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ORIGINAL ARTICLE

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Antimicrobial Susceptibility Patterns of *Staphylococcus aureus* in Decubitus Ulcer Infections

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Abstract

Objective: Decubitus ulcers, also called bedsores or pressure ulcers, are skin and soft tissue injuries caused by sustained or prolonged pressure on the skin. *Staphylococcus aureus* (*S. aureus*) is one of the most frequently isolated bacteria in patients with decubitus ulcer infection. In this study, we aimed to retrospectively determine the antimicrobial susceptibility profile of *S. aureus* strains isolated from wound swab cultures of patients hospitalized in various wards.

Methods: Wound swab cultures were examined from patients with clinical signs of decubitus ulcer infection during inpatient treatment in different wards with various diagnoses between January 2009 and October 2019. In these samples, the antimicrobial susceptibility profile data of 132 *S. aureus* strains belonging to 132 different patients who were considered clinically significant were included in our study.

Results: Among all specimens, 132 (13.83%) *S. aureus* positivity cases were included in our study. The methicillin-resistant (MRSA) rates were 43.85% (24/56) in male patients and 57.14% (32/56) in female patients with decubitus ulcer infection. Of the *S. aureus* strains, 42.42% (56/132) were MRSA and 57.58% (76/132) were methicillin-susceptible (MSSA). Linezolid was found to be the most effective antibiotic among MRSA strains, whereas all MSSA strains were susceptible to amoxicillin + clavulanic acid, rifampicin, and cefoxitin.

Conclusion: Antimicrobial resistant strains such as MRSA may be encountered in half of *S. aureus* infections and may complicate treatment options. We conclude that infections and antimicrobial resistance profiles should be routinely monitored.

Keywords: *Staphylococcus aureus*, MRSA, MSSA, decubitus ulcers

INTRODUCTION

Decubitus ulcers, also called bedsores or pressure ulcers, are skin and soft tissue injuries resulting from continuous or prolonged pressure applied to the skin. Ulcers occur in bony parts of the body, and lesions mostly occur in people with conditions that reduce mobility and make it difficult to change posture (1). They are serious complications resulting from multiple morbidities and immobilization. Decubitus ulcers are rare among bedridden patients owing to the conscious use of pressure-reducing measures and increased mobilization. However, not all decubitus ulcers can be considered preventable or potentially treatable (2). Complications of decubitus ulcers are associated with significant morbidity and mortality. Bacterial infection is the most common complication associated with decubitus ulcers. Infection of the decubitus ulcer may lead to soft tissue and bone infections, such as cellulitis, abscess formation, bursitis, and osteomyelitis, in the bone under the wound bed (3). Decubitus ulcers are most commonly seen in the lower half of the body, along bony prominences, such as the sacrum and

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heels, in bedridden patients. Blood flow to compressed tissue is restricted, and toxic metabolites begin to accumulate over time, while nutrient distribution stops, leading to cell death. In addition, as circulation is restricted, the immunologic response around the wound becomes ineffective, and the ability to heal is compromised (4). *S. aureus* is one of the bacteria frequently isolated in patients with decubitus ulcer infection. *S. aureus* is known to be a common colonizing microorganism in human epithelium, especially in the nose. However, in decubitus ulcers, *S. aureus* may colonize and be a source of infection in the region. It has different virulence factors that help it cause serious infections ranging from decubitus ulcer infection to osteomyelitis and bacteremia (5). *S. aureus* isolates with an auxiliary penicillin-binding protein (PBP2a/PBP2c encoded by *mecA* or *mecC* genes) for which β-lactam agents have low affinity, except for the novel class of cephalosporins having anti-methicillin-resistant (MRSA) activity (ceftaroline and ceftobiprole). European Committee on Antimicrobial Susceptibility Testing's (EUCAST) MRSA definitions: "isolates that test resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to β-lactam β-lactamase inhibitor combinations, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin." The susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility, except for cefixime, ceftazidime, ceftazidimeavibactam, ceftibuten, and ceftolozanetazobactam, which do not have breakpoints and should not be used for staphylococcal infections. For agents given orally, care to achieve sufficient exposure at the site of the infection should be exercised. If cefotaxime and ceftriaxone are reported for methicillin-susceptible (MSSA) staphylococci, these should be reported "susceptible, increased exposure". Some MRSA *S. aureus* are susceptible to ceftaroline and ceftobiprole" (6). Decubitus ulcer infection is an important reservoir for MRSA in hospitals, and these patients are known as high-risk patients for MRSA bacteremia. MRSA detection may contribute to prolonged hospitalization and poor prognosis in these patients. Along with *S. aureus*, Gram-negative bacilli are the most common bacterial pathogens in infected decubitus ulcers (7).

However, it is known that a biofilm layer that protects the pathogen from the effects of many antibiotics can form in decubitus ulcer infections, which contributes to the secretion of toxins by the pathogen that cause more damage to the skin and surrounding tissues and the emergence of multidrug-resistant strains, such as MRSA, making the treatment of infected decubitus ulcers difficult (8). One of the methods used to characterize organisms as multidrug-resistant is based on *in vitro* antimicrobial susceptibility test results, when they test "resistant to multiple antimicrobial agents, classes or subclasses of antimicrobial agents". The definition most frequently used for Gram-positive and Gram-negative bacteria is "resistant to three or more antimicrobial classes" (9). In this study, we aimed to retrospectively determine the antimicrobial susceptibility profile of *S. aureus* strains detected as causative agents of decubitus ulcer infection in wound swab cultures of patients hospitalized in various wards.

METHODS

In our study, we examined wound swab cultures obtained from patients with clinical signs of decubitus ulcer infection during inpatient treatment in different wards with various diagnoses between January 2009 and October 2019. In these samples, the antimicrobial susceptibility profile data of 132 *S. aureus* strains belonging to 132 different patients who were considered clinically significant were included in our study. The data and antimicrobial susceptibility profiles of these strains were retrospectively collected through the hospital information management system. Among consecutive samples from the same patient, only the first positive result was included in the study; results from other repeat strains of the same patient were excluded. Because this was a retrospective study, informed consent was not required. Ethics committee approval was obtained for the use of retrospective antimicrobial susceptibility profile data of *S. aureus* strains [Private Medical Park Fatih Hospital Academic and Ethics Committee (approval number: 2021-1-2, date: 26.04.2021)].

The presence of infection at the ulcer site was based on clinical signs and symptoms (erythema, edema, pain, foul odor, fever, etc.). In addition, the wound was considered infected when the ratio of polymorphonuclear cells to squamous epithelial cells was ≥2:1 after Giemsa staining in the smear of wound swab material (10). To isolate and identify *S. aureus*, wound swab culture samples were cultured on 5% sheep blood agar medium in the laboratory. The preparations prepared from the samples were stained with Gram stain. All suspected strains were identified using the Vitek 2 Compact system (Biomerieux, Marcy-l'Étoile, France), and antimicrobial susceptibility profiles were studied. Antimicrobial susceptibility results were evaluated according to the Clinical Laboratory Standards Institute criteria before 2016 and the EUCAST criteria after 2016. The *S. aureus* ATCC 25923 reference strain was used for quality control in all procedures (11,12).

Statistical Analysis

Only descriptive statistical methods were used in this study.

RESULTS

Our study included 954 specimens from patients hospitalized in various wards between January 2009 and October 2019, from which wound swab cultures were obtained during hospitalization. Among all specimens, 132 (13.83%) *S. aureus* positivity detected as the causative agent of decubitus ulcer infection were analyzed. The mean age of female patients with decubitus ulcer infection who were positive for *S. aureus* was 64.94±12.12 years and the mean age of male patients was 66.08±13.85 years. The rate of MRSA was 43.85% (24/56) in male patients and 57.14% (32/56) in female patients with decubitus ulcer infection. Table 1 presents the distribution of antimicrobial susceptibility profiles of the strains. Of the *S. aureus* strains, 42.42% (56/132) were MRSA and 57.58% (76/132) were MSSA. Linezolid was the most effective antibiotic for all strains, and 99.24% were found to be susceptible. This antibiotic was followed by levofloxacin with 80.30% and cefazolin with 79.55%.

The distribution of antimicrobial susceptibility profile of MRSA and MSSA strains included in this study are presented in Table 2. Linezolid was the most effective antibiotic among MRSA strains, and 98.21% of the strains were susceptible. All MSSA strains were susceptible to amoxicillin + clavulanic acid, rifampicin, and cefoxitin. Ampicillin + sulbactam (98.68%) and gentamicin (92.11%) followed these antibiotics with high susceptibility rates.

Table 1. Distribution of antimicrobial susceptibility profiles of the *S. aureus* strains included in the study

	***S. aureus* (n=132)**			
	S		**R**	
	n	**%**	**n**	**%**
Amoxicillin/clav.	76	57.58%	56	42.42%
Ampicillin/sulbactam	76	57.58%	56	42.42%
Erythromycin	40	30.30%	92	69.70%
Gentamicin	78	59.09%	54	40.91%
Clindamysin	82	62.12%	50	37.88%
Cotrimoxazol	66	50.00%	66	50.00%
Levofloxacin	106	80.30%	26	19.70%
Linezolid	131	99.24%	1	0.76%
Methicillin	76	57.58%	56	42.42%
Rifampicin	76	57.58%	56	42.42%
Cefazolin	105	79.55%	27	20.45%
Cefoxitin	76	57.58%	56	42.42%
Ciprofloxacin	100	75.76%	32	24.24%
Tetracyclin	58	43.94%	74	56.06%

S. aureus: Staphylococcus aureus, S: Susceptible, R: Resistant

Table 2. Distribution of antimicrobial susceptibility profiles of MRSA and MSSA strains included in the study

	MRSA (n=56)				**MSSA (n=76)**			
	S		**R**		**S**		**R**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Amoxicillin/clav.	0	0.00%	56	100.00%	76	100.00%	0	0.00%
Ampicillin/sulbactam	1	1.79%	55	98.21%	75	98.68%	1	1.32%
Erythromycin	1	1.79%	55	98.21%	39	51.32%	37	48.68%
Gentamicin	8	14.29%	48	85.71%	70	92.11%	6	7.89%
Clindamysin	24	42.86%	32	57.14%	58	76.32%	18	23.68%
Cotrimoxazol	28	50.00%	28	50.00%	38	50.00%	38	50.00%
Levofloxacin	47	83.93%	9	16.07%	59	77.63%	17	22.37%
Linezolid	55	98.21%	1	1.79%	76	100.00%	0	0.00%
Methicillin	0	0.00%	56	100.00%	76	100.00%	0	0.00%
Rifampicin	0	0.00%	56	100.00%	76	100.00%	0	0.00%
Cefazolin	31	55.36%	25	44.64%	74	97.37%	2	2.63%
Cefoxitin	0	0.00%	56	100.00%	76	100.00%	0	0.00%
Ciprofloxacin	37	66.07%	19	33.93%	63	82.89%	13	17.11%
Tetracyclin	32	57.14%	24	42.86%	26	34.21%	50	65.79%

MRSA: Methicillin-resistant, MSSA: Methicillin-susceptible, S: Susceptible, R: Resistant

DISCUSSION

Decubitus ulcer infections are a common complication in patients with reduced mobility. They often develop in elderly patients and in patients with debilitating diseases and spinal cord injury (13). The microbiota of the decubitus ulcer site is often polymicrobial and complex and can be colonized by multidrug-resistant Gram-negative bacilli and bacteria such as MRSA. This region may be a reservoir for resistant microorganisms and may turn into local infections due to the effects of these bacteria, and it is also known that it may turn into bacteremia and become an important cause of mortality in hospitalized patients (10). In our study, we retrospectively determined the antimicrobial susceptibility profile of *S. aureus* strains found to be causative agents in patients with decubitus ulcer infections over an 11-year period. In international studies were analyzed; Nery Silva Pirett et al. (7) reported that MRSA was detected in 43.5% of 145 patients. They reported that 42% of patients with MRSA were male and 58% were female. The mean age of patients with MRSA was reported to be 64.2±16.3 years (7). In 2024, Sharp (14) reported that MRSA was colonized in 48% of decubitus ulcers in elderly people over 65 years old staying in residential aged care facilities. Their data were similar to those of our study (7,14). Braga et al. (15) reported that *S. aureus* positivity was detected in 20.7% of 145 patients. Dana and Bauman (3) analyzed studies published between 1996 and 2004 and found that *Staphylococcus* species were reported as causative agents in 23% of the studies. Binsuwaidan et al. (16) reported *S. aureus* as the most frequently isolated bacteria in 2023 and stated that 28% of these *S. aureus* isolates were generally sensitive to clindamycin, mupirocin, trimethoprim, and linezolid. MRSA was detected 60.3% (35 out of 58 *S. aureus* strains) of these ulcers. In our study, 13.83% *S. aureus* (and 42.42% of MRSA) was detected, and although this rate is lower than that reported in the literature, the fact that our samples originated from a private hospital may be the reason for this difference. Chronic wounds or pressure ulcers are characterized by colonization by microorganisms, and infections are known to develop in 5% to 80% of cases due to various factors (17). The observation of a polymicrobial and heterogeneous population of microbes in a pressure ulcer infection as a chronic wound can be attributed to the presence of virulence factors, such as biofilms, especially in the causative strains. Therefore, *S. aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *Peptostreptococcus* spp. are frequently encountered. Multiresistant strains, such as MRSA, *Acinetobacter* spp., and *Pseudomonas* spp., are also frequently detected as dominant agents (17). When national studies are examined; Öztin et al. (18) detected *S. aureus* infection in 7 patients in Erzurum within a 1-year period. Öztürk and Öztin (11) reported that they detected *S. aureus* positivity in 2 (3.7%) of the wound cultures of 42 patients in their study conducted in Erzurum in 2018. They reported that these strains were 100% resistant to ampicillin and ciprofloxacin, 50% resistant to gentamicin, and sensitive to tigecycline (11). Öztürk et al. (19) detected *S. aureus* in 2 (7.69%) patients in their study conducted in Ankara in 2019-2020. They reported 50% ampicillin, 50% ciprofloxacin, and 50% gentamicin resistance in these strains. Turhanoğlu et al. (20) reported that 41.4% of the microorganisms isolated from wound cultures between 2010 and 2015 were *S. aureus*. In this study, similar to our study, 100% susceptibility was found for linezolid, teicoplanin, and vancomycin. Cirit et al. (21) reported 13.7% (150/1093) positivity for *S. aureus* in wound cultures between 2010 and 2012. They reported that 27.3% of these strains were MRSA. They detected 100% susceptibility to teicoplanin and vancomycin. Erdiren et al. (22) reported 15.4% *S. aureus* positivity in wound cultures in a four-year period. They were 100% sensitive to linezolid, teicoplanin, and vancomycin. It can be seen that our study is similar to the literature data. Linezolid was found to be effective against these infections.

