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Taichman DB, Sahni P, Pinborg A, et al. Data sharing statements for clinical trials: a requirement of the international committee of medical journal editors [published online June 6, 2017]. Ann Intern Med. doi: 10.7326/M17-1028.

World Health Organization. WHO Criteria for Diagnosis of Osteoporosis. Last Accessed Date: 15.06.2017. Available from: http://www.4bonehealth.org/education/world-health-organization-criteria-diagnosis-osteoporosis/

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Message from the Editor-in-Chief

Message from the Editor-in-Chief,

Thanks to all the dedicated reviewers, we have launched the second issue of 2023.

Journal publication is a core professional competency for new career-seeking researchers. Nevertheless, apart from local courseworks and self-deployed algorithms from experts with long experience in medicine, systematic training options in paper publication are not typically offered in graduate programs. The GMJ team has long been in an effort to support authors in finding the correct way of submitting a paper properly, to ease the reviewing period. The increase in the number of papers from young, training, or post-training authors is even more encouraging in this context.

In the current issue of the GMJ, we have interesting original articles, review articles and case reports. As the journal's publishing team, we tried to cover a wide range of articles from different disciplines.

I believe that all the papers published in this issue will have a great influence on diverse research disciplines in medicine.

I would like to thank all submitting authors, reviewers, and editors for their contributions.

M. Ali Gülçelik, M.D., Prof.
Editor-in-Chief

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Association between periodontitis and metabolic syndrome: A review

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Keywords: Metabolic syndrome, periodontitis, oxidative stress, cardiovascular disease, and type 2 diabetes mellitus

ABSTRACT

Periodontitis and metabolic syndrome (MetS) are concerning issues affecting well-being and are prevalent. The MetS comprises a conglomerate of numerous physical conditions that occur concurrently, as well as intensifying the likelihood of heart disease and type 2 diabetes mellitus (T2DM). Periodontitis is a microbial oral condition that causes the loss of tooth attachment and can proceed to edentulism if left untreated. Epidemiologic, experimental, and interventional studies have documented that periodontitis could have a consequence on systemic health and share a common pathway with several chronic noncommunicable diseases, namely DM, cardiovascular disease, and MetS. Current data suggest that periodontitis may promote the onset or acceleration of MetS. The overall oxidative load and overactive inflammatory repercussions could be responsible for this interaction. As a result, it is crucial to comprehend the current condition of the association as well as the prospective contribution of periodontitis to MetS. The findings of published studies that provide consistent data on the varied outcomes of periodontitis on MetS are encapsulated in this review. Systematic reviews, meta-analyses, original studies, and review articles were appraised in synthesizing this review, using PubMed and Google Scholar search engines.

Introduction

Periodontitis is a complex multifactorial inflammatory illness presented by dysbiotic plaque biofilms that results in persistent non-resolving and damaging inflammatory responses leading to periodontal attachment and bone loss. It has multifaceted pathophysiology involving microbial, environmental, and host factors (1). Metabolic syndrome (MetS) a burdensome disorder possessed by a range of clinical physical issues and metabolic abnormalities could maximize mortality, through cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (2). MetS, diabetes mellitus (DM), and CVD have been linked to periodontitis. Furthermore, there is evidence that Mets and DM can affect the oral microbiome. The relationship between periodontitis and Mets is considered to be connected by systemic inflammation and insulin resistance, and they may impact one another (3). This review elaborates on the link between periodontitis and MetS, and its association with each of its components.

We conducted a literature search using PubMed and Google Scholar search engines using the keywords “oxidative stress”, “cardiovascular disease”, “type 2 diabetes mellitus”, “metabolic syndrome”, “periodontitis”, “obesity”, and “dyslipidemia”. Systematic reviews, meta-analyses, original studies, and current reviews describing the interaction between periodontitis and MetS were appraised in synthesizing this review.

Metabolic syndrome and its definition

In 1988, Reaven (4) coined the term MetS, also cited as syndrome X or insulin resistance syndrome. MetS is recognized as a multifactorial illness with a cluster of interconnected sociodemographic and biochemical traits, as well as immunological and vascular abnormalities. Its risk profile underpins the gradual development of ailments such as CVD and T2DM (5). 20-25% of the global adult population is estimated to be inflicted with MetS (6).

The definition of MetS has been propounded by several health federations, which deviate vaguely, but chiefly centering on overweight (notably central adiposity), deranged lipid proportions, elevated blood pressure (BP), and glycemic level (7). The International Diabetes Federation reconceptualized the specification for MetS, as an attempt to avoid the perplexity of several definitions. As per its guidelines, to diagnose MetS, an individual must possess central obesity (measured as waist circumference, with different values depending on ethnicity) along with any two among the three components (Table 1) (8).

Etiopathogenesis of metabolic syndrome

The etiology of MetS is diverse, including several interacting mechanisms, genetic variants, and environmental variables. A crucial role is witnessed in a sedentary lifestyle, and obesity, besides genetic and epigenetic variables in promoting the disorder (9). Insulin resistance is the most widely supported and unifying concept for interpreting the pathophysiology of MetS, although the molecular link between insulin resistance and the majority of the MetS components is not fully known (8). Major mechanisms leading to MetS are provoked by visceral adiposity, conferred by surplus calorie intake (10).

The elements accounted for the initiation and advancement of MetS to CVD and T2DM chiefly comprise diminished insulin sensitivity, longstanding inflammation, and neurohormonal activation (11). Adipose tissue releases pro-inflammatory cytokines, which may be involved in insulin resistance, lipolysis, and the creation of pro-thrombotic substances by the liver. Thus, the chronic inflammatory state induced by the obese adipose tissue via aberrant adipokine synthesis leads to endothelial dysfunction (12). The inflammatory milieu created by MetS causes endothelial dysfunction, paving the way for the heightened plausibility of CVD and T2DM (13). Of late, the dysbiotic gut microbial community has gained recognition in the genesis of MetS. Thus, the endotoxins released by bacteria in serum, inflammatory vulnerability, and unstable gut microbial community mainly comprise the primary features in the development of MetS (14).

Periodontitis and metabolic syndrome-a common link

The two chronic inflammatory conditions, periodontitis and MetS, are considered to be linked by inflammation. The regionally liberated inflammatory cytokines in the periodontium in response to virulent pathogens or lipopolysaccharides (LPS) could gain access to the systemic circulation, thereby precipitating MetS (15). Diminished insulin sensitivity is generated as a consequence of oxidative stress provoked by the inflammatory status. Oxidative stress induces insulin resistance by altering the intracellular signaling pathway, which paves the way for MetS through elevated BP, deranged lipid profile, and CVD. This suppresses the antioxidant capability in periodontal tissues either by MetS in-toto or by its contributing elements, which disturb the immune response to the microbial assault, thereby inducing periodontal infection (16). Diverse factors of the host immune system exert an impact on periodontitis and MetS. Risk factors include genetic and environmental factors such as older age, smoking, and lifestyle, which are synergistic between the two conditions (17). Poor periodontal conditions with higher prevalence, severity and extension were exhibited among the individuals diagnosed with MetS, highlighting their interrelationship (18).

The results from a case-control study by Gomes-Filho et al. (19) in 2020 concluded that individuals with moderate or severe periodontitis were twice as likely as those without periodontitis to have MetS, with an increased risk among individuals with severe periodontitis. The salivary microbiome of periodontally compromised individuals with MetS expressed an altered microbial composition compared with healthy individuals (3). The samples retrieved from dental implants from individuals with MetS had significantly higher levels of periodontal pathogens, strengthening the systemic impact of MetS (20). The results from an interventional study reflected that C-reactive protein levels were lowered in MetS individuals following periodontal therapy, signifying that a reduction in periodontal inflammation could decrease systemic inflammation and CVD risk (21). In a

Table 1. Components of the metabolic syndrome (8)

Components	Diagnostic values
Abdominal obesity	Measured as waist circumference, with different values depending on gender and ethnicity
Increased triglycerides	≥150 mg/dL or specific treatment for this abnormality
Decreased HDL cholesterol	<40 mg/dL in males; <50 mg/dL in females or specific treatment for this abnormality
High blood pressure	Systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg or treatment of previously diagnosed hypertension
Increased fasting plasma glucose	≥100 mg/dL or previously diagnosed type 2 diabetes

HDL: High-density lipoprotein, BP: Blood pressure

randomized clinical trial among the Japanese population, dental interventions such as periodontal therapy combined with dietary and exercise guidance showed better waist circumference and anthropometric measurements, thereby lowering the risk of MetS (22).

Obesity and periodontitis

Obesity, a cumbersome multifactorial chronic condition, is interpreted as an atypical exorbitant accumulation of fat that presents health distress, with its prevalence accelerating globally (23). The level of abdominal obesity is reported as waist circumference or waist-hip ratio values, as it is deemed superior to the body mass index (24). The 2017 periodontal diseases classification states a critical alliance of obesity with loss of periodontal tissues and a heightened chance of periodontitis, suggesting a comorbidity effect between the two conditions (25). The complex subgingival biofilm in periodontitis, through interaction with host cells, releases proinflammatory cytokines and reactive oxygen species (ROS) accompanied by their raised levels in serum (26). Pro-inflammatory adipokines namely visfatin, leptin, and resistin, are elaborated by chronically inflamed periodontal tissues similar to adipocytes, highlighting the critical role of excessive adipose tissue in the etiopathogenesis of periodontitis. An increase in serum pro-inflammatory cytokines with diminished anti-inflammatory adipokines such as adiponectin, a characteristic feature of obesity, is involved in periodontitis conditions (27). A cohort study in 2022 concluded that individuals with obesity showed a higher proportion of progression of periodontitis with several common risk factors shared by the two conditions (28). Strong evidence points to hyperinsulinemia as a significant precursor to the metabolic disorders linked with obesity (29). Insulin resistance could get augmented under periodontitis conditions, which is evident by the results obtained from a clinical trial conducted in rat models (30). Hyperinsulinemia, evolved from increased insulin secretion augments the absorption of glucose and fat accumulation, thereby manifesting obesity (31).

Insulin resistance or hyperglycemia and periodontitis

DM has a bidirectional and causal link with periodontitis. Better glycemic control has been suggested to minimize the risk and severity of periodontitis. Furthermore, periodontal inflammation resolution can enhance metabolic regulation (32). Subgingival bacteria in periodontitis could penetrate the host tissues or their products, such as LPS that enter the systemic circulation, which is counteracted by an acute-phase protein burst and elevated levels of pro-inflammatory mediators, resulting in insulin resistance (33).

Through the excessive formation of advanced glycation end products (AGEs), DM/hyperglycemia could pave the way for developing periodontitis. Upon binding with receptors for AGEs, periodontal inflammation and destruction are upregulated by the liberation of active inflammatory molecules. Alveolar bone loss can occur due to collagen cross-linking, impaired periodontal tissue renewal, and apoptosis in osteoblastic cells (34). Microbial invasion and enhanced inflammatory processes are amplified by aberrated immune/inflammatory systems such as compromised chemotaxis and phagocytosis of neutrophils and hyperactive macrophages (35).

An ample number of studies have underpinned the interconnection between hyperglycemia and periodontitis. A systematic review by Chopra et al. (36) in 2022 concluded that escalated level of AGEs was evident in blood, salivary secretions, crevicular fluid, and gingival tissues as a consequence of periodontal tissue inflammation. The authors also emphasized that AGE levels were influenced more by the combined effect of DM and periodontitis. Another systematic review and meta-analysis confirmed such a bidirectional relationship, concluding a 34% higher risk of periodontitis in T2DM, whereas the incidence of T2DM increased by 53% in severe periodontitis (37). The study by Mirzaei et al. (38) in 2021 depicted a positive correlation between hyperglycemia and periodontitis, and the management of hyperglycemia could be considered a preventive strategy for periodontitis.

Dyslipidemia and periodontitis

Dyslipidemia is typically defined by elevated blood levels of cholesterol, triglycerides, or both, as well as elevated levels of associated lipoprotein species, with reduced concentration of high-density lipoprotein cholesterol. It constitutes an established independent marker of CVD risk (39). The shared risk elements, genetic predisposition, and overall inflammatory load could act as the possible facets responsible for the interconnection between the two disorders. In response to periodontal microbiota, the host responds with higher levels of numerous common inflammatory mediators in the inflamed periodontal tissues, thus establishing an inflammatory environment (40).

The LPS released by Porphyromonas gingivalis, a key pathogen in periodontal disease due to its proteolytic enzymes, namely gingipains that degrades host proteins, can alter macrophage gene expression, resulting in foam cell development and overexpression of genes encoding cholesterol synthesis that elicit structural changes in circulating lipoproteins via the emission of ROS, which appear to be a risk factor for atherosclerosis (41).

A Japanese study concluded that high triglyceride in conjunction with enhanced lipolysis produced by infection due to endotoxins could be a mechanism by which periodontal disease might promote atherosclerotic change. The authors claimed that visceral adipose tissues, even in individuals without obesity, play a key role in mediating this harmful effect (42). The results of a meta-analysis conducted in 2017,

showed that individuals with periodontitis exhibited a greater probability of elevated blood triglyceride or total cholesterol levels compared with individuals without periodontitis (43).

