2. Left common iliac artery stenosis with mean lumen area 11 mm 2.

CASE REPORT

A 76-year-old male patient presented to the emergency department with chest pain and shortness of breath. On examination, the patient was diagnosed with severe calcific aortic stenosis and decompensated heart failure and was subsequently admitted to the cardiology department. The patient underwent coronary artery bypass graft surgery 10 years ago. Internal mammary artery-left anterior descending (IMA-LAD) artery, venous saphenous graft circumflex artery (CX), venous saphenous graft-diagonal and venous saphenous graft right coronary artery (RCA) bypass grafts. The patient has known hypertension and type II diabetes.

The patient was normotensive on Valsartan 160 mg 1x1, amlodipine 5 mg 1x1, and metoprolol 50 mg 1x1. Metformin was administered, and blood glucose was regulated. Renal functions were measured and found to be normal.

Echocardiography showed decreased left ventricular function, measured at 40% by the Simpson method. Hypokinetic areas were observed in the septal and anterolateral segments. The aortic valve was tricuspid and highly calcified. Vmax and Pmean were measured at 4.6 m/s and 48 mmHg, respectively. The valve area was 0.7 cm^2. The patient was clinically stabilized after IV furosemide and underwent coronary angiography. LAD, CX, and RCA were completely occluded. The IMA-LAD graft was open, the RCA saphenous vein graft was open, and the CX and Diagonal saphenous vein grafts were totally occluded. The patient had calcific stenoses of 70-80% in both aortoiliac arteries.

Following evaluation by the Heart team, it was decided that the patient, whose Euro score was 18%, should undergo TAVI. The left subclavian artery diameter was measured as 8.3-9.2 mm. Initially, the entry point was considered to be the left subclavian artery. However,

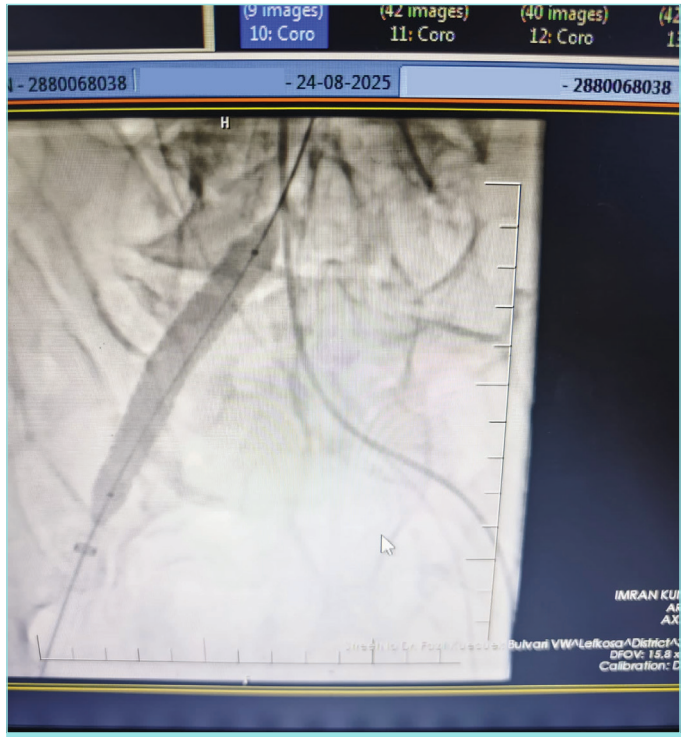

Figure 3. Left iliac artery balloon dilatation.