Study Limitations

Wound cultures were collected at different times and with different methods; therefore, we collected the patients belonging to the most common method, i.e., swab culture method. If appropriate conditions exist, the preferred method for wound culture is to excise and sample the deep tissue. This is a limitation for our study.

CONCLUSION

In conclusion; *S. aureus* can be a causative agent of decubitus ulcer infections. It should be kept in mind that antimicrobial resistant strains, such as MRSA, may be encountered in half of *S. aureus* infections and may complicate treatment options. Although newer antibiotics, such as linezolid, currently appear to be active *in vitro* for the treatment of these infections, it is clear that these strains may lose their *in vivo* activity because of their biofilm properties, and new antimicrobial options are needed. We believe that these infections and antimicrobial resistance profiles should be routinely monitored.

Footnote

Ethics Committee Approval: Ethics committee approval was obtained for the use of retrospective antimicrobial susceptibility profile data of *S. aureus* strains [Private Medical Park Fatih

Hospital Academic and Ethics Committee (approval number: 2021-1-2, date: 26.04.2021)].

Informed Consent: A retrospective study, informed consent was not required.

Authorship Contributions

Concept: A.B., Ö.Ü., M.D., Design: A.B., Ö.Ü., S.G., M.D., Data Collection or Processing: A.B., M.G.E., S.G., Analysis or Interpretation: A.B., M.G.E., Ö.Ü., Literature Search: A.B., S.G., Writing: A.B., M.G.E., M.D.

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ORIGINAL ARTICLE

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Incidence and Impact of Hypophosphatemia on Renal Function in Kidney Transplant Recipients: A Single-center Study

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Abstract

Objective: Hypophosphatemia is a common complication of kidney transplantation. However, the relationship between hypophosphatemia and renal function in patients undergoing kidney transplantation remains uncertain. This study aimed to evaluate the relationship between serum phosphate levels and graft function in patients undergoing renal transplantation within the first 3 months after transplantation.

Methods: We conducted a retrospective cohort study included patients who underwent kidney transplantation between 2016 and 2020. Data on patient demographics and clinical and laboratory findings, such as serum creatinine, phosphate, calcium, hemoglobin and parathormone levels, were collected from the hospital database.

Results: Hypophosphatemia was observed in 59 (47.5%), 41 (33.06%) and 32 (25.8%) patients at the 1st week, 1st month and 3rd month after transplantation. The post-transplant median creatinine levels decreased to 1.36 (1.01-1.58) mg/dL, 1.22 (1.04-1.5) mg/dL, and 1.20 (1.0-1.49) mg/dL at week 1, month 1 and month 3. The median phosphate level before transplantation was 5.1 (4.8-5.7) mg/dL. This value decreased to 2.5 (1.8-3.27) mg/dL, 2.82 (2.05-3.55) mg/dL, and 3.01 (2.30-3.73) mg/dL at week 1, month 1 and month 3. There was no significant difference in serum creatinine and estimated glomerular filtration rate between the hypophosphatemic and normophosphatemic groups at week 1 (p=0.839, p=0.931), month 1 (p=0.453, p=0.441) and month 3 (p=0.592, p=0.570). The causes of end-stage renal disease were chronic glomerulonephritis in 20 patients (16.1%), hypertension in 35 (28.2%), diabetes mellitus in 18 (14.5%) (17 type 2 and 1 type 1), and secondary amyloidosis in 5 (4%). Nephrolithiasis, autosomal dominant polycystic kidney disease, vesicoureteral reflux, and no identifiable cause were found in 7 (5.6%), 4 (3.2%), 16 (12.9%) and 19 (15.3%), patients respectively.

Conclusion: Hypophosphatemia is common after kidney transplantation. No correlation was identified between hypophosphatemia and functional performance of the transplanted kidney.

Keywords: Hypophosphatemia, kidney transplant, graft function

INTRODUCTION

As chronic kidney disease progresses, fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH) levels increase and calcitriol levels decrease and this contributes to hyperphosphatemia (1,2). After successful kidney transplantation, blood levels of certain molecules may rapidly change in the presence of a functioning graft, potentially resulting in hypophosphatemia (3-5). Hypophosphatemia has been reported in approximately 22% to 85% of patients following successful kidney transplantation (3,5-11). However, the relationship between hypophosphatemia and renal function in patients undergoing renal transplantation remains unclear.

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The objective of this study was to assess the correlation between serum phosphate levels and graft function in patients undergoing renal transplantation during the initial 3 months after transplantation.

METHODS

We conducted a retrospective cohort study included patients who underwent kidney transplantation at our hospital between 2016 and 2020. Initially, 127 participants were enrolled in this study. The inclusion criteria for this study were that the participant had undergone their first kidney transplantation for at least one year prior. The exclusion criteria for this study were early post-transplant death (n=2), primary non-functioning transplanted kidney (n=0), loss to follow-up within 3 months after transplantation (n=1), age below 18 years, and history of parathyroidectomy before transplantation. The remaining 124 participants were followed from the date of transplantation until the end of the study (January 31, 2021).

Following the study's objectives and protocol, which were aligned with the ethical standards outlined in the "Declaration of Helsinki" and sanctioned by the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision number: 2020-23-07, date: 16.11.2020), the patients' records were retrospectively examined using the hospital information system.

Patient demographics and clinical and laboratory findings were collected from the hospital database. These included age, sex, dialysis type, donor age, and sex; serum creatinine, phosphate, calcium, hemoglobin, PTH, and tacrolimus levels, as well as follow-up records. We collected data on immunological and clinical factors that may impact the outcomes. These factors include preemptive kidney transplantation (defined as transplantation without prior dialysis treatment), donor status (living or deceased), presence of donor-specific antibodies, and type of immunosuppressive drug administered.

During the first year after transplantation, patients were monitored, and routine laboratory tests were conducted to record data on serum creatinine, phosphate, calcium, albumin, and PTH levels. These tests were conducted before transplantation as well as during the first week, first, and third months after transplantation. Post-transplant hypophosphatemia was defined as a serum phosphate level below 2.3 mg/dL. The assessment of renal allograft function was performed by calculating the estimated glomerular filtration rate (eGFR) using the chronic kidney disease - epidemiology collaboration creatinine 2021 equation.

If necessary, the patients received anti-thymocyte globulin at a dose of 1.5 mg/kg daily for 5 days. Following a total of 1500 mg of intravenous methylprednisolone, the patient was switched to oral prednisolone at 40 mg/day. The prednisolone dosage was gradually reduced to 30 mg/day after one week, 20 mg/day after two weeks, and 5 mg/day after one month.

During the maintenance phase, patients were prescribed a calcineurin inhibitor (tacrolimus or cyclosporin) in two divided doses, along with an antiproliferative agent (mycophenolate mofetil up to 2 g/day or mycophenolate sodium up to 1440 mg/day) in addition to prednisolone. Calcineurin inhibitor dosage was adjusted as necessary to maintain target blood levels.

Renal biopsy was performed in cases of acute rejection. Treatment was administered according to the Banff criteria, including pulse methylprednisolone, anti-thymocyte globulin, plasmapheresis, and intravenous immunoglobulin alone or in combination.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics (Version 23.0; IBM Corp., Armonk, NY). The Mann-Whitney U test was used to compare the findings between the hypophosphatemic and normophosphatemic groups for each time period. Pearson's correlation analysis was used to assess the linear association between serum phosphate levels and other variables. The data are presented in two formats: median interquartile range, and percentages (%), as appropriate. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS

In the study group, females constituted 37.9% (n=47) and males 62.1% (n=77) of the 124 patients, respectively. The median age was 40.00 (30.25-52.00) years, and the median follow-up period was 29 (ranged, 12 to 45) months. Table 1 presents the characteristics of dialysis type, number of human leukocyte antigen mismatches, graft type, and induction and maintenance immunosuppressive treatment.

The causes of end-stage renal disease were chronic glomerulonephritis in 20 patients (16.1%), hypertension in 35 (28.2%), diabetes mellitus in 18 (14.5%) (17 with type 2 and 1 with type 1), and secondary amyloidosis in 5 (4%) patients respectively. Nephrolithiasis, autosomal dominant polycystic kidney disease, vesicoureteral reflux, and no identifiable cause were found in 7 patients (5.6%), 4 patients (3.2%), 16 patients (12.9%), and 19 patients (15.3%), respectively.

During the follow-up period, acute allograft rejection was observed in 24 (19.3%) patients. The median phosphate level before transplantation was 5.1 (4.8-5.7) mg/dL. This value decreased to 2.5 (1.8-3.27) mg/dL, 2.82 (2.05-3.55) mg/dL, and 3.01 (2.30-3.73) mg/dL at 1st week, 1st month and 3rd month, respectively.

Hypophosphatemia was observed in 59 (47.5%), 41 (33.06%), and 32 (25.8%) patients at the 1st week, 1st month and 3rd month after transplantation, respectively. Post-transplant median creatinine levels decreased significantly to 1.36 (1.01-1.58) mg/dL, 1.22 (1.04-1.5) mg/dL, and 1.20 (1.0-1.49) mg/dL at 1st week, 1st month and 3rd month, respectively. Table 2 shows patients' characteristics according to serum phosphate levels at 1 week, 1. and 3. month post-transplant.

Table 1. Clinical characteristics of the cohort

Variables	
Number	124
Recipient gender • Female, n (%) • Male, n (%)	 47 (37.9%) 77 (62.1%)
Donor gender • Female, n (%) • Male, n (%)	 67 (54.03%) 57 (45.97%)
Age, year (median, IQR)	40.00 (30.25-52.00)
Type of dialysis, n (%) • Preemptive • Hemodialysis • Peritoneal dialysis	 67 (54.03%) 55 (44.35%) 2 (1.61%)
Donor type • Living • Deceased	 114 (91.93%) 10 (8.07%)
Miss match count, n (%) • 0 MM • 1 MM • 2 MM • 3 MM • 4 MM • 5 MM • 6 MM	 4 (3.22%) 11 (8.87%) 16 (12.90%) 41 (33.06%) 23 (18.54%) 15 (12.09%) 14 (11.29%)
Follow-up time, (month)	29 (ranged, 12 to 45)
Induction treatment, n (%) • ATG • None	 88 (70.96%) 36 (29.04%)
Maintenance treatment • Tac + MMF • Tac + MFNa • Cyc + MMF • Cyc + MFNa	 109 (87.90%) 14 (11.29%) 1 (0.80%) 0
Acute rejection, n (%)	24 (19.3%)

IQR: Interquartile range, MM: Miss match, ATG: Anti-thymocyte globulin, Tac: Tacrolimus, MMF: Mycophenolate mofetil, MFNa: Mycophenolate sodium, Cyc: Cyclosporine

The median PTH level before transplantation was 275.5 (156.7-474.75) ng/L. This value decreased to 155.4 (96.7-254.50) ng/L at 1st month and 113.42 (86.7-174.50) ng/L at 1st year. There were no significant differences in PTH levels between the normo- and hypophosphatemic patients.

Significant differences were found between the pre-transplant laboratory parameters and the post-transplant parameters at the 1st week, 1st month, and 3rd month ($p<0.05$). Table 3 presents the laboratory parameters before and after transplantation.

No significant difference was found between the serum creatinine and eGFR values of the hypophosphatemic group and normophosphatemic group at 1 week ($p=0.839$, $p=0.931$), 1st month ($p=0.453$, $p=0.441$), and 3rd month ($p=0.592$, $p=0.570$), respectively.