Hypertension and periodontitis

High BP and periodontitis are widespread conditions with a profound impact on the complications of CVD. Various risk constituents, including demographic status namely age, sex, race, and confounding factors such as smoking, and overweight, DM, are distributed between the two abnormalities (44). Inflammation and oxidative stress initiated by periodontitis may promote functional and anatomic vascular disruptions over a period, leading to arterial stiffness, increased vascular resistance, and volume overload, with an eventual elevation in BP (45). Hypertension is speculated to be a low-grade inflammatory illness entailing the stimulation of the adaptive immune system (46).

T-cells exert a significant role in the onset of hypertension. Activated T-cells cluster in the perivascular region and express cytokines (tissue necrosis factor-α, interleukin-6, 17), encouraging the onset of hypertension (47). An interventional study in 2019 reported that rigorous periodontal therapy was attributed to a fall in the proportion of activated T-cell subsets (48). Significantly greater arterial BP values, as well as a higher tendency to hypertension, have been reported in patients with periodontitis (49). Overlapping inflammatory processes and endothelial dysfunction have been hypothesized as the foundation for the substantial impact of hypertension on individuals with periodontal disease, according to a study result (50).

Conclusion

Most current evidence-based literature indicates that periodontitis can be linked to various systemic diseases, including MetS, through several shared mechanisms to each of its components, thereby contributing a potential role in the emergence of T2DM and CVD. Oxidative stress is a common thread between them, which puts an individual under chronic systemic inflammation. Systemic inflammation may lead to the development of components of MetS in individuals with periodontitis, which ultimately heightens the risk of T2DM and CVD. Most of the pathways in the development of MetS appear driven by abdominal adiposity. In addition, dyslipidemia, hyperglycemia, and hypertension are the potential contributors, which are linked to periodontitis. Furthermore, there is evidence suggesting that periodontal intervention could subside the degree of serum inflammatory molecules, thereby contributing to the reduction in the severity of systemic disorders such as MetS.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.A.K., N.S., A.R.B., Design: B.A.K., N.S., Data Collection or Processing: A.R.B., S.S., Literature Search: B.A.K., N.S., S.S., Writing: B.A.K., N.S.

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Adult proximal humerus locking plate for fixation of paediatric intertrochanteric femoral fractures

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Keywords: Children, intertrochanteric femoral fractures, complete displacement, and adult proximal humerus plate

ABSTRACT

Aims: There are multiple fixation methods for the surgical treatment of intertrochanteric femur fractures in children and adolescents, but there is still no consensus on the optimal implant. Recently, adult proximal humeral locking plates have been advocated for the fixation of these fractures; however, insufficient data is available for their efficacy. This retrospective study evaluated the radiological and clinical outcomes of pediatric intertrochanteric fractures treated with adult humerus proximal plates.

Methods: This was a single-center, retrospective study that included children aged between 11 and 16 years who underwent surgery for intertrochanteric hip fractures using adult proximal humeral locking plates between January 2012 and January 2019. The exclusion criteria were nondisplaced fractures, concomitant musculoskeletal and other system injuries, pathological fractures, and a history of previous surgery on the same hip or femur. The duration of fracture union was evaluated in the follow-up radiographs. Clinical outcomes were evaluated using the Harris hip score (HHS) and Ratliff criteria. All complications during the follow-up were recorded.

Results: The study included 24 children (15 males, nine females) with a mean age of 12.6±1.4 years (11 to 15 years). The mean follow-up time was 34±9.4 months (22 to 60 months). The mean fracture union time was 12.8±2.2 weeks (10 to 16 weeks). The HHS was 92±1.9 (89 to 95) at the final follow-up. All patients were rated good according to the Ratliff criteria. None of the patients had avascular necrosis of the femoral head, nonunion, malunion, limb-length discrepancy, or implant failure at the final follow-up. No patient required revision surgery.

Conclusions: The findings of this study showed that the fixation of pediatric intertrochanteric fractures with adult humerus proximal plates is a successful fixation option that provides good clinical outcomes based on the HHS and Ratliff criteria, and excellent radiological outcome with a high rate of fracture union, with low complication rates.

Introduction

Hip fractures in children are rare compared with adults. They comprise less than one percent of all pediatric fractures (1-4). Moreover, the prevalence in children is less than one percent of the prevalence in adults (3). The incidence is highest in children above 11 years of age (1). Pediatric hip fractures typically result from high-energy trauma, such as a motor vehicle accident or a fall from height (5-7). Standard radiographs are generally sufficient for diagnosis (1). The classification described by Delbet and popularized by Colonna is widely accepted and used to determine treatment and prognosis (1,3,4,6,8). An intertrochanteric hip fracture in a child is classified as type IV by Delbet-Colonna (8). Six to 15 percent of all hip fractures in children are Delbet type IV (1,3).

Hip fractures in children have a high rate of complications and poor outcomes. Complications include avascular necrosis (AVN) of the femoral head, nonunion, malunion, premature physeal closure, chondrolysis, and infection. The most common and serious complication is AVN (1). It develops due to problems in the vascular support of the proximal femoral epiphysis (2).

Although type IV hip fractures in children are extracapsular and metaphyseal, AVN may occur in up to 14% of these fractures (3). Coxa vara, leg length discrepancy, and nonunion are other significant complications in type-IV hip fractures (2,5). These complications generally occur due to injury of the epiphyseal plate, insufficient reduction or loss of reduction due to unstable fixation (2,5).

There is no consensus on the treatment approach for hip fractures in children (1,2). The degree of initial displacement, the timing of reduction, the quality of reduction, the stability of fixation, decompression of the joint, and weight-bearing can influence the development of complications (1,3). After reduction, stable fixation is crucial (1). Dynamic hip screw and side plate and transpyhseal screw fixation can be chosen in type IV hip fractures in children (2,3).

In this study, we examined the use of adult proximal humeral locking plates for the fixation of pediatric intertrochanteric hip fractures. We hypothesized that fixation of pediatric intertrochanteric hip fractures using adult proximal humeral locking plates would provide more stability and reduce the complication rate. Because; adult proximal humeral locking plates adapt to the proximal femoral anatomy in children. Additionally, the wide proximal end of these plates provided a stronger grip on the proximal femur. Transphyseal fixation is not required for stable fixation in these plates, as it is possible to apply more than one screw, or it is possible to apply screws at an angle of 130 degrees corresponding to the femoral neck-shaft angle. Additionally, these plates can be applied with the minimally invasive plate osteosynthesis technique, thus reducing the risk of complications. We evaluated in the current study the outcomes of using this procedure.

Methods

Study design

This single-center, retrospective study included children who underwent surgery for an intertrochanteric hip fracture using an adult proximal humeral locking plate between January 2012 and January 2019. We used the classification system described by Delbet and popularized by Colonna (8). The inclusion criteria were intertrochanteric hip fractures (Delbet type IV) (Figure 1). Another inclusion criterion was age between 11 and 16 years. The exclusion criteria were nondisplaced fracture, concomitant musculoskeletal and other system injuries, pathological fractures, and a history of previous surgery on the same hip or femur. The University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Institutional Review Board approved the study protocol (decision number: 395, date: 06.10.2020), and the study was performed under the ethical standards in the Helsinki Declaration. Informed consent was routinely obtained from the parents.

Surgical techniques and postoperative follow-up

In our clinic, fixation of pediatric intertrochanteric fractures with adult humerus proximal plates is performed as described below;

Under general anesthesia, in the lateral decubitus position under fluoroscopy guidance, an incision (approximately 5-7 cm) is performed on the lateral aspect of the thigh, starting from the tip of the trochanter and extending along the long axis of the thigh for the lateral approach of the hip. Evacuation of the intracapsular hematoma is not applied. After a fluoroscopic check of the adequacy of the reduction, the adult proximal humeral locking plate is placed. An unlocking full threaded screw is applied distal to compress the plate to the bone (Figure 2). Then, using the multi-axial screw capability of the plate 4 unlocking and 2 locking screws with a maximum length of 65 mm are applied up to the femoral neck. All proximal screw applications are performed under fluoroscopy control to ensure that no transphyseal fixation occurs. Finally, distal locking screws (at least three) are applied (Figures 3, 4). Anatomical layers are sutured according to the procedure. The hip and quadriceps exercises are started on the third postoperative day. Partial weight-bearing is advised after four weeks, and full weight-bearing is allowed after six weeks.

Radiological outcomes

Sequential anteroposterior and lateral hip radiographs are taken during the follow-up of a patient to evaluate the fracture union time. Bridging of fracture at three cortices, progressive obliteration of the fracture line, and cortical continuity are the criteria used to assess fracture healing. In addition, in the

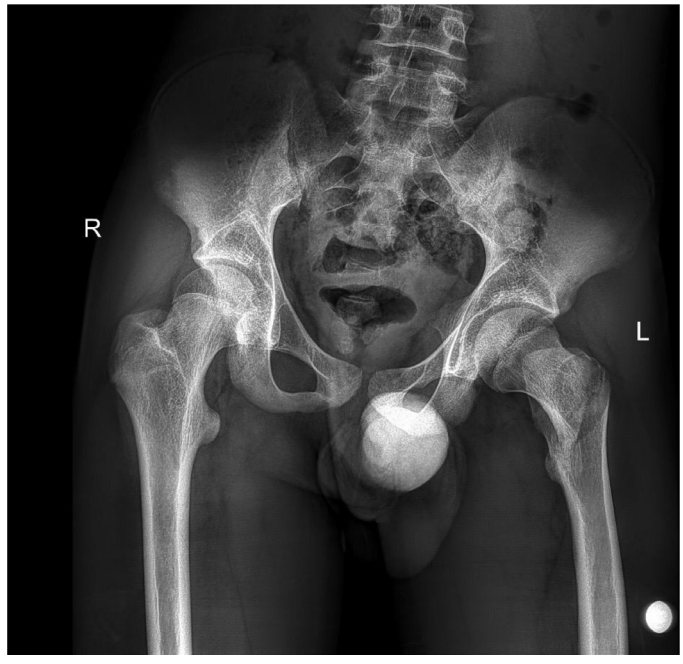

Figure 1. Radiographic imaging of intertrochanteric fracture of the left femur

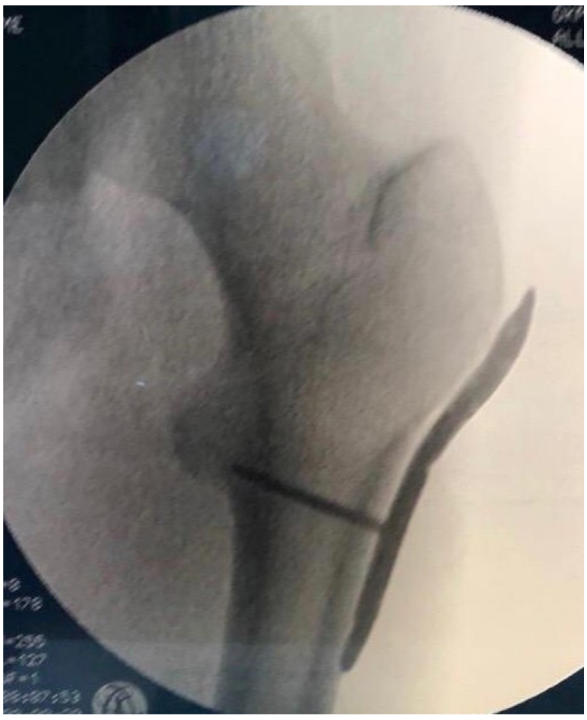

Figure 2. Fluoroscopic imaging showing adapting of the plate in the lateral aspect of the femur

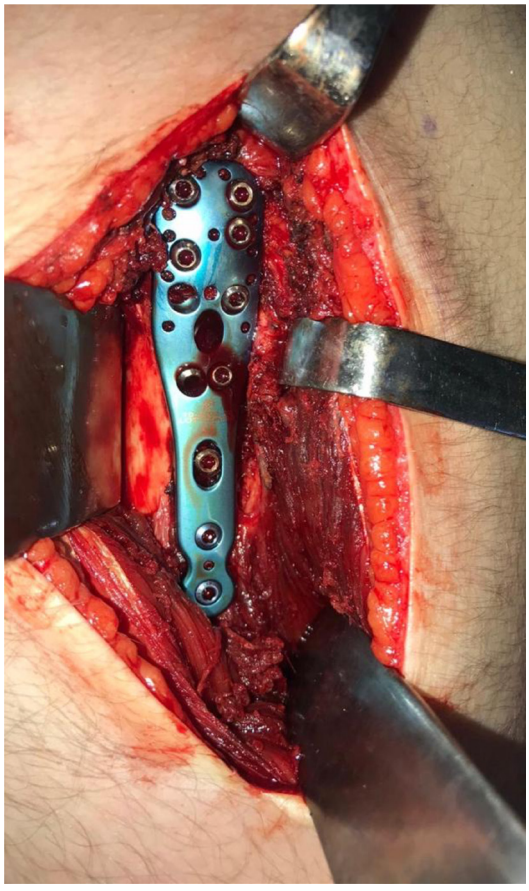

Figure 3. Intra-operative picture showing adult proximal humeral plate applied to the proximal femur

currents study, we evaluated complications such as refracture or deformity that may occur due to the removal of the implant by radiographs during follow-up.