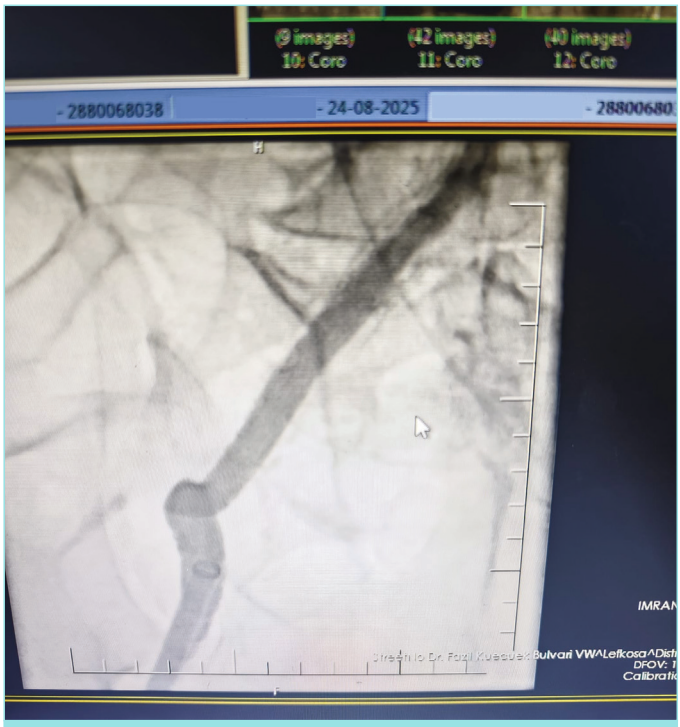

Figure 4. After stent implantationin the left iliac artery.

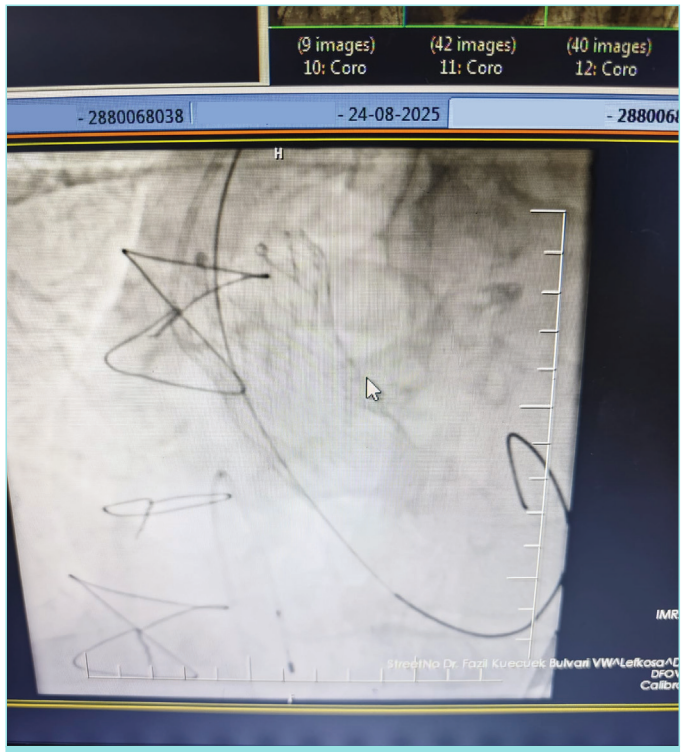

Figure 5. After self expandable aortic valve implantation.

because of severe tortuosity of the left subclavian artery and the risk of decreased left IMA (LIMA) flow from an accordion effect caused by flattening the artery with a stiff wire, the procedure was performed via the transfemoral route. Tomographic measurements were performed, and implantation of a 29 mm Evolute TM self-expandable valve was planned.

In tomographic examinations, the narrowest part of the left aortoiliac region measured 2.9 mm, and that of the right aortoiliac region measured 4.1 mm. The right femoral artery was opened via a surgical cut-down, and the procedure was then started.

A temporary balloon PM was placed via the left femoral vein into the right ventricular apex. A pigtail catheter was placed via the left femoral artery into the noncoronary cusp.

First, an 8-mm x 40-mm peripheral balloon was placed across the stenosis in the right aortoiliac region and dilated to 12 atm. The valve could not be advanced. Subsequently, a 10x60 mm peripheral stent was implanted in that region. An attempt to advance the valve was made again, but the attempt was not successful. The delivery system was flushed with radiopaque contrast material to increase lubrication and this time it could be advanced from the aortoiliac region. The valve was positioned and implanted using the cusp overlapping technique. After the procedure, the peripheral stent was inspected, and no problems were identified. The procedure was completed successfully. After the procedure, the temporary pacemaker was removed because no AV or branch block had developed. The patient was discharged home in good condition after 1 day of monitoring in the coronary intensive care unit and 3 days in the ward.