There was no significant correlation between serum phosphate and creatinine levels at 1 week ($r=0.063$, $p=0.488$), 1st month ($r=0.058$, $p=0.527$), and 3rd month ($r=0.43$, $p=0.642$). Similarly, no significant correlation was found between serum phosphate and eGFR levels at 1st week ($r=-0.031$, $p=0.732$), 1st month ($r=-0.048$, $p=0.600$), and 3rd month ($r=-0.064$, $p=0.485$).

DISCUSSION

Hypophosphatemia is a common electrolyte disorder after successful kidney transplantation and can be observed in up to 85% of patients in the early post-transplant period (11). In the early post-transplant period, hypophosphatemia is often observed, particularly in the first year (4). This is caused by an increase in renal phosphate excretion capacity, which is attributed to high levels of FGF-23 and PTH following the return of renal function (4). In the current study, hypophosphatemia was observed in 41 (33.06%) in the first month after transplantation. A previous study reported hypophosphatemia in 43.6% of patients during the third month after transplantation (12). Our study obtained similar results.

In our study, no significant correlation or difference was found between the serum creatinine and eGFR values of the hypophosphatemic and normophosphatemic group at 1st week, 1st month, and 3rd month, respectively. Similar to our findings, a study by Kim et al. (13) found no relationship between hypophosphatemia and graft outcomes.

In contrast to our study, a study by Nakai et al. (14) on 90 kidney transplant patients found that hypophosphatemia was an independent predictor of good kidney survival at the 1st and 3rd months post-transplant but not at the 12th month post-transplantation (14). Similarly, in contrast to our study, van Londen et al. (15) showed that graft failure was lower

in patients who developed hypophosphatemia after kidney transplantation than in those who did not develop hypophosphatemia. Also, Işıktaş Sayılar (16) found that hypophosphatemia following kidney transplantation was correlated with better kidney function.

After kidney transplantation, it has been demonstrated that elevated PTH levels decrease during the first 3 months (17). In the first 3 months after kidney transplantation, FGF-23 and PTH levels decrease rapidly because of increased 1,25-dihydroxyvitamin D production (18). In our study, no significant difference was found between the patient groups with and without hypophosphatemia regarding PTH levels. This finding is consistent with those of similar studies in the literature (9,19).

Table 2. Patients' characteristics according to serum phosphate levels at 1 week, 1. and 3. month post-transplant

Variables	Hypophosphatemia in 1st week		Hypophosphatemia in 1st month		Hypophosphatemia in 3rd month	
	+	-	+	-	+	-
n (%)	59 (47.58%)	65 (52.42%)	41 (33.06)	83 (66.94)	32 (25.80%)	92 (74.20%)
Age (years) median (IQR 25-75)	42 (30-53)	39 (31-50)	43 (30-54)	38 (31-51)	45.5 (29.25-54.75)	39 (31-49)
Male recipient, n (%)	35 (59.3)	42 (64.6)	27 (65.9)	50 (60.2)	19 (59.4)	58 (63)
Body mass index median (IQR 25-75)	24.67 (20.93-27.42)	24.74 (21.46-28.17)	24.69 (21.46-27.22)	24.65 (21.27-28.58)	26.28 (22.65-30.27)	24.12 (20.76-26.64)
Living donor, n (%)	55 (93.2)	59 (90.8)	37 (90.2)	77 (92.8)	29 (90.6)	85 (92.4)
Preemptive transplantation, n (%)	33 (55.9)	34 (52.3)	23 (56.1)	44 (53)	20 (62.5)	47 (51.1)
Donor age (years) median (IQR 25-75)	49 (42-58)	48 (38-59)	48 (38.5-56.5)	48 (40-58)	47 (34.5-53.75)	51.5 (40.25-59)
Male donor, n (%)	27 (45.8)	30 (46.2)	19 (46.3)	38 (45.8)	15 (46.9)	42 (45.7)
Drug use, n (%)						
· CNIs, n	5	65	0	8	32	92
· Cyclosporin	0	1 (1.5)	0	1 (1.2)	0	1 (1.1)
· Tacrolimus	59 (100)	64 (98.5)	41 (100)	82 (98.8)	32 (100)	91 (98.9)
· ATG, n	34	37	27	44	24	64
· Antiproliferative agent, n	59	65	41	83	32	92
· Mycophenolate mofetil	49 (83.1)	61 (93.8)	36 (87.8)	74 (89.2)	28 (87.5)	82 (89.1)
· Mycophenolate sodium	10 (16.9)	4 (6.2)	5 (12.2)	9 (10.8)	4 (12.5)	10 (10.9)
Preoperative laboratory median (IQR 25-75)						
· Phosphate, mg/dL	5.3 (4.9-5.7)	5.02 (4.8-5.6)	5.4 (4.9-5.7)	5.1 (4.8-5.6)	5.1 (4.8-5.67)	5.1 (4.8-5.7)
· Pre-transplant PTH, ng/L	265 (190-456)	277 (151-506)	291 (157.5-443.5)	265 (156-490)	281.5 (156.75-583)	275.5 (156.75-462.5)
Laboratory in 3. month median (IQR 25-75)						
· Phosphate, mg/dL	2.4 (1.8-3.27)	3.24 (2.76-4.1)	2.19 (1.75-2.78)	3.3 (2.79-3.96)	1.8 (1.6-2.16)	3.28 (2.82-3.95)
· Calcium, mg/dL	9.4 (9.1-9.83)	9.1 (8.74-9.6)	9.3 (9.1-9.8)	9.2 (8.8-9.8)	9.2 (9-9.75)	9.3 (8.92-9.8)
· eGFR, mL/min/1.73 m^2	68 (50.75-87.25)	69 (52.25-86.5)	72 (55.5-87.5)	66 (52-85)	72 (53-88)	68 (52-85)
· Serum creatinine mg/dL	1.2 (1-1.51)	1.23 (1.09-1.48)	1.2 (1-1.48)	1.23 (1.08-1.55)	1.21 (0.93-1.51)	1.23 (1.07-1.5)

n: Number, IQR: Interquartile range, CNIs: Calcineurin inhibitors, ATG: Anti-thymocyte globulin, PTH: Parathyroid hormone, eGFR: Estimated glomerular filtration rate

Table 3. Laboratory parameters before and after transplantation				
Variables (median IQR 25-75)	Pre-transplant	Post-transplant		
		1st Week	1st Month	3rd Month
Phosphate level (mg/dL)	5.1 (4.8-5.7) mg/dL	2.5 (1.8-3.27) mg/dL	2.82 (2.05-3.55) mg/dL	3.01 (2.30-3.73) mg/dL
Creatinine levels (mg/dL)	5.48 (4.92-6.92) mg/dL	1.36 (1.01-1.58) mg/dL	1.22 (1.04-1.5) mg/dL	1.20 (1.0-1.49) mg/dL
eGFR, mL/min/1.73 m^2	10.60 (7.50-12.00)	65.00 (50.00-81.00)	68.50 (52.00-87.00)	72.50 (57.00-85.00)
Calcium (mg/dL)	8.2 (7.94-8.60)	8.6 (8.21-9.00)	9.1 (8.63-9.60)	9.2 (9.00-9.80)
PTH ng/L	275.5 (156.7-474.75) ng/L	-	155.4 (96.7-254.50) ng/L	113.42 (86.7-174.50) ng/L
IQR: Interquartile range, eGFR: Estimated glomerular filtration rate, PTH: Parathyroid hormone				

Drugs such as high-dose steroids and tacrolimus used in immunosuppressive regimens are believed to cause renal phosphate loss (20). Although hypophosphatemia is frequently observed after kidney transplantation, it is not as common in patients undergoing lung transplantation, for which similar and usually higher doses of immunosuppressive drugs are used (21). In our study, while the majority of patients were on the same immunosuppressive regimen, some developed hypophosphatemia. Therefore, although immunosuppressive drugs may cause urinary phosphate loss, they are unlikely to be the main cause of hypophosphatemia.

Study Limitations

Our study has major limitations, including its retrospective design and single-center nature, small sample size, lack of data on dietary phosphate intake, absence of evaluation of fractional phosphate excretion, and absence of evaluation of FGF-23 and 25-hydroxyvitamin D vitamin levels.

CONCLUSION

In conclusion, hypophosphatemia is common after kidney transplantation. No correlation was identified between hypophosphatemia and functional performance of the transplanted kidney. Further prospective, larger, controlled, multicenter studies are needed to determine the effects of phosphate levels on graft function.

Footnote

Ethics Committee Approval: Following the study's objectives and protocol, which were aligned with the ethical standards outlined in the "Declaration of Helsinki" and sanctioned by the Ethics Committee of University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision number: 2020-23-07, date: 16.11.2020).

Informed Consent: Since the study was designed retrospectively, no written informed consent forms were obtained from the patients.

Authorship Contributions

Concept: Z.T., U.K., E.A., Design: Z.T., U.K., S.A., Data Collection or Processing: Z.T., U.K., F.G.A., Analysis or Interpretation: F.G.A., S.A., Literature Search: Z.T., U.K., S.A., Writing: Z.T.

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ORIGINAL ARTICLE

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Benign and Benign Aggressive Bone Lesions Located in the Femoral Head and Neck: Single-center Experience

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Abstract

Objective: The aim of this study was to present the mid-term outcomes and treatment management of benign and benign aggressive lesions of the femoral head and neck treated surgically in pediatric and adult patients.

Methods: A total of 27 patients who underwent surgical treatment for benign tumors and tumor-like lesions of the femoral neck and head were retrospectively analyzed. Patients were evaluated according to age, gender, diagnosis, follow-up period, lesion location, surgical method, complications, and recurrence development. Functional evaluation was performed using the Musculoskeletal Tumor Society (MSTS) and Toronto extremity salvage score (TESS). Early and late complications, such as infection, wound site issues, physeal injury, avascular necrosis (AVN), non-union, malunion, fracture, and implant failure, were investigated.

Results: The average age was 26 years (range, 8-54 years), and the follow-up period was 74 months (49-108). In 24 patients (89%), the tumor was located in the femoral neck, whereas in 3 patients (11%), it was located in the femoral head. The most common diagnosis was simple bone cysts (33.3%), and the most frequently applied surgical method was curettage + grafting + internal fixation (C + G + IF) (51.8%). The mean MSTS score was 84% (range, 50-100), and the mean TESS score was 96.1 (range, 75-100).

Conclusion: Hip-preserving approaches are important for functional outcomes in the treatment of lesions observed in the proximal femur. Attention should be paid to the nutrient arterial structures to prevent complications such as non-union and AVN. These rare tumoral formations should be considered in patients presenting with pain and limping.

Keywords: Bone tumor, femur neck, curettage, femoral head

INTRODUCTION

The proximal femur is a characteristic location for benign bone tumors and tumor-like lesions. Bone lesions, such as simple bone cyst (SBC), giant cell tumor (GCT), aneurysmal bone cyst (ABC), fibrous dysplasia, osteoblastoma, enchondroma, and chondroblastoma, can be seen in this region (1,2). These tumors are usually small and asymptomatic, but can cause symptoms such as pain, limping, bone destruction, deformity, and pathological fractures.

Surgical treatment is indicated for patients with pathological fractures or at risk of fracture, those with deformities or at risk of deformities, aggressive/recurrent lesions, and symptomatic patients with analgesic-resistant pain or antalgic gait pattern (3). Extensile curettage and reconstruction of the defect with appropriate bone grafts are generally the preferred treatment method. Filling the defect with cement is relatively less preferred due to the risk of fracture against shearing and torsional forces. Internal fixation methods are preferred based on the size, localization, and fracture risk of the lesion (4-6). Additionally, the use of local adjuvants is recommended to prevent recurrence (6). For the resection of lesions in the femoral head and neck, the anterior, lateral, anterolateral, or combined anterior and lateral approaches are used (7). Although arthroplasty is not

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recommended as an initial treatment option, it may be inevitable in aggressive, recurrent, and joint-destructive lesions (8).

Complications such as periarticular destruction, degenerative arthritis, avascular necrosis (AVN) of the femoral head, and non-union after pathological fractures may occur due to these lesions and pathological fractures. Due to the location and complex anatomy of the hip joint, the surgical treatment of lesions in the femoral head and neck poses a challenge for orthopedic surgeons. There is a high risk of injury to the periarticular muscles, joint capsule, cartilage, and bone during surgical treatment (7,9). As these tumors often occur in children and young adults with normal life expectancy, preventing these complications and achieving functional resection are essential.

There are few studies in the literature that describe the characteristics and treatment management of benign and benign aggressive lesions located in the femoral head and neck. The aim of this study was to present the mid-term outcomes and treatment management of benign and benign aggressive lesions of the femoral head and neck treated surgically in pediatric and adult patients.