Clinical outcomes

We used the Harris hip score (HHS) (9) to assess hip functions. This instrument contains 10 items divided into 3 categories that include pain, function, range of motion (ROM), and deformity. The first component is a patient-oriented questionnaire and comprises the limitations and activities. The second and third portions which comprise leg length and hip ROM (flexion, abduction, external rotation and adduction) are routinely administered by the physician. Each item has its scale, which correlates with the descriptive response alternatives. A higher score indicates good function, whereas a lower score indicates hip dysfunction. Furthermore, we used the Ratliff criteria (10) (based on hip pain, ROM, daily activities, and radiological findings) to evaluate the clinical status during follow-up (Table 1).

Statistical Analysis

We used the Statistical Package for the Social Sciences for Windows version 20.0 software (SPSS Inc. Chicago, Ill. USA) for statistical analyses. Descriptive statistics included mean±standard deviation (SD), median, minimum, maximum, frequency, and ratio values.

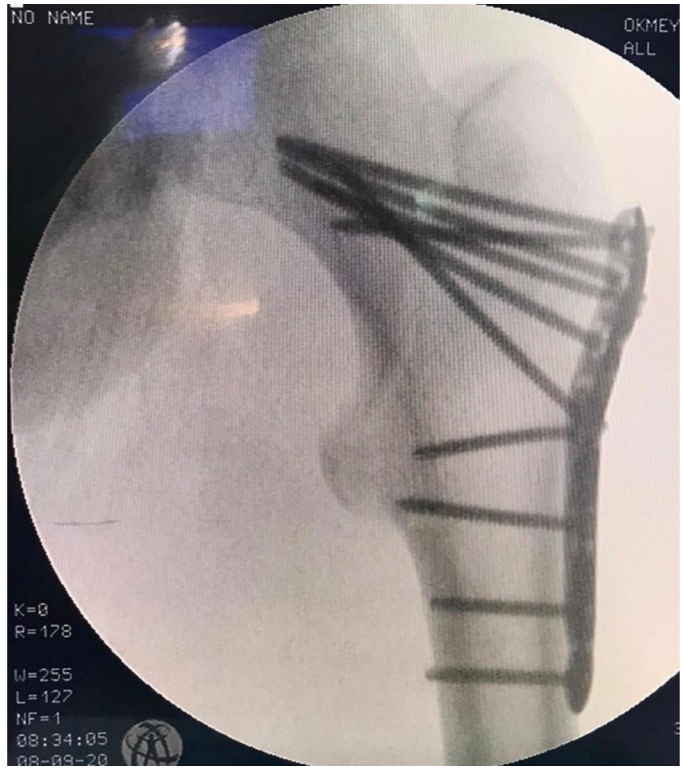

Figure 4. Intra-operative final fluoroscopic imaging

Results

Patient demographics and follow-up data

The study included 24 patients (15 male, 9 female) with a mean±SD age of 12.6±1.4 years (range, 11-15 years). The mean±SD surgical procedure time after trauma was 39±14.5 hours (range, 24-72 hours) and the follow-up duration was 34±9.4 months (range, 22-60 months).

Radiological results

The mean±SD duration of fracture union was 12.8±2.2 weeks (range, 10-16 weeks). No residual deformity was observed. The implants were removed after an average of 30±6.5 months (range, 26-48 months). In patients who had implant removal at the time of final follow-up, no complications such as refracture or deformity were observed due to bone weakening in the lateral cortex during the follow-up period.

Clinical results

The mean±SD final HHS was 92±1.9 (range, 89-95). All patients were rated good according to Ratliff criteria.

Complications

There was no AVN, non-union, malunion, limb-length discrepancy, or implant failure at the end of the follow-up period (Figure 5). Seven days after the operation, two patients had a superficial wound infection that healed in less than 10 days. None of the patients needed a second surgical procedure other than implant removal Patients began the rehabilitation program on the third postoperative day and progressive weight-bearing exercises after four weeks (Table 2).

Discussion

Hip fractures in children are rare and account for less than one percent of all fractures in children (1-3). Delbet type IV fractures account for 6 15% of all hip fractures. Because of their low frequency and high rate of complications, no consensus on the treatment protocol for hip fractures in children has been reached (1). Displaced Delbet type IV fractures in children younger than eight years may be treated by closed reduction and an immediate spica casting. Older children with displaced Delbet type IV fractures should be treated with internal fixation. Furthermore, all unstable intertrochanteric hip fractures after reduction, regardless of the child's age, should be treated with internal fixation (3). First, one or two attempts at closed reduction should be made (1,3). Closed reduction should be performed with gentle longitudinal traction because forceful manipulation may compromise the hip vasculature. If the anatomic reduction can not be achieved by closed reduction, open reduction is recommended for displaced fractures. Stable fixation after

Table 1. Ratliff criteria

	Good	Fair	Poor
Pain	None or ignoring	Occasional	Disabling
Movement	Full or terminal restriction	Greater than 50%	Less than 50%
Activity	Normal or patients avoid games	Normal or patients avoid games	Restricted
Radiographs	Normal or some deformity	Severe deformity and avascular necrosis	Severe avascular necrosis, degenerative osteoarthritis, and arthrodesis

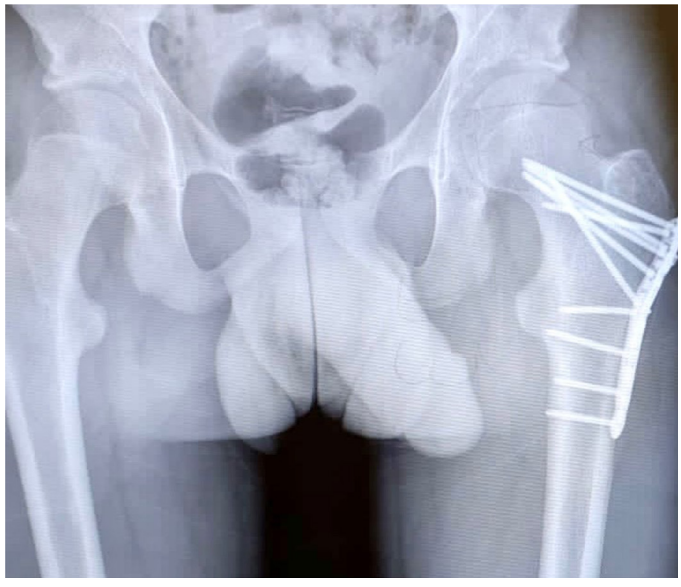

Figure 5. X-ray at fourth-year post-operative showing fracture healing without complications

Table 2. Patient demographics and follow-up		
Age, years, mean±SD		**12.6±1.4**
Sex, n (%)	Male	15 (62.5)
	Female	9 (37.5)
Follow-up, months, mean±SD		34±9.4
Fracture union time, weeks, mean±SD		12.8±2.2
Harris hip score, n, mean±SD		92±1.9
Ratliff criteria, n (%)	Good	24 (100)
	Fair	No
	Poor	No
Complications, n (%)	Superficial wound infection	2 (8)
	Other complications	No

SD: Standard deviation

reduction is essential because it decreases the risk of both malunion and non-union (3). Transphyseal screw fixation is usually recommended despite the risk of damaging the physis. It has been reported that fracture stability is more important than sparing the proximal femoral physis (1,3). It is important to avoid multiple passes of smooth wires or guidewires when stabilizing these fractures (3,11). AVN, malunion, nonunion, premature physeal closure, infection, and chondrolysis are the most commonly reported complications (1-4,6,12). Delbet type IV fractures are generally associated with fewer complications than the other types (4). They have the most favorable prognosis (1).

Hip fractures are associated with higher complication rates and poorer outcomes. The frequency of AVN has been reported between 17% and 47% in hip fractures in children (2,4,13,14). AVN has been reported in Delbet type IV fractures, as many as 14% of cases (3,4,15). Canale and Bourland (6) observed AVN in 1 of 7 patients (14.2%) with type IV fractures. Moon and Mehlman (15) reported AVN in 5% of the cases. The type of fracture, the degree of initial displacement, the age of the patient, and stable internal fixation of the fractures are among the factors associated with AVN (2,14,16-18).

Coxa vara is also a significant complication (1-3). The prevalence of coxa vara has been reported between 20% and 30% (2,14). Canale and Bourland (6) reported coxa vara in 2 of 7 patients (28.5%) with Delbet type IV fractures. Anatomic reduction and stable fixation are the best methods for preventing coxa vara (3,7,15,19).

Non-union has been reported between 2% and 10% of hip fractures in children (3,4,6,9,16). It occurs less frequently when anatomical reduction and stable fixation are applied (2,16,20).

Premature physeal closure has been reported between 5% and 65% of cases (3,6). Premature physeal closure was reported in 28.5% of Delbet type IV hip fractures among children (6). The prevalence of premature physeal closure increases when transphyseal fixation is applied or AVN is present (2,3,6,16). Postoperative infections have been reported in less than 1% of all cases (3).

In this study, we used an adult proximal humeral locking plate to treat 24 children with displaced Delbet-type fractures IV. A pediatric femoral subtrochanteric non-union was treated with an adult proximal humeral locking plate, according to a case study by Cortes et al. (21). In other investigations, the primary treatment for children femoral subtrochanteric fractures were successfully performed using an adult proximal humeral locking device (22-25). However, to the best of our knowledge, no patient has been reported so far in whom an adult proximal humeral locking plate was used to treat a Delbet type IV fracture. We achieved stability and safety fixation with this technique. There was a superficial wound infection in only 1 patient that recovered shortly after antibiotic treatment. We observed no AVN, non-union, coxa vara, premature physeal closure, or chondrolysis. Moreover, none of the patients had poor outcomes. Four weeks after surgery, all patients were allowed to undertake progressive weight-bearing.

Conventional plates are not anatomically pre-formed and must be bent during surgery to accommodate the proximal femoral anatomy. The adult proximal humeral locking plates are pre-contoured to the proximal humerus in adults, and this pre-contoured design adapts to the anatomy of the proximal femur in children. Additionally, the wide proximal end of these plates offers a stronger hold on the proximal femur. The proximal holes of the adult proximal humeral locking plates allow screws to be locked at an angle of 130 degrees, which corresponds to the femoral neck-shaft angle. With this technique, at least 2 rows of long screws towards the femoral neck can be applied, which can provide enough stability that is impossible with conventional methods such as dynamic compression plates, reconstruction plates, or cannulated screw fixation. Because it is possible to apply multiple screws, transphyseal fixation is unnecessary for stable fixation in the adult proximal humerus locking plates. Additionally, a minimally invasive plate osteosynthesis technique

that allows lesser soft tissue dissection and periosteal stripping can be applied using these plates, reducing vascular damage and minor surgical scars. These advantages can decrease the risk of infection, delayed union, and non-union (21-26).

Study Limitations

The difference in our study is that it is the first publication in the literature with excellent results using these plates in pediatric Delbet type IV hip fractures. The limitations of this study are the small number of patients, the short follow-up period, and lacking comparisons with other techniques. The main strength is its single-center design to display the results of procedures applied by the same surgeon team.

Conclusion

In conclusion, there has been no consensus on the treatment of hip fractures in children, which challenges orthopedic surgeons. We concluded that gentle anatomic reduction and stable fixation without crossing the physis can decrease the risk of complications for treating Delbet type IV hip fractures in children. The findings of this study suggest that the fixation of Delbet type IV hip fractures in children using an adult proximal humeral locking plate may be an acceptable treatment option.

Ethics

Ethics Committee Approval: The University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Institutional Review Board approved the study protocol (decision number: 395, date: 06.10.2020).

Informed Consent: Informed consent was obtained from the parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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The association of myeloperoxidase and SYNTAX score in patients with ST-elevation myocardial infarction

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ABSTRACT

Aims: There is evidence that myeloperoxidase (MPO) is a significant biomarker in various cardiovascular diseases. This work explored the relationship between MPO serum levels and SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial) score in patients with ST Elevation Myocardial Infarction (STEMI) after percutaneous coronary intervention.

Methods: The study design was observational and cross-sectional with prospective patient enrollment. Patients were divided into two groups: those with a SYNTAX score >32 and those with a SYNTAX score ≤32. The SYNTAX score was calculated based on the SYNTAX 2.2 score calculator (syntaxscore.org). Patients were analyzed for demographic, and clinical characteristics, including body mass index, carbohydrate and lipid metabolic balance, troponin, and MPO levels. The MPO was measured by ELISA.