On echocardiography performed after the procedure, Vmax was 1.4 m/s and pmean was 8 mmHg. No valvular or paravalvular leakage was observed. Written informed consent was obtained from the patient.

DISCUSSION

In patients undergoing TAVI with severe peripheral arterial stenosis, transfemoral access should not be abandoned prematurely. Careful preprocedural planning, balloon predilatation, and peripheral stent implantation can facilitate valve delivery. In selected cases where device advancement remains difficult, radiopaque contrast lubrication may serve as an adjunctive strategy. This approach may help avoid alternative access routes and reduce procedural complexity.

The TAVI procedure can be difficult, and the complication rate can be high in patients with severe peripheral artery disease. Before TAVI, the patient's tomographic and angiographic images should be examined thoroughly, and the access site should be determined according to a clearly defined strategy.[5,10]

Stenosis of the femoral/iliac arteries and insufficient lumen area prevent passage of the valve, and alternative entry sites are preferred. The most commonly used artery other than the iliac artery is the left subclavian or left axillary artery. A lumen diameter of 7 mm and above allows the procedure to be performed, but the patient's LIMA-LAD and saphenous grafts and the native left system were occluded. In addition, this patient has an extremely tortuous subclavian artery, and the stiff wire will flatten the tortuosity, causing an accordion effect that will reduce LIMA flow. The right subclavian artery is not suitable for some patients because of unfavorable angulation. Therefore, transfemoral TAVI should also be considered in patients with peripheral artery

disease. Detailed tomographic examinations should be performed first, and a management strategy for peripheral arterial disease should then be determined. Narrowed areas should be predilated with a peripheral balloon to facilitate valve passage. In some cases, shock wave lithotripsy can modify dense calcific plaques and widen the lumen. However, shock waves are not widely used due to their high cost. If passage is still not achieved after balloon dilatation, the procedure can be continued by implanting a peripheral stent suitable for the vessel diameter.[11]

If passage does not occur despite this, opaque material can be used to increase lubrication, as was applied in this case. Radiopaque contrast agents are viscous liquids that, when applied between the surfaces of the TAVI delivery system, can act as lubricants by reducing friction. These agents create a thin fluid layer that separates the metal or polymer surface of the device from the rough, calcified arterial wall, thereby minimizing direct mechanical contact and abrasive forces. This fluid layer decreases surface-to-surface friction through a mechanism called hydrodynamic lubrication, where the viscous fluid supports part of the load and allows smoother sliding motion.[12] Additionally, the contrast material may fill microscopic irregularities in the vessel wall and device surface, preventing "snagging" on calcific plaques or rough edges.

On the otherhand, previous reports have demonstrated that propofol and radiopaque material have been used to increase lubrication in cases where stents cannot pass in calcific coronary lesions.[13,14] In addition to this, propofol use has been reported in the literature in challenging TAVI cases.[15] No cases of lubrication of the TAVI valve using a radiopaque lubrication method have been reported. A limitation of this study is that it is a single-case experience; the safety and reproducibility of radiopaque lubrication require further validation in larger studies.

CONCLUSION

In such difficult lesions, lubricating the valve with a radiopaque material may be recommended. Finally if there is peripheral artery stenosis during the TAVI procedure, the facilitating mechanism of this procedure is to place a stent in the stenosis of the peripheral artery and to ensure that the TAVI valve is lubricated with radiopaque liquid material so that the TAVI valve can pass through the severe peripherial artery stenosis.

MAIN POINTS

- Severe iliac artery stenosis may preclude transfemoral access during transcatheter aortic valve implantation.
- Stepwise vascular optimization with balloon dilatation and iliac stenting can restore transfemoral feasibility.
- Radiopaque contrast and pofol lubrication of the delivery system may facilitate device passage in selected, difficult cases.

ETHICS

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

Footnotes

Authorship Contributions

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

DISCLOSURES

Conflict of Interest: One author of this article, Cenk Conkbayır, is a member of the Editorial Board of the Cyprus Journal of Medical Sciences. However, he did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other author declared no conflict of interest.

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