METHODS

This single-center, retrospective study was conducted at the Orthopedic and Traumatology Clinic of University of Health Sciences Turkey, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital between 2014 and 2022. Twenty-seven patients (15 women, 12 men) who underwent surgical treatment for benign tumors and tumor-like lesions of the femoral neck and head were retrospectively analyzed. Incidental small lesions diagnosed and treated by observation alone were not included in this study. The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Turkey, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (approval number: 2024-04/42, date: 18.04.2024). The study was conducted in accordance with the principles of the Helsinki Declaration and written informed consent was obtained from all patients. Patients with uncertain histopathological results, those whose initial surgery was performed at another center and referred to our clinic due to recurrence, and patients who developed pathological fractures were excluded from the study. Patient data were collected by retrospective review of the patient information system and pathology reports. Indications for surgery included the risk of pathological fracture or pathological fracture, pain, growth of the lesion during follow-up, and aggressive lesions. All patients were evaluated preoperatively with direct radiography and magnetic resonance imaging, and in some patients, computed tomography was additionally used. Patients with characteristic benign lesions, such as simple bone cysts, enchondroma, or fibrous dysplasia, did not undergo preoperative biopsy, and the final histopathological diagnosis was confirmed using tissues obtained during surgery. Patients were evaluated according to age, gender, diagnosis, follow-up period, lesion location, surgical method, complications, and recurrence development. Functional evaluation was performed using the Musculoskeletal Tumor Society (MSTS) and Toronto extremity salvage score (TESS). Early and late complications, such as infection, wound site issues, physeal injury, AVN, non-union, malunion, fracture, and implant failure, were investigated.

Surgical Technique

Depending on the location of the lesion, direct anterior, anterolateral, or posterolateral approaches are used. For patients who did not undergo preoperative biopsy, tissue samples are taken for intraoperative frozen pathological examination to diagnose and confirm the diagnosis for those who underwent preoperative biopsy. The window of the cortical bone must be large enough to allow adequate curettage of the tumor until the underlying normal bone is exposed. Vascular and nerve structures were preserved in all patients. Extended curettage is performed using curettes and a high-speed burr. In particular, for lesions such as GCTs, ABCs, and fibrous dysplasia, local adjuvant treatment with cauterization and agents like phenol or alcohol is applied to extend the margin. In patients who have not completed skeletal growth, care is taken not to damage the physis during these procedures. After curettage, the resulting defect is filled with autogenous-allogeneic bone grafts or cement. In patients with pathological fractures or at risk of fracture, internal fixation (proximal femur plate, cannulated screw) is added to the treatment.

Statistical Analysis

Statistical analyses were performed using the SPSS (IBM SPSS Statistics 27) software package. Frequency tables and descriptive statistics were used to interpret the findings.

RESULTS

The average age during surgery was 26 years (range, 8-54 years), and the follow-up period was 74 months (49-108). In 24 patients (89%), the tumor was located in the femoral neck, whereas in 3 patients (11%), it was located in the femoral head (Table 1).

Histological diagnosis was simple bone cysts in 9 cases (33.3%), enchondroma in 4 cases (14.8%), chondroblastoma in 4 cases

Table 1. Demographics, localization, diagnosis, and treatment					
Age	**Gender**	**Side**	**Location**	**Diagnosis**	**Treatment**
33	F	L	Femoral neck	Giant cell tumor	C + G + IF
27	M	R	Femoral neck	Aneurysmal bone cyst	C + S + IF
8	M	R	Femoral neck	Simple bone cyst	C + G
13	F	R	Femoral neck	Simple bone cyst	C + G + IF
10	M	R	Femoral head	Chondroblastoma	C
45	M	L	Femoral neck	Enchondroma	C + G + IF
38	F	L	Femoral neck	Enchondroma	C + G + IF
32	F	R	Femoral neck	Enchondroma	C + G + IF
17	M	L	Femoral neck	Simple bone cyst	C + G + IF
33	F	R	Femoral neck	Simple bone cyst	C + G + IF
16	F	L	Femoral neck	Aneurysmal bone cyst	C + S + IF
38	M	R	Femoral neck	Fibrous dysplasia	C + G + IF
20	F	R	Femoral neck	Simple bone cyst	C + G + IF
27	M	R	Femoral neck	Simple bone cyst	C + G + IF
18	M	L	Femoral neck	Osteoid osteoma	Total excision
49	F	L	Femoral neck	Fibrous dysplasia	C + G + IF
19	F	R	Femoral neck	Simple bone cyst	C + G + IF
54	F	R	Femoral neck	Fibrous dysplasia	C + G + IF
22	M	R	Femoral neck	Simple bone cyst	C + G + IF
29	M	R	Femoral neck	Osteochondroma	Total excision
54	F	R	Femoral neck	Enchondroma	C + G + IF
19	F	R	Femoral neck	Aneurysmal bone cyst	C + S + IF
8	M	L	Femoral neck	Simple bone cyst	C + G
17	F	L	Femoral neck	Osteochondroma	Total excision
14	M	L	Femoral neck	Chondroblastoma	C + G
21	F	R	Femoral head	Chondroblastoma	C + G
19	F	R	Femoral head	Chondroblastoma	C + G
C: Curettage, G: Grafting, IF: Internal fixation, S: Cement, F: Female, M: Male, L: Left, R: Right					

(14.8%), ABC in 3 cases (11.1%), fibrous dysplasia in 3 cases (11.1%), osteochondroma in 2 cases (7.4%), osteoid osteoma in 1 case (3.7%), and GCT in 1 case (3.7%). The most common symptoms were pain and limping. The primary surgical method applied was curettage + grafting + internal fixation (C + G + IF) in 14 patients (51.8%), followed by curettage + cementation + internal fixation (C + S + IF) in 4 patients (14.8%), curettage + grafting in 5 patients (18.5%), total excision in 3 patients (11.1%), and curettage alone in 1 patient (3.7%) (Table 1, Figure 1). All 27 patients returned to full weight-bearing walking at an average of 13.5 weeks (4-20) postoperatively. The mean MSTS score was 84% (range, 50-100), and the mean TESS score was 96.1 (range, 75-100). Two patients who underwent anterolateral approach showed Trendelenburg gait in the early postoperative period. This pathological gait pattern disappeared after abductor strengthening exercises in these two patients. No infections, implant failures, pathological fractures, physeal injuries, femoral head AVN, or recurrences were observed in any patient. At the final follow-up, all patients had returned to normal unrestricted activities without pain in the operation area.

DISCUSSION

In the proximal femur, which is an anatomical region subjected to heavy mechanical load, there is a risk of fracture and deformation in the presence of active or aggressive benign tumors. These lesions are usually cystic or cyst-like bone defects extending from the subtrochanteric region to the femoral neck (10). Because these lesions typically occur in young and active individuals; thus, proper management is required after treatment to prevent fractures and ensure a functional joint (4).

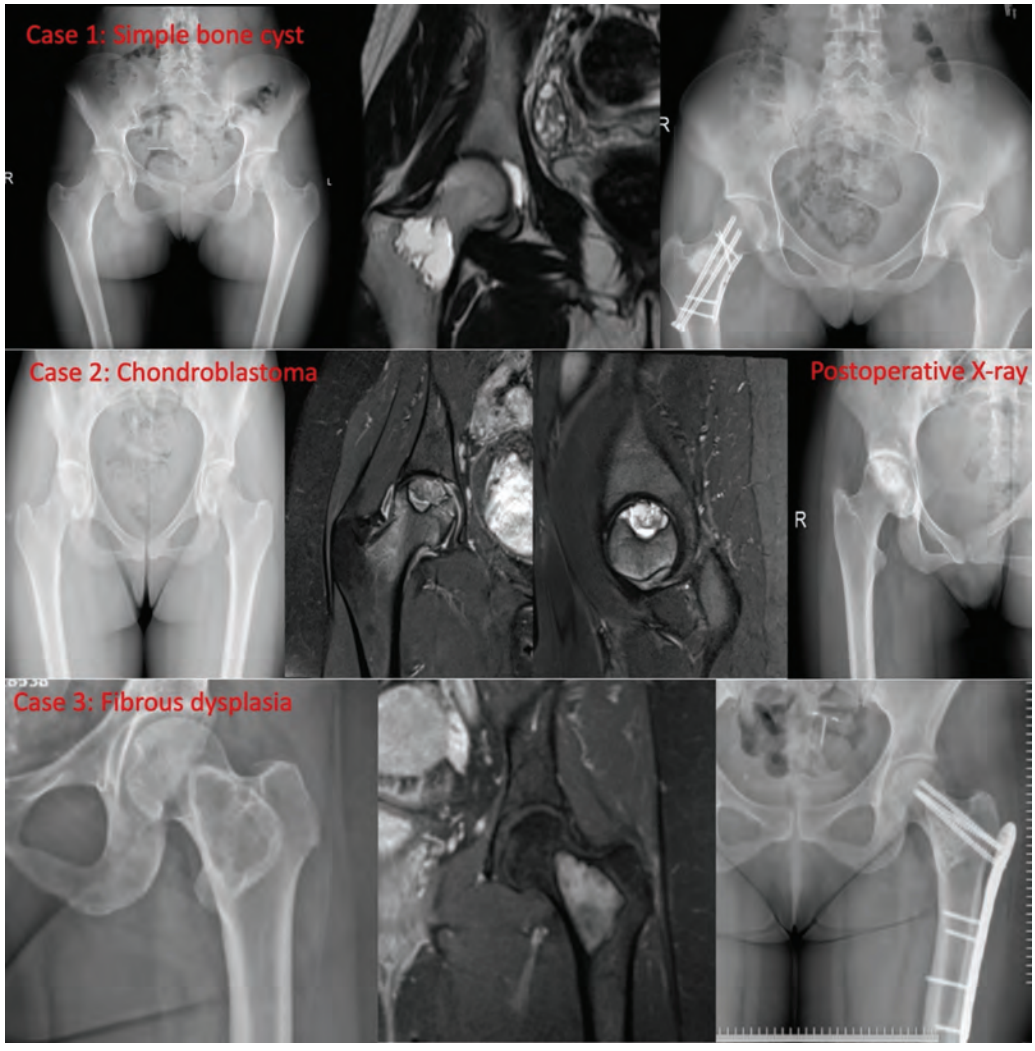

Figure 1. Case examples

When we reviewed the literature, the distribution of benign and benign aggressive lesions observed in the proximal femur significantly varied among case series. In some series, the frequency of GCT was high, whereas in others, fibrous dysplasia or ABC diagnoses predominate (3,11-13). In our case series, the most common pathology diagnosed was a SBC at a rate of 33.3%.

Enchondroma is a rare pathology of the femoral neck, and literature reports it mostly in case reports (1,14). In our case series, a total of 4 patients were diagnosed with enchondroma.

Osteochondromas can occur in any bone but are usually found in the metaphyseal region near the physis of a long bone. They are most commonly seen in the distal femur, proximal tibia, and proximal humerus (15). Rarely, intracapsular osteochondromas can be observed in the femoral neck. These lesions can cause problems, such as femoroacetabular impingement, labrum tears, nerve compression, hip dislocation, external snapping of the hip, and malignant transformation (16-19). Surgical exploration for resection also carries the risk of AVN (18,20). In our series, surgical resection of intracapsular osteochondroma cases was performed using the posterolateral approach without hip dislocation. No complications of AVN occurred during follow-up, and patients' pain and mechanical complaints were completely resolved.

The proximal femur is one of the anatomical regions where osteoid osteoma is frequently seen, but intra-articular osteoid osteomas are rare (21,22). Intra-articular lesions can cause pain, limping, synovitis, effusion, stiffness, local warmth, atrophy in surrounding muscles, and movement restrictions, mimicking inflammatory synovitis. In chronic cases, deformities, such as widening and shortening of the femoral neck with reduced epiphyseal height of the femoral head, may occur (23,24). In cases resistant to conservative treatment, surgical en bloc resection or minimally invasive methods, such as radiofrequency ablation

and cryoablation, are indicated (25). Postoperative follow-up showed resolution of symptoms and no recurrence.

For the surgical treatment of lesions in the femoral head and neck, anterior, lateral, anterolateral, or combined approaches are used, each with its advantages and disadvantages (3,7,10-13). The anterior approach is advantageous for lesions localized in the femoral head because curettage is difficult with the lateral approach because of its distance to the femoral head. However, a significant disadvantage of the anterior approach is that if the postoperative histopathological diagnosis favors malignancy, contamination around the femoral artery can lead to catastrophic outcomes such as amputation (3). The disadvantage of the lateral approach is usually temporary, but it may include limping due to abductor muscle damage (12). In our clinical practice, we decide the surgical approach based on the location of the lesion rather than using a single approach. For example, the direct anterior approach is preferred for lesions involving the femoral head, whereas the posterolateral approach is preferred for a posteriorly located osteochondroma. Consequently, we use direct anterior, anterolateral, or posterolateral approaches. Two patients in our case series showed postoperative abductor limping, both of whom underwent anterolateral approaches. Their limping complaints were resolved after abductor strengthening exercises, and they returned to normal walking patterns and were comfortably engaged in daily activities. Sharfman et al. (9) reported successful results in treating intra-capsular benign lesions of the proximal femur with arthroscopic surgical resection in a series of 3 cases published in 2016. Their series included 2 cases of enchondroma and 1 case of osteochondroma. In our opinion, hip arthroscopy can be performed in selected cases, but there may be issues with bone stability after lesion resection or curettage. We believe that it should be used only in selected rare cases.