Results: Ninety-three patients with STEMI were enrolled with a mean age of 63.77±8.55 years, and 50.5% were males. The MPO level had a significant positive correlation with the SYNTAX score in patients with SYNTAX score >32, r=0.58, p<0.001, and in low SYNTAX score ≤32 patients: r=0.42, p=0.006. Multivariate regression analysis showed that MPO was a significant predictor for SYNTAX score >32 [odds ratio (OR): 1.055, 95% confidence interval (CI): 1.007-1.101, p=0.009], also age (OR: 1.129, 95% CI: 1.031-1.401, p=0.007), high sensitivity of C-reactive protein (OR: 1.309, 95% CI: 1.167-2.878, p=0.030), and triglycerides (OR: 1.181, 95% CI: 1.077-1.992, p=0.021) were significant predictors.

Conclusions: The elevated MPO levels are related to a higher SYNTAX score and may help predict further STEMI development.

Introduction

Myeloperoxidase (MPO) is a protein from the heme peroxidase superfamily and is deposited primarily in leukocytes (1). This enzyme is secreted upon the activation of leukocytes and is an essential player in innate immunity (2). Additionally, MPO can also be found in the endothelial cells (3). MPO has several important functions, such as the antimicrobial activity of neutrophils and phagocytosis (4). Studies have also shown that MPO is a local mediator of tissue damage due to inflammation in various pathologies (1,5,6). Recent studies have shown that changes in the concentration of MPO lead to an inflammatory response and affect the production of cytokines, and it has also been reported that increased oxidative stress and inflammation are associated with an increased level of MPO (7).

MPO is among the biomarkers defined for cardiovascular diseases (CVD), including acute coronary syndrome (ACS), atherosclerosis, heart failure (HF), and hypertension (8-10). On the other hand, the current knowledge is also conflicting. For instance, some studies have reported a positive relationship between high MPO levels and poor prognosis and an increased risk of death in CVD (5,11). In contrast, other studies have not found such a clear correlation (12). Therefore, the existing data do not provide an unambiguous answer to the certainty of MPO as a prognostic marker.

Researchers and cardiologists increasingly use the SYNTAX (from the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial) scale in routine clinical practice to assess patients with ST Elevation Myocardial Infarction (STEMI). This scale effectively predicts the future course of patients with STEMI after percutaneous coronary intervention (PCI) since numerous studies have confirmed that patients with a high SYNTAX score are more likely to have a poor prognosis (13,14). This scale is also a significant independent predictor of severe cardiovascular outcomes (15-17). However, there is no data on the relationship of MPO with the SYNTAX scale, while it may be useful from a practical perspective to consider MPO as a factor in determining the complexity of patients with STEMI.

We hypothesized that high levels of MPO may be associated with SYNTAX scores and subsequently with serious adverse cardiovascular events during the post-infarction period.

Therefore, this study investigated the relationship between MPO level and SYNTAX score in patients with STEMI patients after PCI.

Methods

Study population

The study design was observational and cross-sectional with prospective patient enrollment. The patients were diagnosed with STEMI and underwent coronary angiography. All participants were hospitalized and examined during the first 12 h at the Department of Prevention and Treatment of Emergency Conditions in Government Institution "L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine", Kharkiv May 2021 to December 2021. We diagnosed STEMI according to the European Guidelines for the Diagnosis and Treatment of STEMI, 2017. All patients received therapy according to the current recommendations of the European Society of Cardiology.

STEMI, hospital admission within 24 h after the onset of the first signs, age ≥40 ≤80 years, and informed consent to participate in the study were the inclusion criteria. Exclusion criteria were informed consent refusal, prior coronary bypass surgery, diabetes mellitus, body mass index >39 kg/m^2, glomerular filtration rate <60 mL/min/1.73 m^2, malignancy, infectious and inflammatory diseases in the acute stage, type 1 diabetes mellitus, hypertrophic cardiomyopathy, life-threatening arrhythmias, thyroid disease, inability to follow the study protocol.

This study conformed to the principles outlined in the Declaration of Helsinki. The National Institute of Therapy named after A.I. L.T. Malaya NAMS of Ukraine Local Ethics and Deontology Commission approved the study protocol (no. 12 from 21/10/2020), and all patients gave informed consent.

Laboratory and instrumental investigations

The investigator team assessed the clinical and biochemical parameters in the first 24 h of admission, including smoking status, body mass index, blood pressure, and medications. Laboratory tests were performed according to standard methods to determine white blood cell count, platelet count, hemoglobin level, blood glucose, lipids, serum creatinine, glycated hemoglobin (HbA1c), high sensitivity of C-reactive protein (hs-CRP) and highly sensitive cardiac troponin I (hs-cTnI), MPO.

Whole blood (10 mL) was taken for MPO measurement. Then, the sample was centrifuged, and the serum samples were stored at -80 °C until assayed. MPO was measured using reagents (Ref. BMS2038INST Human MPO Instant ELISA kit) from Invitrogen, Austria, as recommended by the manufacturer.

Echocardiography was performed using the Medison SonoAceX6 apparatus (Korea) to evaluate end-systolic and end-diastolic volumes of the left ventricle (LV), maximum early diastolic filling velocity E (m/s), the maximum speed of atrial diastolic filling A (m/s), their ratio E/A, and LV ejection fraction (EF).

Coronary angiography was performed through the femoral or radial artery according to the approved protocol immediately after hospitalization using the Integris Allura system (Philips Healthcare, Best, the Netherlands). Each coronary artery was visualized with two to three orthogonal projections according to the usual protocol. An automatic contrast injector was used to support the procedure with "Ultravist-370" contrast (Bayer Pharma GmbH, Germany). Primary PCI was performed with a bare-metal Rebel TM stent (Platinum Chromium Coronary Stent System, Boston Scientific, USA) for infarction of the dependent artery.

The SYNTAX score was calculated by interventional cardiologists based on the SYNTAX 2.2 score calculator (syntaxscore.org). The patients were divided into two groups according to the SYNTAX score >32 and ≤32.

Statistical Analysis

The MedCalc® Statistical Software version 20.111 (MedCalc Software Ltd., Ostend, Belgium) was used for statistical analysis. Continuous variables with a normal distribution are presented as mean±standard deviation. Skewed continuous variables are presented as median (interquartile range). Categorical variables are expressed as percentages and numbers. The Shapiro-Wilk test was used to test the normality of distribution. T-test was used to compare normally distributed continuous variables, and the Mann-Whitney U test to compare nonnormal distribution. Categorical variables were compared using a χ^2 test or Fisher's exact test. Univariate and multivariate analyses with the forward stepwise method were performed to determine the independent predictors of a high SYNTAX score. The results of the regression analyses were presented as odds ratios (OR)

and 95% confidence intervals (CI). A p-value of <0.05 was considered statistically significant.

Results

The study included 93 patients with a mean age of 63.77±8.55 years and 50.5% of males. As shown in Table 1, patients who were more severely ill with a high SYNTAX level (score >32) were older than the low SYNTAX group (score ≤32) (67.23±8.89 vs. 60.95±9.02; p=0.001). Additionally, patients with high SYNTAX scores had significantly higher hs-CRP levels (p=0.004), body mass index (p=0.021), systolic blood pressure (SBP) (p=0.007), and triglyceride level (p=0.012) and lower LV EF (p<0.001) compared with those in the low SYNTAX group.

Table 1 shows the comparison of the baseline characteristics of the study participants accordingly to the SYNTAX score. Smoking, diastolic blood pressure, creatinine, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, HbA1c, and hs-cTnI on admission were not statistically different between the high and low SYNTAX groups. Also, both groups were statically similar by gender.

Patients with STEMI with a high SYNTAX score had significantly increased serum MPO levels (81.05±16.33 ng/mL) compared to patients with STEMI who had a low SYNTAX score (69.81±15.07 ng/mL) (p<0.001). MPO level showed a significant positive correlation with the SYNTAX score in patients with STEMI (r=0.65, p<0.001). In patients with a SYNTAX score ≤32 correlation was weaker but still significant (r=0.42, p=0.006); and in patients with a SYNTAX score >32, it was also significant (r=0.58, p<0.001) (Figure 1A, 1B, 1C).

To assess the impact of MPO on the SYNTAX results, we performed univariate and multivariate logistic regression analyses (Table 2). Univariate associations were found between higher SYNTAX score >32 and age (OR: 1.151, 95% CI: 1.040-1.331, p=0.003), MPO (OR: 1.067, 95% CI: 1.011-1.153, p=0.010), SBP (OR: 1.155, 95% CI: 1.097-3.121, p=0.022); hs-CRP (OR: 1.547, 95% CI: 1.121-3.109, p=0.012), triglycerides (OR: 1.210, 95% CI: 1.090-2.021, p=0.019), and left ventricle EF (LVEF) (OR: 0.902, 95% CI: 0.587-0.963, p=0.042) in patients with STEMI.

Multivariate logistic regression analyses showed that MPO was an independent predictor of SYNTAX score >32 in patients with STEMI (OR: 1.055, 95% CI: 1.007-1.101, p=0.009) as shown in Table 2. In addition to MPO, age (OR: 1.129, 95% CI: 1.031-1.401, p=0.007), hs-CRP (OR: 1.309, 95% CI: 1.167-2.878, p=0.030), and triglycerides (OR: 1.181, 95% CI: 1.077-1.992, p=0.021) were the other predictors of SYNTAX score >32.

Discussion

This study showed that higher MPO levels were associated with higher SYNTAX scores in patients with STEMI. An increased MPO level was also an independent predictor of STEMI

Table 1. Comparison of baseline characteristics of the study participants accordingly to the SYNTAX score level

Parameters	All patients (n=93)	SYNTAX score ≤32 (n=47)	SYNTAX score >32 (n=46)	p
Age, years, mean±SD	63.77±8.55	60.95±9.02	67.23±8.89	0.001
Gender, males, n (%)	47 (50.5)	24 (51.1)	23 (50)	0.919
BMI, kg/m^2, mean±SD	24.31±2.15	23.57±2.31	22.44±2.32	0.021
Smoking, n (%)	43 (43.87)	20 (42.55)	22 (47.83)	0.610
HbA1c, %, mean±SD	5.89±1.23	5.77±1.34	6.02±1.19	0.344
SBP, mmHg, mean±SD	149.11±12.75	147.84±13.09	154.99±11.82	0.007
DBP, mmHg, mean±SD	90.04±8.91	88.59±8.12	91.70±7.65	0.060
Creatinine, mg/dL, mean±SD	0.95±0.19	0.95±0.17	1.01±0.15	0.075
TC, mg/dL, mean±SD	186.75±33.91	183.34±29.78	193.61±28.55	0.093
HDL, mg/dL, mean±SD	41.02±8.44	42.05±7.89	39.08±9.32	0.100
LDL, mg/dL, mean±SD	133.03±31.80	131.91±34.65	140.88±31.22	0.193
Triglyceride, mg/dL, mean±SD	170.96±47.53	159.81±51.91	185.35±43.17	0.012
hs-CRP, mg/L, mean±SD	15.99±3.22	15.05±3.63	17.38±3.89	0.004
LVEF, %, mean±SD	58.70±7.99	59.88±7.51	54.32±6.81	<0.001
hs-cTnI on admission ng/mL, median (interquartile range)	76.99 (58.11-89.79)	72.21 (55.17-85.16)	83.91 (59.98-89.21)	0.062
MPO, ng/mL, mean±SD	78.11±16.85	69.81±15.07	81.05±16.33	<0.001

P-level of significance comparing high SYNTAX score and low SYNTAX score groups.
BMI: Body mass index, LVEF: Left ventricle ejection fraction, HbA1c: Glycated hemoglobin, TC: Total cholesterol, HDL: High-density lipoprotein-cholesterol, LDL: Low-density lipoprotein-cholesterol, hs-CRP: High-sensitive C-reactive protein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hs-cTnI: High sensitive-cardiac troponin I, MPO: Myeloperoxidase, SD: Standard deviation

complexity. Our results highlight the significance of MPO, as well as in immune response, inflammation, and oxidative stress in patients with STEMI.

MPO is a widely studied biomarker suspected to be important in evaluating the severity of CVD. Several recent studies have reported a significant connection between MPO and CVD. Increased circulating MPO levels were found to be associated with poor prognosis and increased risk of mortality from CVD (5,8).

Several authors have suggested that due to its involvement in oxidative stress and inflammation, MPO may play an important role in destabilizing atherosclerotic plaques in coronary arteries (18), which in turn determines the clinical value of this marker.

MPO has been studied as a diagnostic indicator for chest pain in ACS (8,18) and as a prognostic marker for acute coronary events (19). We compared the obtained data with the findings of Omran et al. (18) who showed that MPO was very effective in diagnosing myocardial infarction in patients with ACS with suspected infarction. They noted that the combination of MPO, creatine kinase-MB, and TnI was the most useful in patients with ACS. They have attributed such a high diagnostic value to its significant role in the inflammatory response.