There are various treatment protocols for benign bone tumors and tumor-like lesions in the proximal femur. These protocols include curettage with or without internal fixation (10-13,26,27). In pediatric patients, the treatment of these lesions is relatively more difficult because of the small diameter of the femoral neck and the open epiphyseal plate (10). Materials used to fill defects after curettage of the lesions include autografts, allografts, and cement. Literature shows that autografts are more commonly preferred for defect reconstruction (11,12,27). The use of fibular autografts, iliac crest autografts, and combined autografts and allografts has also been reported (6,10). Although autografts provide better bone integration, donor site complications are considered as a disadvantage (28,29). Allografts have disadvantages, such as poor bone integration, but the absence of donor site complications and the ability to use large amounts are advantages (11,30). Long-term successful results have also been reported with the use of allografts after curettage of benign lesions in the proximal femur (3,4). As a result, there is no consensus in the literature on which bone graft should be used to fill defects after curettage. In our case series, allografts were used in 4 patients.

It has been reported that the cytotoxic and thermal effects of methyl methacrylate monomer during the hardening of cement kill the remaining tumor cells and reduce the risk of recurrence (31). Considering these properties, the use of cement may be advantageous for aggressive lesions. Literature shows studies using cement after curettage for the treatment of aggressive lesions in the proximal femur (32,33). Filling the cavity with bone cement provides mechanical support and allows early weight bearing on the extremity (31,34). However, the use of cement in the proximal femoral region is limited because of its susceptibility to shearing and torsional forces and the risk of subchondral damage (34). In our case series, cement was used after curettage in only 4 patients. Of these patients, 1 had GCT and 3 had ABC.

Complications associated with these lesions and pathological fractures include growth disorders, varus or valgus deformity, infection, periarticular destruction, degenerative arthritis, heterotopic ossification, AVN, implant failure, malunion, and non-union (10,11,26,35). In Luo et al.'s (35) series of 16 pediatric cases, postoperative complications included varus deformity in 2 patients and early epiphyseal closure in 2 patients. They reported that patients who developed varus deformity initially presented with pathological fractures, and those with early epiphyseal closure had epiphysis affected by the lesion at the time of presentation. During follow-up, only 1 patient developed local recurrence (35). A systematic review published in 2021, which included 274 patients, reported a complication rate of 10.5% after surgical treatment of benign lesions in the femoral head and neck. The local recurrence rate was reported to be 12.5%. The recurrence rate was higher (29.7%) in patients with an open growth plate. The average time to recurrence after the initial surgery was 19.8 months. GCT had the highest recurrence rate (33.3%) after curettage. In cases of recurrence, it was reported that the recurrence rates were significantly lower in patients who received adjuvant therapy than in those who underwent curettage alone (26). No recurrences were observed in the 27 patients in our case series. The routine addition of physical and chemical adjuvant therapies after curettage in our clinical practice may have provided an advantage in preventing recurrence in our series.

Preventing complications and achieving a functional and painless hip joint is crucial in the treatment approach for bone lesions located in the proximal femur. Carvallo et al. (36) used the TESS and MSTS scoring systems to evaluate functional outcomes in patients with benign bone tumors in the proximal femur who underwent surgical treatment without pathological fractures. Consistent with our study results, they found an average TESS score of 89.9 and an MSTS score of 91.6 (36). Similarly, a study by Kundu et al. (13) found satisfactory MSTS scores after surgical treatment of bone lesions located in the femoral neck.

Study Limitations

This study has some limitations, such as its single-center and retrospective design. The relatively small number of patients can be seen as another limitation, although this is due to the inclusion of only benign tumors located in the head and neck of the proximal femur in our series rather than all benign tumoral lesions located in the proximal femur. The application of the same treatment approach by an experienced orthopedic oncology surgical team and the sufficient number of patients compared with the literature are the strengths of this study.

CONCLUSION

Hip-preserving approaches are important for functional outcomes in the treatment of lesions observed in the proximal femur. Attention should be paid to the nutrient arterial structures to prevent complications such as non-union and AVN. These rare tumoral formations should be considered in patients presenting with pain and limping.

Footnote

Ethics Committee Approval: The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of University of Health Sciences Turkey, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (approval number: 2024-04/42, date: 18.04.2024).

Informed Consent: The study was conducted in accordance with the principles of the Helsinki Declaration and written informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: İ.K., R.B., C.U., İ.B.A., Concept: E.A., C.U., Design: B.A., R.B., C.U., Data Collection or Processing: B.A., İ.B.A., Analysis or Interpretation: İ.K., E.A., İ.B.A., Literature Search: B.A., E.A., C.U., Writing: İ.K., R.B.

Conflict of Interest: No conflicts of interest were declared by the authors.

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ORIGINAL ARTICLE

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Evaluation of Cutaneous Drug Reactions due to Pirfenidone: A Histopathological Study and Management of Clinical Findings

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Abstract

Objective: Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrotic, and fatal lung disease associated with the inevitable loss of lung function. Pirfenidone, which has antifibrotic properties and has been used orally in recent years, slows down the progression of the disease and increases survival rates. However, photosensitive skin rash caused by absorbing ultraviolet rays is the most frequently encountered adverse effect in clinical practice.

Methods: Thirteen patients who were treated for IPF in the department of chest diseases between September 2018 and January 2022, used pirfenidone, and applied to the dermatology outpatient clinic due to rash were retrospectively examined. During this period, the number of patients receiving pirfenidone for IPF in chest diseases was fifty-six.

Results: In dermatological examination, scaly plaques on an erythematous background were common in seven patients, whereas lichenoid papules and plaques were dominant in six. In the histopathological evaluation of biopsies taken from the lesional skin area, the findings were consistent with superficial perivascular dermatitis in two, psoriasiform dermatitis in five, and lichenoid reaction pattern in six patients. When photosensitivity reactions occurred, pirfenidone treatment was continued in eleven patients at a reduced dose, and only two patients discontinued pirfenidone and switched to nintedanib therapy.

Conclusion: We aimed to show that photosensitivity reactions can be managed in the majority of patients without discontinuing pirfenidone, which plays a vital role in the treatment of IPF symptom control and survival by reducing the dose, using sun protection, and taking additional protective measures, and to provide further insight to clinicians in this regard.

Keywords: Pirfenidone, idiopathic pulmonary fibrosis, photosensitivity, drug eruption

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial pneumonia of unknown cause characterized by chronic, progressive fibrosis. The walls of the alveoli in the lungs thicken with scarring in this disease, which is observed mainly in older adults. It causes long-term cough, shortness of breath, fatigue, weakness, loss of appetite, and weight loss, and has a serious course (1). It also causes progressive and permanent damage to the lungs. Oxygen transfer from the lungs thickened by scar tissue to the blood circulation system is reduced, negatively affecting all organs. If left untreated, severe hypoxemic cases develop pulmonary hypertension and right heart failure. The average survival time of patients diagnosed with IPF is 2-5 years (2). The timely diagnosis of IPF is crucial but, unfortunately, is often delayed. Treatment of this disease that causes irreversible damage aims to reduce the patient's symptoms and slow the progression of

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the disease. In recent years, two antifibrotic agents that can slow the progression of IPF have taken their place among the treatment options. Pirfenidone and nintedanib were shown to partially prolong life expectancy and improve quality of life by preventing the progression of fibrosis in the lung when started at an early stage (3). Pirfenidone transforming growth factor-beta has an antifibrotic, anti-inflammatory effect by inhibiting the overexpression of fibroblast growth factor, proliferation and transformation of fibroblasts into myofibroblasts, and collagen synthesis (4,5). This increasingly used agent's most common side effects are related to the skin and gastrointestinal system. The other antifibrotic agent, nintedanib, most commonly causes diarrhea. Cutaneous drug reactions, which are frequently encountered in dermatology practice, can occur in various severities, ranging from asymptomatic to severe clinical manifestations. Although pirfenidone, one of the antifibrotic drugs that has found increasing use in recent years, is well tolerated, it can cause widespread phototoxic and photoallergic reactions on the skin (6). It may be necessary to reduce the dose or change the current treatment, considering the clinical course, lesion severity, and patient tolerance. In the literature, data on skin rash caused by pirfenidone are limited to case reports, and there are few publications with extensive studies on the prognosis. In this article, we aimed to review the skin rash caused by pirfenidone, its clinical course, and its treatment and to provide further insight to clinicians in this regard.

METHODS

Thirteen patients who were treated by the chest diseases department at Necmettin Erbakan University Faculty of Medicine Hospital for IPF between September 2018 and January 2022, used pirfenidone, and applied to the dermatology outpatient clinic due to rash were retrospectively examined. During this period, the number of patients receiving pirfenidone for IPF in chest diseases was 56. The patients' age, gender, clinical findings, time of starting and stopping pirfenidone treatment, lesional skin histopathology findings, skin-specific treatment, and responses were obtained from file records. Forty-four (79%) of 56 patients were male and 12 (21%) were female. Eleven (85%) of the cases with drug reactions were male.

Ethical approval for the study was obtained from the Pharmaceutical and Non-Medical Device Research Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (decision number: 2020/2429, date: 17.04.2020). Patients with any photosensitive skin disease or a history of photosensitizing drug or non-photosensitizing drug use were not included in the study. The patients did not have any history of chronic inflammatory skin diseases, such as psoriasis and lichen. Informed consent was obtained from all patients participating in the study.

Statistical Analysis

The data were examined using SPSS 22.0 statistical software.

RESULTS

IPF between September 2018 and January 2022 who used pirfenidone and applied to the dermatology outpatient clinic due to rash were retrospectively examined. During this period, the number of patients receiving pirfenidone for IPF in chest diseases was 56. Forty-four (79%) of the 56 patients were male and 12 (21%) were female. Of the 13 patients included in our study, 11 were male (85%), and two were female. Their average age was 78.61 years (range 69-83). The average time from the onset of skin symptoms on pirfenidone for IPF was 5 months (mean: 5.15, minimum: 3, maximum: 12).

The most common site of lesions caused by pirfenidone was the hand in eleven of the patients. Seven patients had lesions on the feet, four on the neck, three on the face, and three on the arms. One patient also had photosensitivity lesions on the trunk, one patient with the lip, and two on the anterior front of the tibia. In dermatological examination, scaly plaques on an erythematous background were common in seven, while lichenoid papules and plaques were dominant in six of our patients (Figure 1,2).

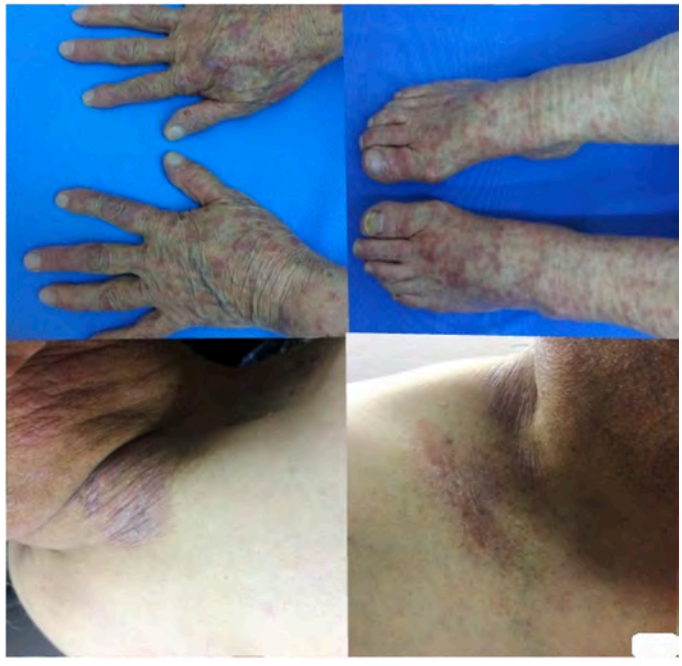

Figure 1. Lichenoid pattern, clinical findings in cutaneous drug reactions due to pirfenidone

In the histopathological evaluation of biopsies taken from the lesional skin area, the findings were consistent with superficial perivascular dermatitis in two, psoriasiform dermatitis in five, and lichenoid reaction pattern in six patients (Figure 3,4). All histopathologies showed necrotic keratinocytes and eosinophil infiltration, consistent with drug eruption. When photosensitivity reactions occurred, pirfenidone treatment was maintained in 11 patients by decreasing the dose, and two patients stopped using pirfenidone and were switched to nintedanib therapy. The two patients who were switched to nintedanib treatment were patients with resistant drug reactions that did not respond to treatments. All patients were treated with topical corticosteroids and antihistamines, and full recovery was observed in six patients within an average of 3.3 weeks (range 2-4), with no recurrence observed. In five patients, a 70-80% recovery was observed in an average of 6.4 weeks (range 4-8), and recurrence was observed within 1 year. In two patients, there was a 60-70% improvement in an average of 9 weeks (between 8-10) and occasional relapses were observed during the 1-year period. Relapse occurred in patients who continued pirfenidone but were controlled with topical corticosteroid and antihistamine treatment. The clinical characteristics of all patients are summarized in Table 1.

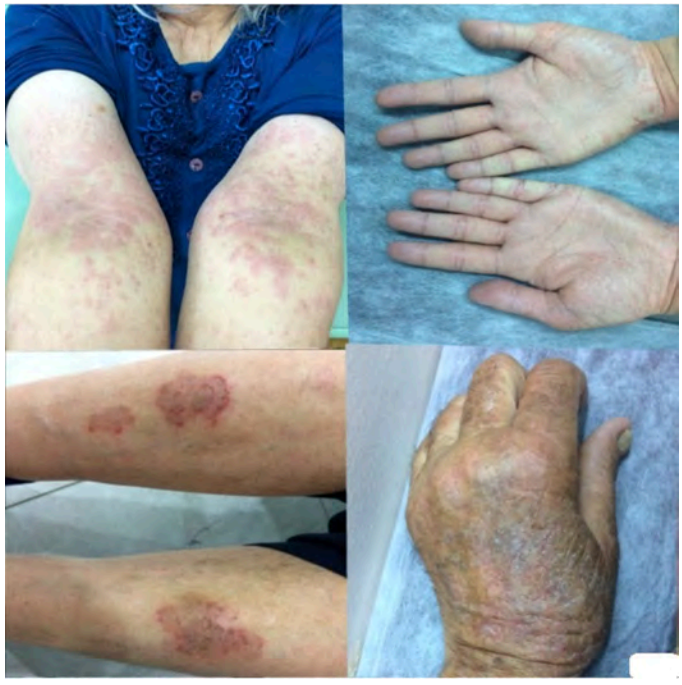

Figure 2. Psoriasiform pattern, clinical findings in cutaneous drug reactions due to pirfenidone

DISCUSSION

The common side effect of pirfenidone is photosensitive rashes, particularly in sun-exposed areas such as the face, neck, hands, and arms. Apart from pirfenidone, low-molecular-weight diuretics, nonsteroidal anti-inflammatory drugs, and antibiotics such as tetracycline-fluoroquinolones-sulfonamide are other essential drugs that can cause photosensitivity (7). Photosensitive drug reactions are divided into two major types: phototoxic and photoallergic. In phototoxic drug reactions, ultraviolet light interacts with the drug or its metabolites on the skin and causes nonimmunological cellular damage with the reactive oxygen molecules formed (8). In photoallergic reactions, ultraviolet rays convert drugs into immunologically active metabolites that stimulate cell-mediated hypersensitivity, causing rash (9). Since all photoallergic chemicals bind to proteins with the formation of free oxygen radicals, there are publications stating that the first step of photoallergic reactions is phototoxicity (10,11). In clinical distinction, early-onset reactions can be evaluated as

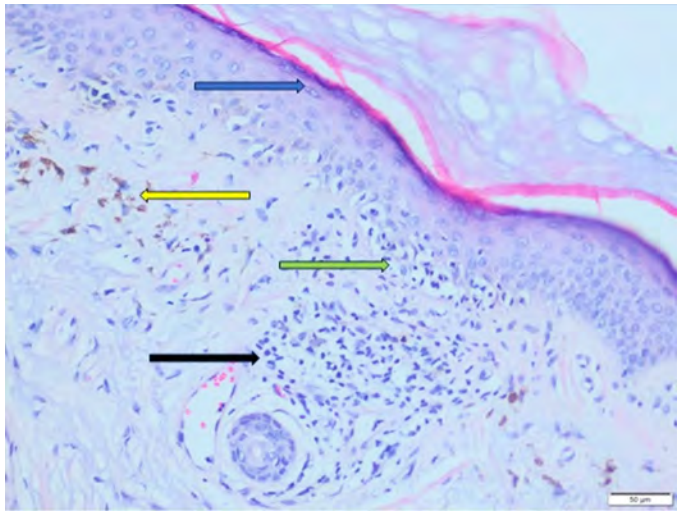

Figure 3. Lichenoid pattern, histopathological findings in cutaneous drug reactions due to pirfenidone

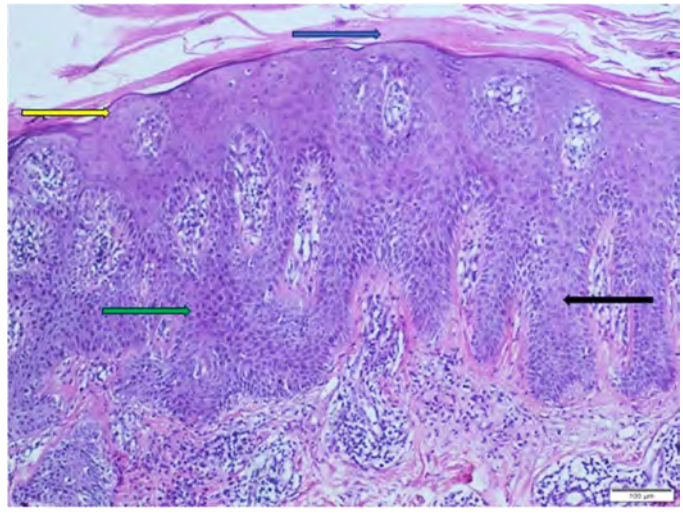

Figure 4. Psoriasiform pattern, histopathological findings in cutaneous drug reactions due to pirfenidone

phototoxic and late-onset reactions as photoallergic. They are very difficult to distinguish clinically and can often be seen together (11). Photoallergic reactions have a more chronic course than phototoxic reactions. In phototoxic reactions, lesions are generally limited to areas exposed to the sun, whereas in photoallergic reactions start primarily in areas exposed to the sun and spread to other regions over time (12).

Rashes were more common in male patients in our study. We attribute this result to the fact that IPF is more common in men. There is a male predominance in studies on the incidence and prevalence of IPF (13). In the literature, the average time between the initiation of pirfenidone and the appearance of skin findings was found to be four months, and in our study, this period was 5 months on average (6).

Table 1. Clinical characteristics of our patients who developed photosensitivity due to pirfenidone use

Age	Gender	Rash onset time	Lesion body location	Lesion characteristics	Histopathology	Treatment	Follow-up
71	M	6th month	Face, neck, tibia anterior face	Squamous plaques on an erythematous base	Psoriasiform dermatitis	The patient discontinued pirfenidone. Nintedanib treatment was started.	Complete cure. No relapse.
83	F	7th month	Bilateral hands and feet	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
76	M	3rd month	Bilateral hands and feet	Squamous plaques on an erythematous base	Psoriasiform dermatitis	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
63	M	4th month	Torso, arm, hand, foot	Squamous plaques on an erythematous base	Psoriasiform dermatitis	Pirfenidone was continued with a reduced dose.	Improved by 60-70%. Needed treatment from time to time.
73	M	3rd month	Face, neck and hands	Widespread erythema, sporadicsquamous plaques on an erythematous base	Superficial perivascular dermatitis	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
74	M	4th month	Bilateral feet, arms, hands	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
71	M	6th month	Neck and hands	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 60-70%. Needed treatment from time to time.
71	M	12th month	Bilateral hands, lip	Violese lichenoid papules and plaques, lip hyperpigmentation	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
77	M	4th month	Bilateral hands and feet	Squamous plaques on an erythematous base	Psoriasiform dermatitis	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.
72	M	3rd month	Tibia anterior face	Squamous plaques on an erythematous base	Psoriasiform dermatitis	The patient discontinued pirfenidone. Nintedanib treatment was started.	Complete cure. No relapse.
80	F	7th month	Bilateral hands and feet	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
70	M	3rd month	Face, neck and hands	Widespread erythema, sporadicsquamous plaques on an erythematous base	Superficial perivascular dermatitis	Pirfenidone was continued with a reduced dose.	Complete cure. No relapse.
69	M	5th month	Bilateral feet, arms, hands	Violese lichenoid papules and plaques	Lichenoid reaction pattern	Pirfenidone was continued with a reduced dose.	Improved by 70-80%. Needed treatment from time to time.

F: Female, M: Male

In our two patients whose rashes started in the 3rd month of pirfenidone treatment, skin biopsy histopathological evaluation was consistent with superficial perivascular dermatitis. The pirfenidone dose was reduced, and the lesions responded to treatment with no recurrence. This suggests that the reactions were rather phototoxic. Although the lesions started later in most patients with histopathology indicating psoriasiform dermatitis or lichenoid dermatitis, a response rate of 60-80% was obtained from the treatment of rashes while continuing the low-dose pirfenidone, which is more suggestive of a photoallergic reaction. However, we also have two patients with early-onset rash of this character and a complete response to treatment. Therefore, it is almost impossible to make a precise distinction. Phototoxicity is the basis of all reactions observed.

In our study, rashes that occurred due to pirfenidone entirely or largely regressed in all patients after the dose was reduced without the need for discontinuation of the drug. Sun protection methods effectively prevent photosensitivity reactions due to pirfenidone and constitute an essential treatment step. Broad-spectrum sunscreens that provide protection against ultraviolet A and ultraviolet B should be used; exposure should be avoided during hours when the sun's rays are most intense; heavy artificial light sources should be avoided; and protective clothing should be worn as much as possible (14). It is also important to avoid exposure to sunlight for a few hours following pirfenidone intake because of its high blood concentration to prevent the development of reactions (14). The dose should first be reduced in cases of photosensitive reactions, and mild reactions can be controlled by sun protection methods and symptomatic treatment of lesions. Once the symptoms subside and the lesion regress, the dose can be increased slowly. In extremely severe cases that cannot be controlled with simple symptomatic treatment, systemic corticosteroid treatment may be used, and pirfenidone may need to be discontinued.

CONCLUSION

In conclusion, it should be kept in mind that the most common adverse effect of pirfenidone is photosensitive skin rash. The rash can be asymptomatic, self-limiting, and in the form of mild lesions, or it can be chronic, covering large areas and causing severe symptoms that reduce quality of life. The effective treatment of IPF is limited, and photosensitivity drug rash can be controlled without discontinuing pirfenidone, which is important in this regard, by reducing the dose, taking adequate sun protection, and other additional measures (6). Informing the patient in this respect, patient compliance, and the clinician's approach in this situation in light of this information are of great importance.

Footnote

Ethics Committee Approval: Ethical approval for the study was obtained from the Pharmaceutical and Non-Medical Device Research Ethics Committee of Necmettin Erbakan University Meram Faculty of Medicine (decision number: 2020/2429, date: 17.04.2020).

Informed Consent: Informed consent was obtained from all patients participating in the study.

Authorship Contributions

Surgical and Medical Practices: S.A.T., S.Y., A.A., A.Z., N.K., P.O., Concept: S.A.T., S.Y., A.Z., Design: S.A.T., S.Y., A.A., A.Z., Data Collection or Processing: S.A.T., S.Y., A.Z., N.K., P.O., Analysis or Interpretation: S.A.T., S.Y., A.A., A.Z., P.O., Literature Search: S.A.T., S.Y., Writing: S.A.T., S.Y.

Conflict of Interest: No conflicts of interest were declared by the authors.

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ORIGINAL ARTICLE

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Evaluation of the Short and Long-term Impact of the COVID-19 Pandemic on Non-gynecological Cytology Practice

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Abstract

Objective: During the Coronavirus disease-2019 (COVID-19) pandemic, many screening and elective procedures were deferred, leading to a notable reduction in the volume of materials handled by the cytopathology laboratory. This study seeks to explore both the immediate and prolonged impacts of the pandemic on non-gynecologic cytology practices in a hospital, focusing on the timeframe beginning in March 2020, when the first case was identified in our country.

Methods: Starting from March 2020, when our country reported its first COVID-19 case, we compared the percentages of cytological samples processed at the cytopathology laboratory of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, for the three-month period of March to May in 2020 with those from the same months in 2019, 2021, and 2022. We also assessed the differences in malignancy rates.

Results: In the three-month study period of 2020, there was an 81.5% reduction in the total number of non-gynecologic cytological specimens compared to 2019. Conversely, the overall malignancy rate saw a significant increase (6.1% in 2019 and 10.8% in 2020). During the 3-month study period in 2021, cytologic specimens increased compared with 2020 (127.8%) but continued to decrease compared with 2019 (-57.8%). In 2021, the overall malignancy rate was higher than that in other years (12.5%). Similarly, in the 3-month period in 2022, cytologic samples increased compared with 2020 (221.6%), but despite this increase, the number of cases was still lower than in the pre-pandemic period (-40.5%). The overall malignancy rate continued to be higher than before the pandemic (2019: 6.1%, 2022: 10.1%).

Conclusion: The delay of elective procedures due to the COVID-19 pandemic has had a major impact on cytopathology practices. In both 2021 and 2022, the volume of non-gynecologic cytologic materials remained significantly lower than in 2019, highlighting the ongoing effects of the pandemic on cytopathology. Meanwhile, the rise in the overall malignancy rate underscores the need to prioritize diagnostic procedures for patients at high risk for cancer.

Keywords: Coronavirus, COVID-19, cytopathology, malignancy rate, work load

INTRODUCTION

The Coronavirus disease-2019 (COVID-19) pandemic is a type of virus outbreak that first emerged in the Wuhan region of China toward the end of 2019. The transmission rate of this virus, which spreads easily from person to person, increased in mid-January 2020, and cases began to be reported in various parts of the world over time (1,2). In March 2020, a global pandemic was declared by the World Health Organization (3). During this period, the global health system was affected, and approximately 7.1 million people died (4). To reduce exposure and mortality, each country-initiated periods of home quarantine, limiting people's freedom of movement and activities of daily living. In pandemic hospitals, physicians, regardless of their specialty, were employed only in wards and outpatient clinics dedicated to COVID-19. Additionally, most non-urgent medical procedures, including cytopathology screening, were postponed (5,6). Naturally, there was a

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significant reduction in the amount of material processed in the cytopathology laboratory. This study aimed to investigate the short- and long-term impacts of the pandemic on the practice of non-gynecologic cytology in a hospital during the pandemic period in March 2020, when the first case was detected in our country.