Trentini et al. (20) have evaluated the role of MPO in patients with myocardial infarction. They studied patients with acute myocardial infarction (AMI), patients with stable coronary artery disease (CAD), and controls. AMI patients had significantly higher MPO levels than controls, but they also showed that

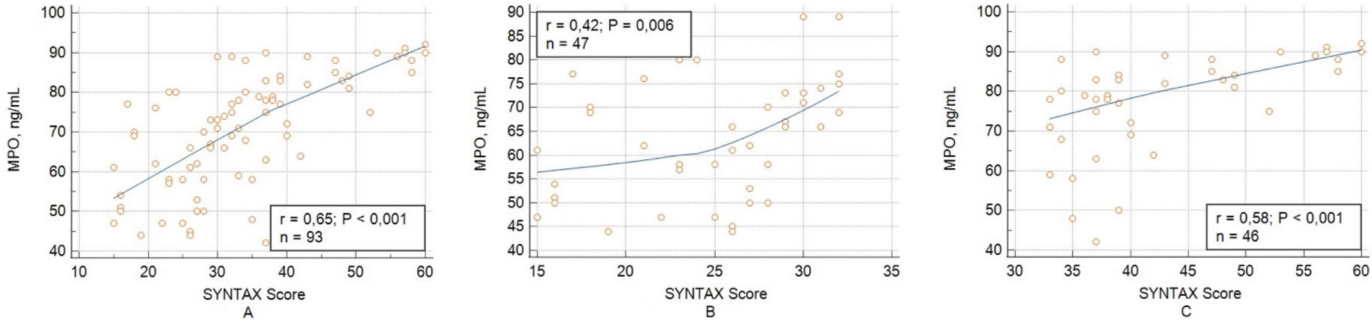

Figure 1. Correlations between myeloperoxidase serum levels and SYNTAX score. **A)** In all enrolled patients, n=93; **B)** In the first group with SYNTAX score <32, n=47; **C)** in the second group with SYNTAX score ≥32, n=46
MPO: Myeloperoxidase

Table 2. Univariate and multivariate linear regression analysis showing independent predictors of the SYNTAX score

Variables	Univariate regression analysis		Multivariate regression analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
BMI	1.073 (0.993-1.069)	0.105		
Age	1.151 (1.040-1.331)	0.003	1.129 (1.031-1.401)	0.007
LVEF	0.902 (0.587-0.963)	0.042	0.902 (0.571-1.212)	0.069
Creatinine	1.049 (0.922-1.881)	0.237		
HbA1c	1.183 (0.879-1.599)	0.190		
Triglyceride	1.791 (0.879-2.625)	0.483		
HDL	0.810 (0.323-2.052)	0.654		
LDL	1.553 (0.930-1.980)	0.091		
Triglyceride	1.210 (1.090-2.021)	0.019	1.181 (1.077-1.992)	0.021
hs-CRP	1.547 (1.121-3.109)	0.012	1.309 (1.167-2.878)	0.030
Smoking	1.311 (0.903-1.566)	0.107		
SBP	1.155 (1.097-3.121)	0.022	1.161 (0.988-3.418)	0.072
DBP	1.030 (0.925-1.088)	0.158		
hs-cTnI	1.034 (0.980-1.059)	0.083		
MPO	1.067 (1.011-1.153)	0.010	1.055 (1.007-1.101)	0.009

Significant p-values are shown in bold.
CI: Confidence interval, BMI: Body mass index, LVEF: Left ventricle ejection fraction, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein-cholesterol, LDL: Low-density lipoprotein-cholesterol, hs-CRP: High-sensitive C-reactive protein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hs-cTnI: High sensitive-cardiac troponin I, MPO: Myeloperoxidase

MPO was higher in patients with stable CAD compared with AMI, although the patients with CAD had concomitant chronic obstructive pulmonary disease.

Based on data from previous studies that have shown an association of MPO with atherosclerosis (21-23), Tan et al. (24) studied the relationship of MPO with plaque erosion in 252 patients with STEMI, of whom 37% and 32% were diagnosed with plaque rupture and erosion, respectively. They found significantly higher levels of MPO in patients with plaque erosion compared with those with plaque rupture. Also, plasma MPO level was independently associated with plaque erosion (OR: 3.25, 95% CI: 1.37-7.76, p<0.01). MPO level correlated significantly with plaque erosion in patients, as well.

A recent, small study showed that patients with AMI correlated significantly with MPO with lesion size and microvascular obstruction (25). Higher MPO levels were observed in patients who had a larger infarct size, more prominent LV remodeling, and greater microvascular obstruction. MPO was directly correlated with cardiac troponin and peak creatine kinase (25). These results are to some extent comparable to our results.

Khalil et al. (26) have also observed results close to our investigation. In 215 patients with STEMI patients admitted for primary PCI, the authors showed that a higher level of MPO was an independent predictor of the severity of the disease and mortality. MPO levels significantly increased the quality of the prediction of adverse events and disease severity in patients with STEMI, which broadly coincides with the results obtained from us.

The large CLARITY-TIMI study with a 30-day observation found that MPO, along with two other markers (suppression of tumorigenicity 2 protein and troponin T), was a significant predictor of cardiovascular death or HF in patients with STEMI (27). These markers, when added to the TIMI risk scale, significantly improved the prognosis. Thus, MPO provided additional information for predicting death from CVD or HF.

In another study, investigators evaluated MPO levels as a predictor of long-term adverse cardiac events in patients with STEMI patients who underwent PCI (28). They found that during 14 months of follow-up, 20% of 127 patients experienced serious adverse cardiovascular events (unscheduled coronary revascularization procedure, stroke, re-infarction, or death from all causes). Higher MPO levels were independent predictors of all adverse events studied. That work has shown that MPO levels were more predictive of major cardiovascular adverse events than NT-proBNP levels.

Kolodziej et al. (29) analyzed 13 studies with 9090 participants and showed that high levels of MPO were significantly associated with mortality (OR: 2.03, 95% CI: 1.40-2.94, p<0.001). However, the author did not identify MPO as a significant predictor of serious adverse cardiac events and recurrent myocardial infarction. Similar to our study, this analysis showed that diabetes mellitus did not affect the predictive value of MPO, whereas, gender and smoking status had a strong influence on the predictive value of MPO regarding mortality and recurrence of myocardial infarction.

Cheng et al. (30) found that patients with CAD had elevated plasma levels of MPO, and MPO was positively correlated with the severity of CAD and the risk of major adverse cardiovascular events (MACE) during 6 months of follow-up. In this regard, the prognostic value of MPO was higher than that of homocysteine and hs-CRP. Thus, it was assumed that MPO could predict MACE and that this protein played an important role and showed clinical significance in assessing the patient's condition to improve the prognosis of patients.

Simultaneously, some data do not confirm the diagnostic and prognostic role of MPO and some works did not find a significant correlation between the level of MPO and clinical results in patients with CVD (31,32). For instance, a recent study by Pek et al. (31) evaluated MPO in predicting 30-day and 6-month adverse cardiac events, defined as HF-related death, myocardial infarction, and ventricular fibrillation. The results showed that MPO levels were almost the same with and without adverse cardiac events, both after 30 days and after 6 months. Thus, MPO did not show its effectiveness as a marker for the diagnosis and prognosis of ACS. On the other hand, that work was different from our study because the patients had concomitant renal pathology. The presence of such severe comorbidity could reduce the diagnostic and prognostic efficacy of MPO. Additionally, there was only one stage and not a serial measurement of MPO.

In the study by Liu et al. (32), which studied the prediction of short-term and long-term outcomes in patients with ACS, the researchers found that MPO could not significantly predict short-term or long-term outcomes. Simultaneously, the authors found that patients with STEMI had significantly higher plasma MPO levels than patients with ACS without ST-segment elevation.

Study Limitations

Our study has several limitations. First, we had a small sample size, and thus the conclusions deserve reconfirming. We also believe that only a single center can be considered a limitation. Third, the study design was cross-sectional. Additionally, we only measured the MPO concentration on admission and did not have serial measurements. Finally, we measured only the SYNTAX score without considering other possible markers of severity and prediction. However, this scale is the most relevant from our viewpoint of view.

Conclusion

In conclusion, this is the first study showing that elevated MPO levels are associated with a higher SYNTAX score and may help predict further STEMI development. Our findings may provide a new approach to the prognosis of patients with STEMI patients and make an additional tool for early risk stratification and management. However, further research is needed to elucidate the mechanism through which the observed relationship between the MPO level and severity of STEMI is realized (e.g., a reactive response to inflammation, a consequence of a more extensive endothelial lesion, response to atherosclerotic rupture, and destabilization). Identifying this pathogenic mechanism would likely lead to a better understanding of the role of MPO in the clinical management of patients with STEMI patients.

Ethics

Ethics Committee Approval and Informed Consent: The L.T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine Local Ethics and Deontology Commission approved the study protocol (no. 12 from 21/10/2020), and all patients gave informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: I.R., I.K., Concept: M.K., Design: M.K., I.K., Data Collection or Processing: N.T., Y.H., Analysis or Interpretation: I.R., N.T., Y.H., Literature Search: I.K., B.S., Writing: I.R., N.T., Y.H., B.S.

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The relationship of depression with fatigue, quality of life, and gastrointestinal symptoms in patients with restless legs syndrome

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ABSTRACT

Aims: This study examined the relationship between depression with fatigue, quality of life (QoL), and gastrointestinal symptoms in patients with restless legs syndrome (RLS).

Methods: This prospective study included patients diagnosed with RLS. Depression, fatigue, QoL and gastrointestinal symptoms were evaluated with Hospital Anxiety and Depression Scale, the Fatigue Severity Scale, RLS QoL Questionnaire and Gastrointestinal Symptom Rating Scale, respectively. Multiple regression was performed to determine the relationship between fatigue, QoL, gastrointestinal symptoms, and depression.

Results: The final sample included 19 patients [mean age: 42.6±12.7 years, female: 11 (57.9%)]. The level of depression positively correlated with fatigue, QoL, and gastrointestinal symptoms scores. These variables explained 57.1% of the variance in depression scores in patients with RLS ($R=0.755$, $R^2=0.571$ $F=6.645$; $p=0.005$).

Conclusions: This study showed that patients with RLS experience worsening QoL, fatigue, and increased gastrointestinal symptoms with increasing depression scores. Managing RLS may require tackling depression and depression-related symptoms with a multifaceted approach.

Introduction

Restless legs syndrome (RLS) is a neurological sensorimotor disorder diagnosed by four main criteria (unintentional need to move the legs, typically accompanied by unpleasant leg sensations; induction or exacerbation of symptoms while at rest; symptom relief while activity; and daily fluctuations with symptoms getting worse in the evening and at night) (1). The most common symptoms of RLS are sleep disturbances such as reduced sleep duration, periodic extremity movements, and changes in sleep architecture (2).

Depression and anxiety, which often negatively affect sleep, are common in patients with RLS. Generally, many functions of patients with RLS patients are restricted, and these patients have a higher level of somatic stress and worsened sleep (3). It has also been suggested that RLS patients have a lower quality of life (QoL) than patients with other chronic medical conditions such as high blood pressure, congestive heart failure, and diabetes mellitus (4). The impact of RLS on mental health has been well recognized and the diagnostic criteria for RLS are included in the Diagnostic and Statistical Manual of Mental Disorders-V (5).

Studies have shown that people with RLS have a 2- to 4-fold increased risk of developing a depressive illness. The high frequency of depression in RLS suggests a link between the two conditions (6,7). Moreover, the severity of RLS correlates with the symptoms of depression and anxiety (8). Finally, comorbid

depression may substantially impact overall treatment success (7). On the other hand, some antidepressant drugs can trigger or worsen symptoms and periodic limb movements in RLS (9). Cuellar et al. (10) investigated the effect of depression on sleep quality, sleepiness, and fatigue in patients with RLS, some of whom were receiving RLS therapy and antidepressant medications. They showed that depressed patients with RLS had worse sleep quality and fatigue, but their sleepiness was not affected by depression. Additionally, although the association between QoL and depression has been previously investigated, the relationship between RLS-specific QoL and depression is still unknown.

The World Health Organization defines health as a condition of whole (physical, mental, and social) well-being and not only the absence of sickness or infirmity (11). Because health has many components, it is not effective enough to treat symptoms alone in patients with RLS. Thus, a holistic approach that includes mental and social health components such as fatigue, depression, and QoL is needed. Additionally, the importance of gastrointestinal symptoms, which have dramatic adverse effects on patients' QoL has increased rapidly. However, there are limited studies on gastrointestinal symptoms in patients with RLS. Determining the relationship between depression, which is common in RLS (6,7), and QoL, gastrointestinal symptoms, and fatigue may help improve the management of the disease. Therefore, this study examined the relationship between depression with fatigue, QoL, and in patients with RLS.

Methods

Study design and participants

We prospectively enrolled patients with RLS admitted to the Department of Movement Disorders of the Neurology Outpatient Clinic, Gülhane Training and Research Hospital, at the University of Health Sciences Türkiye, between September 2021 and March 2022. The ethics board of the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (protocol number: 2020-422, date: 17.12.2020) approved the study protocol. The procedures were conducted in accordance with the Declaration of Helsinki. All participants were informed about the protocol and gave written consent.

The inclusion criteria were (1) diagnosis of RLS by the neurologist according to the International RLS Study Group 2014 criteria (12), (2) age over 18 years, and (3) being literate. The exclusion criteria were (1) the presence of other sleep disorders, (2) gastrointestinal system diseases, (3) the use of antipsychotics, psychoactive, and antidepressant drugs, and (4) scores <24 on the Mini-Mental State Examination (13).

Outcome measures

The same researcher performed the procedures. Standardized questionnaires were used to collect demographic and physical characteristics and medical history. All the questionnaires were self-reported. The Mini-Mental State Examination was used to determine the cognitive status of the patients (13).

Depression

The Hospital Anxiety and Depression Scale (HADS) was used as a self-assessment tool to determine the state of depression (14,15). It has two domains that determine the level of anxiety (HADS-A) and depression (HADS-D) and consists of 14 items, of which odd-numbered items investigate anxiety (HADS-A) and even-numbered items investigate depression (HADS-D). Each item is scored between 0 and 3, and the total score ranges between 0 and 21 for each domain. Higher scores indicate more severe depression. We used only HADS-D in the current study.

Fatigue

We evaluated fatigue using the "Fatigue Severity Scale (FSS)" (16,17), which consists of 9 sub-items related to fatigue-related daily activities. Each item is scored between 0 and 7 and the total score is the sum of arithmetic means. A total score of 4 or higher indicates severe fatigue.

Quality of life

The RLS QoL Questionnaire (RLS-QoL) was used to evaluate the QoL (18,19). It consists of 18 items, and items 1-5-7-10 and 13 are scored between 1 and 5. The total score is calculated using the formula:

[(Actual raw score - lowest possible raw score) / Possible raw score range] × 100.

Higher scores indicate worse QoL.

Gastrointestinal symptoms

The Gastrointestinal Symptom Rating Scale (GSRS) was used to determine common gastrointestinal symptoms, which consisted of 15 items and five subdimensions: abdominal pain (items 1, 4, and 5), reflux (items 2 and 3), indigestion (items 6, 7, 8, and 9), diarrhea (items 11, 12, and 14), and constipation (items 10, 13, and 15) (20,21). Each item is scored between 0 (no symptom) and 7 (severe discomfort) on a Likert scale and calculated as the mean score. Higher scores indicate more severe symptoms.

Statistical Analysis

The Statistical Package for the Social Sciences version 25.0 (IBM Corporation, Armonk, NY, United States) was used for analysis. Data were expressed as mean±standard deviation, medians (minimum maximum), and percentages. Data normality was checked by normal probability plots, the Shapiro-Wilk test, and coefficients of skewness and kurtosis.

Pearson correlation was used to assess the linear relationships between continuous variables. Multiple regression was used to estimate the relationship between fatigue, QoL, gastrointestinal symptoms, and depression scores. Regression analysis was performed using the depression score as the dependent variable and fatigue, QoL, and gastrointestinal symptoms as independent variables. Analysis of variance (ANOVA) was used to check the validity of the regression model. Correlation levels were rated: <0.20: poor; 0.20-0.39: fair; 0.40-0.69: moderate; 0.70-0.89: excellent; >0.90: excellent. The significance level was set at α=0.05 (22).

Results

We evaluated 27 patients for eligibility. Three participants with non-RLS sleep disorders, 4 patients who were on antipsychotics, psychoactive, or antidepressant medications, and 1 patient with cognitive problems were excluded. The study was completed with 19 patients. The mean age was 42.6±12.7 years and 57.9% of the participants were women. The mean body mass index was 27.3±4.9. Table 1 shows the characteristics of the patients. No patient reported alcohol intake and 15.8% (n=3) reported smoking. Family history of RLS was recorded by 47.4% (n=9). The disease duration varied between 2 months and 17 years.

Of the patients, 36.8% showed depression symptoms. Four of the depressed patients were women and 3 were men. The mean±SD age of patients with RLS with depression was 37.1±11.7 years, while the mean±SD age of non-depressed patients was 45.9±12.5 years. The FSS score of the patients was 4.9±1.6 and 3.1±0.9 in depressed and non-depressed patients, respectively. The RLS-QoL score of patients with depression and without depression was 66.7±19 and 37.9±19.6, respectively. The GSRS score was 12.0±4.13 and 8.6±3.5 in depressed and non-depressed patients, respectively.

HADS-D scores positively correlated with FSS, RLS-QoL and GSRS (r=0.66, p=0.001; r=0.49, p=0.015 and r=0.39, p=0.049, respectively). Multiple linear regression was performed to predict the HADS-D score based on fatigue, QoL, and gastrointestinal symptoms. A significant regression equation was found [F (3,15)=6.645, p=0.005, with an R2 of 0.571]. Participants predicted HADS-D score is equal to -2.920 (constant) + 1.195 (fatigue score) + 0.051 (QoL score) + 0.320 (gastrointestinal symptoms score), where fatigue, QoL, and gastrointestinal symptoms were assessed as scale variables. The results of multiple regression analyzes are shown in Table 2. The variance inflation factor of a maximum of 1.5 indicates the absence of multicollinearity in the regression model. There was no heteroscedasticity in the final model.

Table 1. Basic characteristics of patients

Characteristics	Patients (n=19)
Gender, n (%)	
Female	11 (57.9)
Male	8 (42.1)
Age, year, mean±SD	42.6±12.7
BMI, kg/m², mean±SD	27.3±4.9
Marital status, n (%)	
Married	14 (73.7)
Single	5 (26.3)
Education, n (%)	
Primary school	3 (15.8)
Middle school	2 (10.5)
High school	5 (26.3)
College	7 (36.8)
Master's degree	2 (10.5)
Smoking, n (%)	
Yes	3 (15.8)
No	16 (84.2)
Family history of RLS, n (%)	
Yes	9 (47.4)
No	10 (52.6)
Occupation, n (%)	
Unemployed	5 (26.2)
Retired	2 (10.5)
Blue-collar worker	5 (26.3)
Student	3 (15.8)
White-collar worker	4 (21.1)
Alcohol use, n (%)	
Yes	**0 (0)**
No	**19 (100)**
Medication use, n (%)	
Yes	12 (63.2)
No	7 (36.8)
Medical history, n (%)	
None	12 (56.4)
Varicose veins	2 (9.5)
Hashimoto's thyroiditis	2 (9.5)
Familial Mediterranean fever	1 (4.7)
Arrhythmia	1 (4.7)
Diabetes mellitus	1 (4.7)
Hypertension	1 (4.7)
Thyroid nodule	1 (4.7)
Disease duration, [month, median (min-max)]	48 (2-204)
Hospital Anxiety and Depression Scale, mean±SD	7.2±4.0
Fatigue Severity Scale, mean±SD	3.7±1.4
RLS Quality of Life, mean±SD	48.5±23.9
Gastrointestinal Symptom Rating Scale mean±SD	9.8±4.0

SD: Standard deviation, BMI: Body mass index, RLS: Restless legs syndrome, min-max: Minimum-maximum

Table 2. Results of the analysis of variance (ANOVA) and multiple regression

	Unstandardized coefficient (t)		Standardized coefficient	95% confidence interval for B		p	VIF
	B	S	Beta (t)	Lower bound	Upper bound		
Constant	-2.920	2.467	-	-8.179	2.339	0.255	-
Fatigue	1.195	0.563	0.441	-0.004	2.394	0.051	1.503
Quality of life	0.051	0.034	0.304	-0.022	0.125	0.155	1.437
Gastrointestinal symptoms	0.320	0.180	0.318	-0.064	0.704	0.096	1.123

n=19, R=0.755, R^2=0.571, Adj. R^2=0.485, (F=6.645; p=0.005).
SD: Standard deviation, VIF: Variance inflation factor

Discussion

The current study found strong associations between the levels of depression and fatigue, QoL, and gastrointestinal symptoms. These variables explained about 60% of the depression level in patients with RLS. Demographic findings were in line with the literature, with examples of RLS being more common in women, frequent familial history, and the presence of different comorbidities (3,23,24).

The findings of the study demonstrated a relationship between fatigue and depression in patients with RLS patients. Similarly, the study by Cuellar et al. (10) showed more exhaustion among depressed patients with RLS. The authors also investigated sleepiness and sleep quality among depressed patients with RLS taking or not taking antidepressants and observed that while the sleep quality of depressed people deteriorated sleeplessness was not altered. Our study differs from that study in that we excluded patients taking antidepressants because medications can alter the level of depression and gastrointestinal symptoms. Evidence indicating inflammation plays a role in the development of various forms of depression and fatigue includes the connection between fatigue, depression, and immunological activity, the psychological effects of proinflammatory insults, and the effectiveness of anti-inflammatory medications as therapy (25). The finding of the current study suggests that depression, besides sleep difficulties, contributes to the fatigue experienced by patients with RLS.

RLS causes a unique burden on both the physical and mental dimensions of patients' QoL (26). The decrease in QoL appears more significant than other common chronic diseases (4). This study evaluated QoL in terms of RLS rather than a general perspective. For this reason, we applied an RLS-specific QoL measurement scale. QoL is a multifaceted concept that can be affected by different conditions. Revealing the relationship between depression and QoL may show the importance of approaching RLS such as fibromyalgia, which also has a higher prevalence in these patients, within a biopsychological model (27).

The link between psychological problems and gastrointestinal symptoms is often explained by the brain-gut axis, which refers to the rich bidirectional molecular interaction between the gastrointestinal tract and the central nervous system (28). People who do not have high levels of anxiety and depression at baseline feel significantly depressed and anxious during the follow-up period in the presence of functional gastrointestinal diseases, including functional dyspepsia (29). Simultaneously, higher levels of depression predict functional dyspepsia (29). Chronic diarrhea and constipation have also been common among depressed patients (30). Furthermore, even in the absence of severe gastrointestinal diseases, abdominal pain is linked to depression symptoms (31). Finally, indigestion can cause depression (32). RLS is prevalent in patients with irritable bowel syndrome, which presents in the form of diarrhea predominance, constipation predominance, or both (33). Dyspepsia incidence is eight times higher in patients with irritable bowel syndrome (34). Therefore, our findings of increased gastrointestinal symptoms along with depression symptoms are in line with the previous studies (30,31).

Study Limitations

The major strength of this study is its focus on the relationship between depression and fatigue, QoL, and gastrointestinal symptoms in patients with RLS who were not on antidepressant treatment. One major limitation of the study is the small sample size caused by the single-center study design, exclusion of antidepressant users, and difficulties in patient enrollment during the Coronavirus disease-2019 pandemic. The other major limitation is the lack of a control group.

Conclusion

In conclusion, this study determined that as the level of depression increases, the QoL decreases, and the complaints of fatigue and gastrointestinal symptoms increase in patients with RLS. Treatment of depression may be effective in reducing the associated fatigue and gastrointestinal symptoms and improving the QoL.

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Ethics

Ethics Committee Approval: The ethics board of the University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee (protocol number: 2020-422, date: 17.12.2020) approved the study protocol.

Informed Consent: All participants were informed about the research, and written consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.R.S., Concept: Ö.Ç., M.E.Y., A.R.S., N.Ü.Y., Design: Ö.Ç., M.E.Y., A.R.S., N.Ü.Y., Data Collection or Processing: Ö.Ç., Analysis or Interpretation: Ö.Ç., Literature Search: Ö.Ç., Writing: Ö.Ç., M.E.Y., A.R.S., N.Ü.Y.

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Ponticulus posticus in skeletal malocclusions: A lateral cephalometric study

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ABSTRACT

Aims: The ponticulus posticus (PP), a morphological variation in the atlanto-occipital region, is considered a cause of potential entrapment of the vertebral artery segment that traverses the foramen. This study investigated the prevalence and characteristics of PP in different skeletal malocclusion groups using lateral cephalograms.

Methods: This retrospective study evaluated 1,400 lateral cephalometric radiographs of subjects aged between 18-40 years. The radiographs were scrutinized for the presence of PP and its types as partial or complete. We evaluated PP according to gender and skeletal malformations as skeletal class-I, II, or III (determined using Point A - Nasion - Point B angle) by two independent examiners.

Results: The study included 1400 cephalograms from 607 males (43.4%) and 793 females (56.6%). The mean age was 21.96±0.24 years. PP was more common among male subjects (30.9%) compared with the female subjects (p=0.001). It was predominantly observed among the skeletal class-III (27.8%) malocclusion, followed by class-I (23.1%) and class-II (20.6%) malocclusion (p=0.049). Considering the types of PP, the partial form was more frequent among males (71.8%) and females (75.2%).

Conclusions: In this study, the occurrence of PP was observed in 23.5% of the population, predominantly among males. The highest frequency of PP was in the population with skeletal class-III malocclusion.

Introduction

A precise radiographic assessment and interpretation of various anatomic structures are critical as these structures may serve as a nidus to an underlying disease process. In dentistry, lateral cephalogram is one of the most widely used diagnostic radiographs in clinical orthodontics for cephalometric tracings, which can also help analyse any significant pathology of the cervical spine region. One of the important anatomical findings in the cervical spine region is ponticulus posticus (PP), an abnormally deformed bony bridge of the atlas first reported by Macalister in 1893 (1,2). It connects the posterior region of the superior articular process to the postero-lateral region of the superior margin of the posterior arch of the atlas (3). It is assumed to result from the lateral margin of the posterior aspect of atlanto-occipital membrane ossification that varies at different levels (4). Some terminologies for PP include the Arcuate foramen, Kimmerle anomaly, Retroarticular canal, Canalis arteriae vertebralis, Pons posticus, Foramen sagitale, and Foramen atlantoideum (5-8). The association of this structure with disorders such as vertebrobasilar insufficiency, migraine without aura, cervical pain syndrome, sudden sensorineural hearing loss, diplopia, chronic tension-type, and cervicogenic headaches is of great clinical significance (9,10). Often, negligence in the detection of PP may result in serious complications during cervical spine surgical interventions for managing atlantoaxial instability (11).