METHODS

Based on March 2020, when the first COVID-19 case was detected in our country, non-gynecological cytological samples processed in the cytopathology laboratory of University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital between March and May 2020 (3-month period) were retrospectively evaluated and compared with samples from the same period in 2019, 2021, and 2022. All non-gynecologic cytology reports for the relevant periods were obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital database. Cases were divided into 10 subgroups; cerebrospinal fluid (CSF), urine-urinary bladder flush fluid, peritoneal-pleural-pericardial fluid, thyroid, lymph node, soft tissue, bone, salivary gland, breast, and other fine niddle aspiration biopsies (FNAB). The total number of specimens was recorded. The numbers of non-diagnostic (NDC) and malignant cases were recorded and compared by year. Ethical approval for this study was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Research Ethics Committee (decisison number: 177, date: 25.09.2023).

Statistical Analysis

Statistical analysis was performed using the SPSS software, with p-values <0.05 deemed statistically significant.

RESULTS

During the 3-month study period in 2020, overall non-gynecological cytological specimens decreased by 81.5% compared with 2019. The decrease rates for sample types were as follows: thyroid -87.9%, lymph node -74.8%, breast -86.1%, salivary gland -75%, bone -27.2%, soft tissue -25%, serous effusions (pleura, peritoneum, pericardium) -55.3%, urinary bladder-urine 78.2%, CSF -55% (Figure 1). In contrast, the overall malignancy rate increased significantly (2019: 6.1%, 2020: 10.8%) (Table 1).

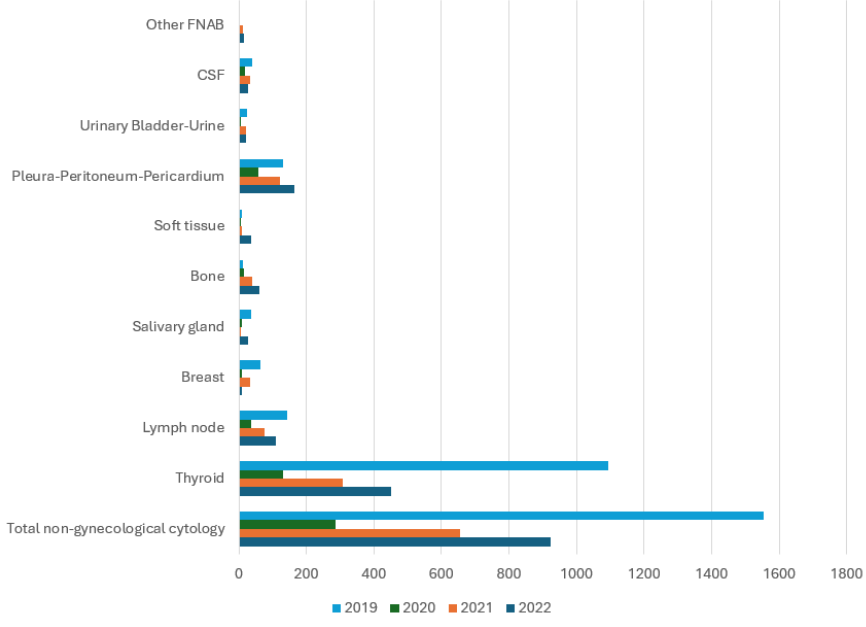

Figure 1. Distribution of cases according to sample locations and years
FNAB: Fine niddle aspiration biopsies, CSF: Cerebrospinal fluid

Table 1. Total number of non-gynecological cytology materials, number of malignant cases, and malignancy rates by year

	2019	2020	2021	2022
Non-gynecological samples	1553	287	654	923
Malign	95	31	82	94
Malignancy rates	6.11	10.80	12.53	10.18

During the 3-month study period in 2021, cytologic samples increased compared with 2020 (127.8%) but continued to decrease compared with 2019 (-57.8%). In 2021, the decrease rates of samples compared with 2019 were as follows: thyroid -71.9%, lymph node -47.5%, breast -49.2%, salivary gland -83.3%, serous effusions -6.1%, urinary bladder-urine -8.6%, CSF -0.2%. In 2021, bone fine needle aspirations (FNAs) increased (+2.6%), whereas soft tissue FNAs did not change (Table 2). The overall malignancy rate in 2021 was higher than that in other years (12.5%) (Table 1).

During the 3-month study period in 2022, there was an increase in cytologic samples compared with 2020 (221.6%), but a continued decrease compared with 2019 (-40.5%). In 2022, compared with 2020, the decrease rates were as follows: thyroid -58.7%, lymph node -23.7%, breast -86.1%, salivary gland -0.25%, urinary bladder-urine -8.6%, CSF -3%. There was also an increase of 27% in serous effusions, 35% in soft tissue FNAs and 4.6% in bone FNAs. When 2022 was compared with 2021, there was an overall increase in the number of samples, except for breast FNAs and CSF sampling, but this increase remained below the levels observed in the pre-pandemic period (2019) (Figure 1, Table 2).

Total non-gynecologic cytology material, malignancy, and NDC rates by years are shown in Figure 2.

Table 2. Sample locations and the number of cases by year

Years	2019	2020	2021	2022	2019-2020	2019-2021	2019-2022
Total non-gynecological cytology	1553	287	654	923	-0.81519639	-0.57887959	-0.405666
Thyroid	1094	132	307	451	-0.87934186	-0.71937843	-0.587751
Lymph node	143	36	75	109	-0.74825175	-0.47552448	-0.237762
Breast	65	9	33	9	-0.86153846	-0.49230769	-0.861538
Salivary gland	36	9	6	27	-0.75	-0.83333333	-0.25
Bone	11	14	40	61	0.272727273	2.636363636	4.5454545
Soft tissue	8	6	8	36	-0.25	0	3.5
Pleura-peritoneum-pericardium	130	58	122	165	-0.55384615	-0.06153846	0.2692308
Urinary bladder-urine	23	5	21	21	-0.7826087	-0.08695652	-0.086957
CSF	40	18	32	28	-0.55	-0.2	-0.3
Other FNAB	3	0	11	16	-1	2.666666667	4.3333333

CSF: Cerebrospinal fluid, FNAB: Fine niddle aspiration biopsies

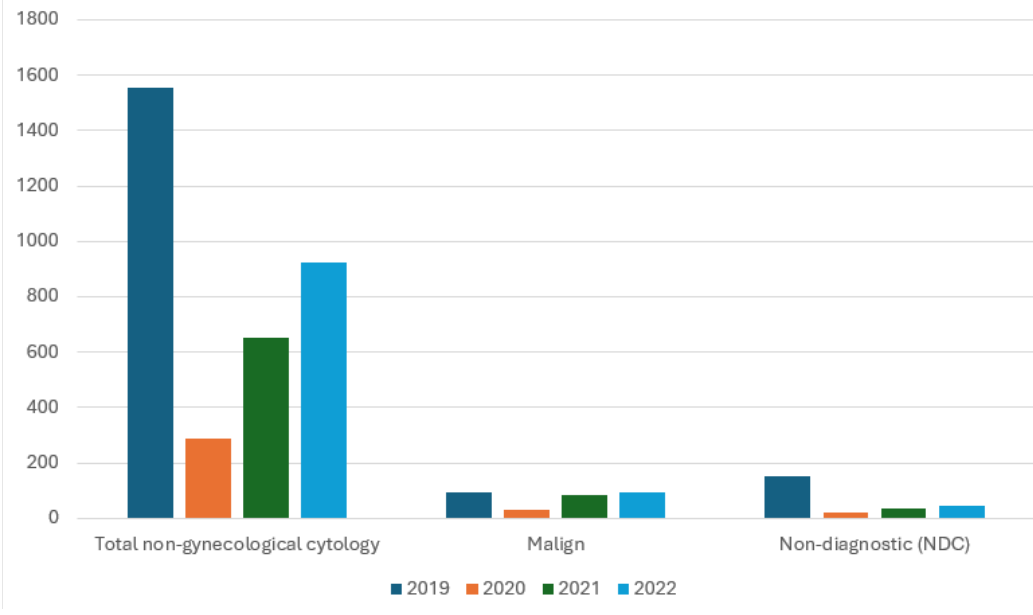

Figure 2. Total non-gynecologic cytology material, malignancy and non-diagnostic cytology (NDC) rates by year
NDC: Non-diagnostic cytology

DISCUSSION

The COVID-19 pandemic led to a considerable decline in cytopathology practices in our country due to the fact that almost all physicians, including pathologists, worked in pandemic clinics in pandemic hospitals, and elective procedures were postponed based on recommendations of the pathology scientific communities. Similar to studies conducted by Vigliar et al. (6) in Italy, de Pelsemaeker et al. (11) in Belgium, Hong et al. (13) in South Korea, and Kurtulan and Önder Çelik (9) in our country, our study observed an absolute decrease in the overall count of cytology samples during the COVID-19 quarantine period (March-April-May 2019) (6-13). Additionally, during and after the pandemic period, Vigliar et al. (6) reported in international and multicenter studies conducted in 3-month periods in 2020 and 2021, similar to our study, that there was a 26.5% decrease in cytological samples during the pandemic period (2020) compared with the same period of 2019, but a trend toward a return to pre-pandemic numbers over time (7). This study identified the most significant decreases in the following sample categories: thyroid (-32.8%), cervical-vaginal tract (-30.7%), breast (-20.8%), serous cavity (-16.8%), salivary gland (-14.4%), respiratory tract (-12.2%), urine (-10.5%), and lymph node samples (-7.5%). Conversely, four sample categories-central nervous system, gastrointestinal tract, biliary tract, and bone marrow-exhibited an increase in the number of cytological samples. Moreover, the malignancy rate and the rate of suspected malignancies were greater in the post-quarantine period than in the same timeframe in 2019 (7,14). In our study, the rate of decrease during the pandemic period compared with the pre-pandemic period (2020-2019) was 81.5%. In 2021 and 2022, the number of samples increased compared with the pandemic period but was lower than the pre-pandemic period (57.8% and 40.5%, respectively). However, in 2022, the rate of decline in samples decreased compared to 2021. The most dramatic decreases during the pandemic period were seen in thyroid, lymph node, breast, salivary gland FNAs, and urinary bladder-urine cytologies. However, their percentage in the overall cytologic material increased relatively compared to 2019. In the post-pandemic periods (2021 and 2022), there was also a decrease in the number of these samples. However, some samples, such as serous effusions, bone and soft tissue FNAs increased compared to the pre-pandemic period. This suggests that clinicians in our hospital continued to prioritize cytology for diagnostic and therapeutic purposes rather than screening purposes. As in studies conducted worldwide and our study, despite the increase in routine activities of health services and cytologic samples during the same period in 2021 and 2022, fewer samples and higher malignancy rates were observed compared to the pre-pandemic period (2020: +4.69%, 2021: +6.42%, 2022: +4.07%). This underscores the significance of prioritizing patients at high oncological risk. during the pandemic and the continuation of this practice. Additionally, we know that there were significant decreases in the PAP smear screening tests. Wang et al. (15) demonstrated that the pandemic led to a significant decline in the number of cervical smears in the Asia-Pacific region. The Ontario Cervical Screening Program study found a 63% reduction in the number of PAP tests and a 68% decrease in colposcopies during the pandemic in Canada (16). Similarly, there were significant disruptions in gynecology practices in Germany, with a 38% decrease in cervical cancer screening during the pandemic (17). We know that the number of PAP smear screenings decreased in our hospital during the pandemic, but our study focused on evaluating how non-gynecologic cytology was impacted by the COVID-19 pandemic both in the short term and long-term. Studies on the effects of the COVID-19 pandemic, It is believed that the reduction in hospital admissions and the number of samples for cancer screening caused delays in the diagnosis of possible malignancies. Therefore, there was an expectation of a corresponding increase in the number of malignancy diagnoses during the post-pandemic period (18-20). Our study showed that malignancy rates did not follow a linear decrease or increase across the pre-pandemic, pandemic, and post-pandemic periods (2019: 6.1%, 2020: 10.80%, 2021: 12.53%, 2022: 10.18%). We anticipate that malignancy rates will return to pre-pandemic levels as the sample size increases.

Study Limitations

Our study has certain limitations. We focused exclusively on the three-month periods of 2019, 2021, and 2022, comparing them to the equivalent period in 2020. Information for the other months of these years is not available. We also included only non-gynecological cytology material.

CONCLUSION

In conclusion, while the data indicate a notable decrease in the overall cytological workload during the COVID-19 lockdown, most samples were collected for diagnostic and therapeutic purposes, and high-risk oncological patients continued to receive care. It can be said that with the start of controlled social life in the post-quarantine period, screening programs and routine activities for health services and cytopathology laboratories quickly returned to pre-pandemic levels. To the best of our knowledge, no other study has investigated the long-term effects of post-pandemic COVID-19 on non-gynecological cytology.