The origin of PP is associated with the activity of neural crest cells throughout fetal development (12). A major portion of the

skull, vertebral column, maxilla, mandible, and dental tissues originated from these pluripotent stem cells. Any anomalies involving the neural tube may raise the likelihood of aberrant development of the skull, vertebral column, and teeth (13,14). Thus, the dentoskeletal aberrations including malocclusions can be linked to abnormalities in the head and neck position, cervical inclination and orthopedic abnormalities (15). To date, various approaches have been used to assess the frequency of PP in different populations, most commonly in cadaveric specimens, dried atlas specimens, and plain radiography (4). A recent meta-analysis by Elliott and Tanweer (11) showed that PP is as common as 16.6% in lateral radiographic studies and 18.8% in cadaveric investigations. Previous studies have examined the prevalence of PP in various cultural groups and its association with other conditions such as cervicogenic headache (16), narrow disc space (17), cleft lip and palate (18), and elongated styloid process (19). However, the data on the prevalence of PP and its radiographic characteristics observed among the various sagittal skeletal patterns and other maxillofacial conditions are sparse. Hence, this study evaluated the association of PP in various skeletal malocclusion groups.

Methods

In this retrospective study, we collected lateral cephalograms of the subjects who had visited the Department of Maxillofacial Radiology [AB Shetty Memorial Institute of Dental Sciences, Constituent College of NITTE (treated as University), Mangalore] from January 2020 to December 2021. Radiographs were screened based on selection criteria. We included lateral cephalograms of subjects aged 18 to 40 years, taken with good diagnostic quality for various diagnostic purposes. A total of 1564 radiographs were obtained to analyse for PP based on the subject's skeletal malformations. The radiographs obtained from the archives underwent quality assessment in terms of dimensional stability and image clarity. However, we excluded 164 radiographs due to poor image clarity, the presence of facial deforming pathologies, evidence of surgical interventions of the maxillofacial skeleton, and radiographic images that had poor visibility of the posterior arch of the atlas (due to overlapping of the occiput or the mastoid region over the area of interest). Radiographs of subjects with any artifacts affecting the craniofacial region were also excluded. The study was performed following the AB Shetty Memorial Institute of Dental Sciences Institutional Ethical Committee approval (Ethics/ABSMIDS/188/2022, date: 21.01.2022).

Image acquisition

The lateral cephalograms were procured with Planmeca ProMax S2-2D (Helsinki, Finland, 2008) under standard imaging techniques with the exposure parameters of 60-84 kV; 5-16 mA, and an average exposure time of 18.7 s. The image analysis was carried out in Planmeca Romexis software (version 2.4.2). Two independent oral and maxillofacial radiologists with a minimum of 10 years of clinical experience evaluated the radiographs. They examined no more than 10 longitudinal sets of graphs at a time to reduce bias caused by fatigue. There were no significant discrepancies in the radiographic interpretation between the two radiologists, and the inter-examiner variability was assessed using the Kappa test.

Image analysis

Lateral cephalometric radiographs were carefully examined under appropriate lighting for the presence of PP, along with the sagittal skeletal patterns of the subjects. In lateral cephalometrics, the ANB angle is a parameter that defines the mutual sagittal relationship between the upper and lower jaws either as orthognathic, mesial, or distal (20). Based on the relationship of Point A - Nasion - Point B (ANB) angle measurements, the anteroposterior skeletal relationship between the maxilla and mandible was categorized as skeletal class-I (with ANB angle of 0-4°), class-II (with ANB angle of >4°) and class-III (with ANB angle of <0°) (21). Further, the morphology of PP was analysed based on the classification given by Lo Giudice et al. (22) as follows:

- Complete type - Presence of a fully extended/completed bony ring above the posterior arch of the atlas (Figure 1A).

- Partial type - The presence of less than a half-extended bone bridge from the condyle to the posterior dental arch (Figure 1B).

- Absence of PP.

Statistical Analysis

Statistical analysis was performed with a Statistical Package for Social Sciences Software (International Business Machines Corporation, Armonk, NY, USA) version 26. The categorical data were represented as percentages and analyzed using the Pearson chi-square test. A p-value of 0.05 was considered statistically significant.

Results

The analyses included 1,564 lateral cephalograms and 1,400 were selected based on the inclusion and exclusion criteria. Table 1 displays the characteristics of the sample. The mean age of the subjects was 21.96±0.24 years, and there were 607 males and 793 females. Table 2 displays the frequency of PP and its types across genders and different skeletal malocclusion. Out of 1,400 radiographs, 329 (23.5%) showed PP, of which 188 (57.1%) belonged to males and 141 (42.9%) belonged to females. There was a statistically significant association between the occurrence of PP and male gender (p=0.001). The partial type (73.3%) was predominant compared with the complete type (26.7%). Although the partial type was more common among females, there was no statistical

difference. However, we observed a statistically significant association between PP across different skeletal malocclusion groups (p=0.049). PP was predominantly found in the class-III (27.8%) skeletal malocclusion followed by class-I (23.1%) and class-II (20.6%). The occurrence of the complete form of PP was higher in skeletal class-III (31.3%) followed by class-I (27.8%) and class-II (20.6%) malocclusion. The partial type was predominant in skeletal class-II (79.4%), followed by class-I (72.2%) and class-III (68.7%) malocclusion. However, there was no significant difference between the different types of PP among the skeletal malocclusion groups.

Discussion

Over the last few decades, the relationship between minor atlanto-occipital abnormalities and their clinical impact has gained interest among various specialties, including head and neck surgery and orthopedics. Considering its serious complications in the surgical interventions of the cervical spine, clinicians and maxillofacial radiologists must have an in-depth knowledge of the anatomical variations of the cervical vertebrae and their characteristics using routine imaging modalities for the identification of any pathologies and for establishing an appropriate referral strategy.

The congenital origin of PP from the neural crest cells can be indicated by the presence of lamellar patterns inside the bone matrix, signifying endochondral ossification. PP has been thought to arise from neural crest cells (23,24). However, different theories have also been proposed. According to Geist et al. (25), PP was unlikely to mature as hypertrophic adaption, while Schilling et al. (26) considered it an osteophytic formation to safeguard the passage of the vertebral arteries during head and neck movements.

Our study reported a prevalence rate of 23.5%, which is comparatively higher than the previous studies that reported a rate from 11.5% to 18.8% (27,28). Variations in the prevalence of PP may be associated with the characteristics of the

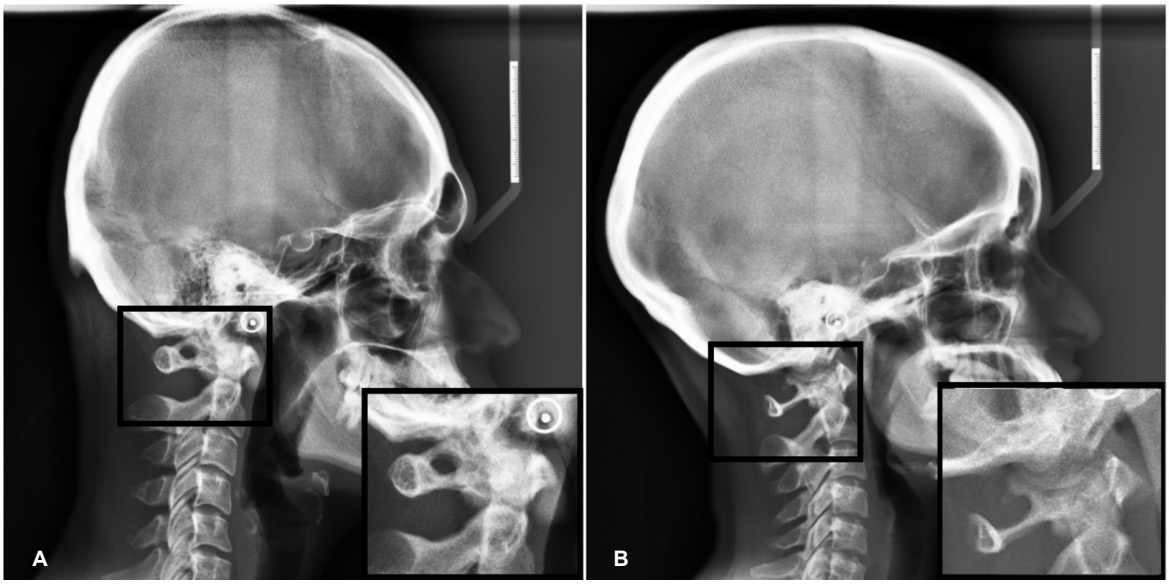

Figure 1. A) Lateral cephalogram demonstrating a complete-type ponticulus posticus in the cervical spine region. **B)** Lateral cephalogram demonstrating a partial-type ponticulus posticus in the cervical spine region

Table 1. Characteristics of the study sample		
Total no. of lateral cephalometric radiographs screened		**1,564**
No. of lateral cephalometric radiographs excluded		**164**
No. of lateral cephalometric radiographs included		**1,400**
Characteristics of the radiographs		
Gender	**Total**	**%**
Males	607	43.4
Females	793	56.6
Skeletal malocclusion	**n**	**%**
Class-I	575	41
Class-II	470	33.6
Class-III	355	25.4

Table 2. **Frequency of ponticulus ponticus and its types based on gender and skeletal malocclusion**

	Ponticulus posticus		Total	p
	Present	Absent		
Gender				
Male	188 (30.9%)	419 (69.1%)	607	**0.001**
Female	141 (17.8%)	652 (82.2%)	793	
Malocclusion				
Class-I	133 (23.1%)	442 (76.9%)	575	**0.049**
Class-II	97 (20.6%)	373 (79.4%)	470	
Class-III	99 (27.8%)	256 (72.1%)	355	
	Type of ponticulus posticus		**Total**	**p**
	Complete	**Partial**		
Gender				
Male	53 (28.2%)	135 (71.8%)	188	0.495
Female	35 (24.8%)	106 (75.2%)	141	
Malocclusion				
Class-I	37 (27.8%)	96 (72.2%)	133	0.224
Class-II	20 (20.6%)	77 (79.4%)	97	
Class-III	31 (31.3%)	68 (68.7%)	99	

study population, such as racial and geographic differences. Additionally, radiographic factors like imaging modality and exposure parameters could also lead to variation in the identification of PP (29,30). Considering the variability across gender, the prevalence of PP was statistically significant and more frequent among the male population (57.1%) than females (42.9%). These findings were parallel to the observations of Adisen and Misirlioglu (27), Bayrakdar et al. (31), Geist et al. (25), and Tripodi et al. (32) who also observed a male predominance. This could be attributed to the increased stress exerted on the atlanto-axial junction due to cervical movements (33). We found the partial form of PP to be predominant among the study population; however, we did not find any statistically significant difference between gender and types of PP. Our findings are in agreement with the observations of Chitroda et al. (34) and Pękala et al. (35).

Additionally, we considered the possibility of a relationship between cervical vertebrae aberrations and skeletal malocclusions due to their similar embryologic origin in which the cranial base acts as the linking factor (13,36). The evaluation and classification of orthodontic malocclusion are based on diverse clinical manifestations and cephalometric morphology. The utility of the lateral cephalometric radiographs to precisely evaluate skeletal malocclusions is higher since the skeletal relationship of the maxillar and mandibular arches is not affected by discrepancies in the tooth structure like dental caries and fractures (37). We found skeletal class-I malocclusions more frequent in our study population, followed by class-II and class-III. Our findings are similar to that of Dinesh et al. (38), who also reported class-I as the most predominant type of skeletal malocclusion. We observed PP more prevalent in the skeletal class-III malocclusion groups. The results were in agreement with the findings of Bayrakdar et al. (31) and Sonnesen and Kjaer (14), who have reported an association of morphological abnormalities of the cervical column with increased mandibular overjet. The higher frequency of vertebral body fusion was linked to craniofacial abnormalities in the sagittal plane based on early genetic signals related to the diverse functions of the notochord (39). We analyzed the types of PP among the various skeletal malocclusion groups and found that the partial form was the most common type. The partial type was predominant among the skeletal class-II malocclusion, which is similar to the previous studies by Lo Giudice et al. (22) (3.9%) and Ain et al. (40) (49.5%) (26). Our findings also emphasize the positive correlations between skeletal malocclusion, craniofacial deformities, and cervical vertebral anomalies (1,31).

The clinical importance of PP may be related to surgical concerns in the management of atlantoaxial instability (41). This anomaly of the skeletal column is present in the region of the vertebral artery, greater occipital nerve, and epidural venous plexus, which are all essential neuro-vascular structures (41-43). The intraforaminal segment of the vertebral artery can be severely compressed by PP, resulting in blood flow abnormalities in the vertebral arteries and a spreading deficiency in the inferior branches of the posterior cerebellar arteries (43,44) and increasing the risk of neurological disorders such as Barré-Lieou syndrome, migraine, and vertigo that may cause nausea, vision problems, retro-orbital pain, tinnitus, dizziness, headaches, paralysis of the extremities, and disturbances in swallowing and phonation (9,45). Significant bleeding and occipital neuralgia

can result from any vertebral injury inflicted on this region during the atlantoaxial fusion (42,43,45). According to Young et al. (41), the misinterpretation of PP for a broad posterior arch of the atlas during the placement of a lateral mass screw can lead to stroke or even death due to embolism, thrombosis, or arterial dissection due to vertebral artery injury. Furthermore, given the extensive range of osseous involvement in Nevoid Basal Cell Carcinoma Syndrome (NBCCS), the calcification of atlanto-occipital ligament has recently been postulated as an additional radiological finding in NBCCS (46). NBCCS, also known as Gorlin-Goltz syndrome, is a rare multisystemic disease often inherited as an autosomal dominant trait with high penetrance and varied expression (47). Based on the observations from Leonardi et al. (46) and Friedrich (48), a strong association of PP in individuals with NBCCS syndromic patients has been reported. Thus, the understanding of anomalies and pathologies of the craniofacial junction using radiological imaging as a baseline screening tool is essential to assist in the diagnosis and prediction of any likely consequences, which might be beneficial for the patients.

Study Limitations

The current study has an inherent limitation of the inability to evaluate the three-dimensional morphology and symmetry of PP. Although the findings of our study suggest that these radiographs are adequate for screening cervical spine anomalies such as PP, a 3D imaging modality is essential for the accurate diagnosis and morphological evaluation of the skeletal column anomalies.

Conclusion

In conclusion, PP was more common among the skeletal class-III malocclusion groups. Although PP did not show any predilection for a particular age range, male predominance was observed. We also suggest that the possible relationship between the maxillofacial region and vertebra needs to be studied in large-scale future prospective studies as their association is still unclear.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics and Research Committee, AB Shetty Memorial Institute of Dental Sciences, Constituent College of NITTE (treated as University), Mangalore (protocol number: Ethics/ABSMIDS/188/2022, date: 21.01.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.D., Design: S.B., R.L.C., Data Collection or Processing: M.F.A., Analysis or Interpretation: S.B., Literature Search: V.A., Writing: D.D.

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Primary gastric squamous cell carcinoma: A diagnostic dilemma

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Keywords: Primary gastric squamous cell carcinoma, metastatic carcinoma, poorly differentiated carcinoma of the stomach, gastric cancer, PGSCC

ABSTRACT

Primary gastric squamous cell carcinoma (SCC) is an extremely rare entity with very few cases reported worldwide. We present a case of a large locally advanced gastric mass with liver metastasis, with no involvement of the gastric mucosa. Clinical presentation, serum markers, imaging, endoscopy, and histopathology, created a dilemma in its diagnosis. However, immunohistochemistry helped in the diagnosis. This case serves as a reminder to consider primary gastric SCC as a differential while evaluating a gastric mass.

Introduction

Primary gastric squamous cell carcinoma (PGSCC) is extremely rare, with very few case reports seen in the literature, accounting for 0.2% of all primary gastric cancers (1). The pathogenesis of PGSCC remains unclear, and the optimal treatment strategy is controversial. We describe a case of PGSCC presenting as a large exophytic mass with metastasis, with no involvement of the gastric mucosa.

Case Presentation

A 47-year-old male with a history of significant daily alcohol intake, presented with vague upper abdominal pain and fullness and early satiety for three 3 months. He reported no vomiting, hematemesis, melena, weight loss, or fever. There were no medical comorbidities. His physical examination revealed an ill-defined, smooth, non-tender mass of around 10x12 cm in the epigastric region, with variable consistency and not moving with respiration. Blood tests showed anemia (hemoglobin 8 g/dL) and hypoalbuminemia (2.3 g/dL).

Contrast-enhanced computed tomography (CECT) showed a 14x18.7 cm sized, lobulated, heterogeneous enhancing lesion in the lesser sac, not separately visualized from the lesser curvature of the stomach with loss of fat planes with the left lobe of the liver, duodenum, body of pancreas, common hepatic artery, portal vein, splenic artery, and splenic vein. Multiple enlarged, peri-gastric, celiac, periportal, and para-aortic lymph nodes, and heterogeneously enhancing nodular lesions in the left lobe of the liver were detected (Figure 1A). CA 19.9 was 56.69 U/mL (<27 U/mL), CEA was 1.20 ng/mL (≤4.7 ng/dL) and alpha-fetoprotein was 361 ng/mL (≤7 ng/mL). Gastroscopy revealed

no involvement of the mucosa but luminal narrowing in the body of the stomach (Figure 1B). Endoscopic ultrasonography suggested a large paragastric mass with necrotic areas and the involved layers of the stomach could not be delineated (Figure 1C). An endoscopic ultrasonography-guided fine-needle biopsy was sent for cytology and histopathological examination.

Cytology and histopathology sections showed sheets of large pleomorphic cells with a high N: C ratio, abundant eosinophilic cytoplasm with a round to oval vesicular nuclei with occasional cells showing prominent nucleoli. Many bizarre forms, tumor giant cells, a high mitotic count, and atypical mitosis were also seen. Immunohistochemistry revealed positivity for cytokeratin (CK) and P63 (Figure 2). All other markers such as LCA, CK7, CK 20, CDX2, DOG1, CD117, synaptophysin, chromogranin, beta-catenin, heppar 1, arginase, HMB45, and HER2 were negative, thus ruling out other possible primaries. A diagnosis of poorly differentiated SCC was rendered. Due to its rarity, before diagnosing a primary from the stomach, we wanted to rule out other primary sites. Hence, positron emission tomography (PET) scan was performed which showed a hypermetabolic exophytic mass arising from the body and antro-pyloric region of the stomach with metastasis in both lobes of the liver and compression of the pancreas and duodenum (Figure 1D). Palliative chemotherapy was planned by the medical oncology team. After one cycle of gemcitabine and carboplatin, the patient was discharged. Before his 2nd cycle of chemotherapy, he succumbed to his illness.

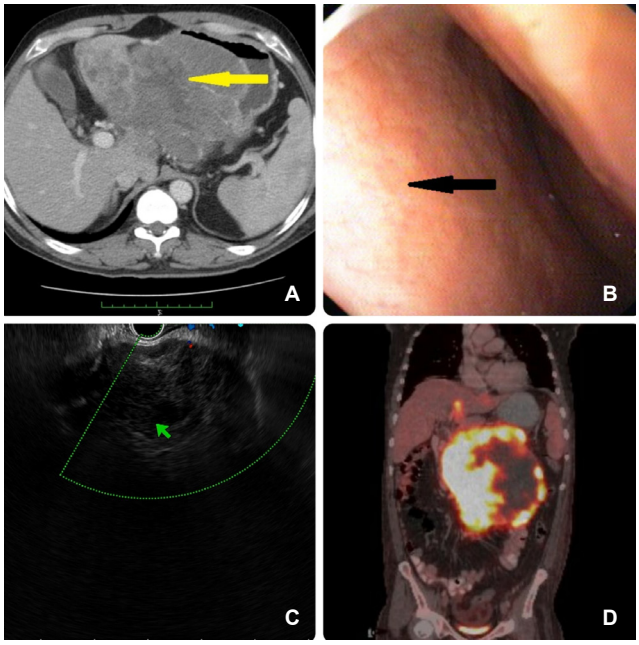

Figure 1. A) CECT image showing a large lobulated mass in the lesser sac, adjacent to the stomach. **B)** Endoscopic image showing a large mass causing luminal narrowing with normal mucosa. **C)** Endoscopic ultrasonography showing a large para gastric mass. **D)** PET/CT image showing hypermetabolic, large, exophytic growth from the stomach, and liver metastasis with no other lesions

CECT: Contrast-enhanced computed tomography, PET/CT: Positron emission tomography/computed tomography

Discussion

Gastric carcinoma is the fifth most common malignancy worldwide and the fourth leading cause of cancer death. There are different histological types, among which adenocarcinoma is the commonest (90%) (1). However, PGSCC is the rarest type with an incidence of 0.04 to 0.07% (2).

The pathogenesis of this is not well known; therefore, several hypotheses have been proposed, such as the presence of totipotent cells, squamous differentiation of pre-existing adenocarcinoma, presence of ectopic squamous cell nests, squamous metaplasia of the glandular epithelium, secondary to chronic mucosal damage, SCC from the vascular endothelium, and Epstein Barr virus infection (3). The reported cases show male predominance and higher prevalence in the sixth decade of life (1,3-5). Most of these cases had a history of smoking and alcohol intake (4,6). The clinical presentation is not specific and shares similarities with other gastric malignancies. Typical symtoms are non-specific abdominal pain and discomfort, vomiting, hematemesis, melena, weight loss, bloating, and early satiety (4).

Certain studies have shown anemia (66.7%), hypoalbuminemia (42.9%), and elevated cancer antigen 19-9 (33.3%) (3). Variable presentations such as submucosal mass, polypoid growth, ulcerated necrotic growth and exophytic growth have been noted (2,4,7,8). In our case, endoscopy looked like a submucosal growth, leading to a misdiagnosis of either gastrointestinal stromal tumor (GIST), gastric schwannoma, or leiomyoma. Using CECT and PET, which showed an infiltrative malignant tumor with metastasis, benign and slow-growing tumors like gastric schwannoma and leiomyoma (9) were ruled out. In the next step, differential diagnoses of a primary gastric tumor with metastasis, malignant GIST, hepatocellular carcinoma, and pancreatic lesion with metastasis were considered. Histopathology revealed features of poorly

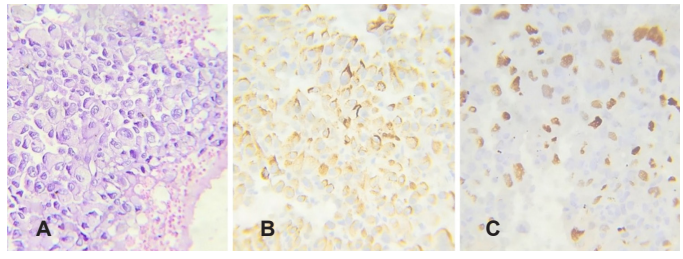

Figure 2. Immunomorphological features of poorly differentiated SCC of the stomach with neoplastic poorly differentiated cells displaying pleomorphic features (**A**, hematoxylin-eosin stain, x400). The neoplastic cells are immunoreactive for pan-cytokeratin (cytoplasmic and membranous) (**B**, x400) and P63 (nuclear) (**C**, x400) (immunoperoxidase stain, HRP polymer method)

SCC: Squamous cell carcinoma

differentiated carcinoma, which is the most common subtype (46.5%) of all gastric SCCs (5). The positivity of immune markers such as CK and P63 indicated gastric SCC. Since previous studies have shown strong staining for P63 has a specificity of 99% and sensitivity of 98% for SCC (3), we ruled out other pathologies using histopathology and immunohistochemistry.

Diagnostic criteria for gastric SCC, described in 1967, indicate that the tumor should not be located at the cardia and extend to the esophagus without evidence of SCC in another part of the body (10). Later in 2011, the Japanese Gastric Cancer Association suggested new criteria, recommending that all tumor cells should be SCC cells without any gland cancer cells and that SCC must originate from the gastric mucosa (11).

Due to its rarity, no standard treatment protocol exists for gastric SCC. Surgical resection is the choice for the local disease. Adjuvant and neo-adjuvant chemotherapy and radiotherapy have also been used in managing such cases (6). Since our patient had an advanced-stage disease, we planned palliative chemotherapy with gemcitabine and carboplatin. Different combinations of paclitaxel, carboplatin, docetaxel, fluorouracil, oxaliplatin, gemcitabine, and pirarubicin have been tried (3,4). However, there is no consensus on a particular regimen. Our patient succumbed to his illness within two months of diagnosis, before the completion of the treatment. Gastric SCC has a poor prognosis with a median survival of about eight months (1,5), probably due to its locally aggressive behavior, diagnosis at an advanced stage, poorly differentiated tumor grade, and early metastasis (3,4).

Conclusion

PGSCC is a rare type of gastric cancer with unclear pathogenesis, variable presentations, aggressive behavior, no standard treatment protocol and poor prognosis. Hence, clinical suspicion is crucial for early diagnosis and management. More so, increased awareness is important in the correct evaluation of gastric tumors.

Ethics

Informed Consent: Written consent was obtained from the patient's wife for reporting the case report, as the patient succumbed to his illness.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.P., A.K., C.D., J.S., Concept: C.D., J.S., Design: C.D., J.S., Data Collection or Processing: S.P., A.K., Analysis or Interpretation: S.P., A.K., Literature Search: S.P., A.K., Writing: S.P., A.K., C.D., J.S.

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