Footnote

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (decisison number: 177, date: 25.09.2023).

Informed Consent: Were retrospectively evaluated and compared with samples from the same period.

Authorship Contributions

Concept: H.B., Ş.E.D., C.Ç., Ö.Y., Design: H.B., Ş.E.D., C.Ç., Ö.Y., Data Collection or Processing: H.B., Ş.E.D., Analysis or Interpretation: H.B., Ş.E.D., Literature Search: H.B., Writing: H.B.

Conflict of Interest: Özben Yalçın is an Associate Editor in the European Archives of Medical Research. She had no involvement in the peer-review of this article and had no access to information regarding its peer-review. Other authors declared no conflict of interest.

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ORIGINAL ARTICLE

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Clinical and Radiologic Evaluation of Mucopolygen Complex on Patients Who Underwent Arthroscopic Full Thickness Supraspinatus Tendon Repair

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Abstract

Objective: The use of food supplements to enhance tendon healing is increasing. This study aimed to evaluate the clinical and radiological effects of mucopolygen complex (MPC) in patients who underwent arthroscopic full-thickness supraspinatus tear repair (ASR).

Methods: Forty-six patients with ASR were divided into two groups: one receiving MPC and the other serving as a control. At 1-year follow-up, ultrasound was used to assess the supraspinatus tendon for integrity, pathology, and maximum swelling thickness. Joint function and pain were evaluated preoperatively and at follow-up using physical examination, The University of California-Los Angeles (UCLA) shoulder scale, and visual analog scale (VAS).

Results: Pathologies in the supraspinatus tendon were found in 26.1% of patients in the MPC group compared with 60.9% in the control group, a statistically significant difference (p=0.017). However, the mean tendon thickness did not significantly differ between the groups (5.11 mm in MPC vs. 3.87 mm in control). No significant differences were observed in pain, function, or patient satisfaction between the groups based on the UCLA and VAS scores.

Conclusion: Although MPC did not affect pain or functional outcomes in ASR patients, the lower incidence of radiological tendon pathologies and the trend toward greater tendon thickness in the MPC group suggest that MPC may promote better tendon healing. This finding supports previous findings that MPC may be beneficial for tendon repair.

Keywords: Shoulder arthroscopy, dietary supplement, supraspinatus tendon, mucopolygen complex

INTRODUCTION

Rotator cuff tendon tear (RCT) is the most common muscle-tendon rupture. Although treatment results for mild and moderate tears are successful, the success rate of treatments for severe and massive ruptures is reduced due to atrophy and degeneration (1). Tears associated with these pathologies have re-rupture rates of up to 94% (2). Therefore, interest in improving the biomechanical and biological properties of surgical repairs continues (3). Clinical studies examining tendon-bone healing in RCTs have demonstrated that the repair tissue is significantly

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different from the natural fibrocartilaginous transition zone and it has been shown that failure occurs at this site (4,5). The aims of these studies were to prevent the formation of scar tissue by arranging the microenvironment around the repair area in order to find away to ensure optimal recovery (6). Biopsies from torn tendons show that there are a large number of apoptotic cells, and considering the low proliferative capacity of tenocyte, improving only mechanical factors is insufficient (7,8). There are reports claiming that adding stem cells to the repair site (9), implementation of intracellular or extracellular fluid components produced by bioengineering methods (10), therapeutic use of musculoskeletal growth factors (11), adding a group of cytokines and proteins that induce mitosis, extracellular matrix production, revascularization, and cell differentiation increase tendon healing. Although the theoretical effects of these cytokines and proteins have been shown, the clinical effects are still controversial.

In addition to these molecular studies, researchers reported that integrating nutritional supplement products into the normal diet had positive effects on tendon healing and tendon- bone integration. A nutritional supplement containing mucopolysaccharides (MPS), type I collagen, and vitamin C mucopolygen complex (MPC) had *in vitro* and clinical studies stating that it may be effective in tendon healing (12,13). In laboratory studies, MPC was found to impact the metabolism of tenocyte and its proliferation, which help preserve the structure of the extracellular matrix (12). Additionally, MCVC was found to stimulate the production of collagen type I and prevent the buildup of collagen type III and aggrecan, which may prevent degeneration of tendon tissue. In a study conducted on rabbits, it was shown that glucosamine chondroitin sulphate increases the tendon's adhesion to bone by increasing collagen synthesis and cell maturation (14).

The aim of this study was to evaluate the clinical and radiological effects of MPC, whose effects had previously been demonstrated under laboratory conditions, in patients who underwent arthroscopic full-thickness supraspinatus tear repair treatment.

METHODS

This study was conducted in patients who were admitted to our clinic between June 2015 and March 2016 with the complaint of chronic shoulder pain, received an arthroscopically confirmed diagnosis of isolated full-thickness supraspinatus tear, and who underwent arthroscopic rotator cuff repair.

The study was conducted in accordance with national and international guidelines concerning research on human subjects, such as the Declaration of Helsinki. All participants provided written informed consent for their participation, and the protocol was approved by the Gazi University Clinical Research Ethics Committee. (decision number: 101, date: 22.02.2016).

Among those admitted to our clinic between the abovementioned date, a total of 46 patients with similar demographic characteristics were included. Twenty-three patients were selected as the study group and received MPC for 3 months after surgery, while the control group consisted of 23 patients that did not receive a dietary supplement. Patients with acute rupture, partial rupture, muscle atrophy (fatty infiltration), diabetes mellitus, degenerative joint pathologies, or humeral head cysts, active athletes, calcific tendinitis symptoms, pseudoparalytic or frozen shoulder symptoms; psychiatric, rheumatologic, hematological, and oncological diseases were excluded from the study.

All surgical interventions were performed by the same surgeon under 5 kg traction in the lateral decubitus position. A standard posterior portal was used for imaging, while repair was performed using the anterior and lateral portals. The supraspinatus tendon was repaired with three anchors using the double row repair technique. Acromioplasty was added to the procedure when subacromial impingement was observed in clinical and arthroscopic findings. All patients received the same postoperative physical therapy program.

In the study group, all patients were given 2 capsules of MPC (Assos Pharmaceuticals, Retendo, İstanbul, Turkey) per day, which contained 440 mg of MPS, 80 mg of type I collagen, and 60 mg of vitamin C, for 90 days. Patients were monitored regularly with visits at days 30, 60, and 90 after starting the treatment. The baseline visit was established as the day before surgical repair of the supraspinatus tendon (day 0).

Joint function was assessed at each visit and the University of California-Los Angeles (UCLA) shoulder scale was applied to each patient preoperatively and at the one year follow-up. Pain intensity was determined using visual analogue scale (VAS).

The supraspinatus tendon was characterized by ultrasound at the one year follow-up, including the situation of the tendon (re-rupture, tendinitis etc.) and thickness measurement at the point of maximum swelling. All radiographic assessments were performed by a highly experienced radiologist on musculoskeletal disorders.

Statistical Analysis

All statistical analyses were performed using IBM SPSS 24.0 software, and $p<0.05$ was considered statistically significant.

A frequency analysis of all data was performed. For the comparison of qualitative data, Mann-Whitney U and Wilcoxon tests were used for the comparison of numerical data.

RESULTS

A total of 46 patients complied with the inclusion criteria and agreed to participate in the study. The study group consisted of 13 female and 10 male patients, whereas the control group were 15 female and 8 male patients. The mean age of the participants was 58±11.7 years for the study group, 59±6.91 years for the control group. There were no significant differences between the groups in demographic data like age, sex, etc.

When patients using MPC were compared with patients who did not; no significant difference in re-rupture was observed. However, in 73.9% of the study group, supraspinatus was observed normal (without inflammation); while only in 39.1% of the control group, supraspinatus was observed as normal (p=0.044) (Figure 1). It was found that supraspinatus lesions were statistically significantly decreased in study group patients (p=0.017) (Table 1).

The incidence of tendinosis was 8.7% and the rate of complete rupture was 4.3% in the study group, whereas the incidence of tendinosis was 39.1% and the rate of complete rupture was 13% in the control group (Figure 2). When supraspinatus thicknesses were compared between the two groups, no statistically significant difference was observed, but the difference in the mean thicknesses was considered as striking (5.11 mm study group -3.87 mm control group).

Determining differences in pain, clinical condition, and patient satisfaction between the groups was evaluated using the UCLA shoulder scale and VAS, and no statistically significant differences were observed between both groups. However, there was a statistically significant difference between pre-operative scores and first-year control values in both groups (Table 2).

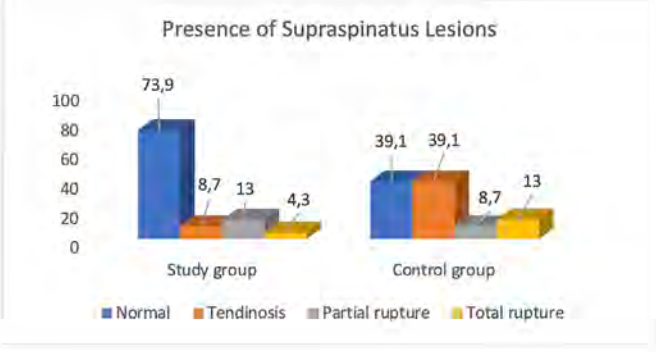

Figure 1. Graph of differences between groups in patients with supraspinatus lesion after arthroscopy

DISCUSSION

Failed rotator cuff repair is one of the major challenges to which an orthopedic surgeon will encounter. Although there are

Table 1. Statistical analysis of patients using mucopolygen complex and control group for supraspinatus lesion prevalence and re-rupture rate

	Study group		Control group		
Supraspinatus	**n**	**%**	**n**	**%**	**p***
Lesion present	6	26.1	14	60.9	**0.017**
Lesion absent	17	73.9	9	39.1	
Supraspinatus					
Normal	17	73.9	9	39.1	**0.044**
Tendinosis	2	8.7	9	39.1	
Partial rupture	3	13.0	2	8.7	
Total rupture	1	4.3	3	13.0	
Re-rupture					
Present	4	17.4	5	21.7	0.710
Absent	19	82.6	18	78.3	

*: Chi-square test

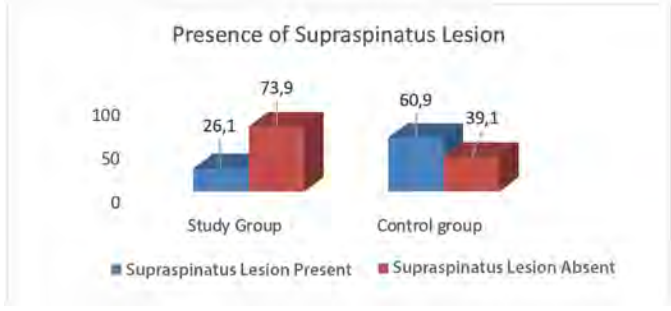

Figure 2. Graph of differences between control and study groups of lesions detected in supraspinatus after arthroscopy

Table 2. UCLA and VAS scores of patients taking mucopolygen complex and control group

	Study group	Control group	p*
	Mean (Min.-Max.)	**Mean (Min.-Max.)**	
Pre-op UCLA	17 (6-26)	16 (8-26)	0.523
Post-op UCLA	13 (11-22)	12 (10-20)	0.116
Pre-op VAS	6 (2-9)	6 (2-10)	0.511
Post-op VAS	2 (0-8)	2 (0-9)	0.639
Pre-post UCLA	****p=0.014**	****p=0.013**	
Pre-post AS	****p=0.001**	****p=0.001**	

*: Mann-Whitney U test, **: Wilcoxon test
UCLA: The University of California-Los Angeles, VAS: Visual analogue scale, Min.: Minimum, Max.: Maximum

different treatment strategies for retears, such as arthroscopic revision, tendon/allograft transfer, arthroplasty (15) etc. the common preference is not encountering retears in the first place.

Formulations such as food supplements, which are considered as one of the alternatives that can be used to improve tendon healing have been used increasingly. Arquer et al. (13) used MPC on patients with tendonitis at their Achilles tendon, patellar tendon, and lateral epicondyle and found that pain scores and ultrasonographic findings were statistically better in patients who did not use this complex. In another study performed by Balius et al. (16) patients with Achilles tendinopathy were divided into three groups, with two of the groups having MPC as a dietary supplement. Patients who had MPC showed statistically significantly better results for pain management. In our study, we observed that MPC did not affect the pain and functional results of operated supraspinatus tears. This was thought to be due to arthroscopic repair in all patients; hence, in the aforementioned article patients were not operated but were treated with physical therapy.

The statistically significant observation of radiological tendon pathologies (tendinitis, re-rupture) and detection of thinner supraspinatus thickness in the control groups as compared with the study group, as reported previously by other authors (12,13,17) supports the idea that the use of MPC supports tendon healing in a positive manner.

Another remarkable finding of this study is that the percentage of patients without a supraspinatus lesion in the study group was 73.9%; this ratio was calculated as 39.1% in the control group. Considering that the incidence of nutritional disorders increases with advancing age (18,19), the difference in lesion prevalence in this study can be explained by the advanced average age of the patients.

Study Limitations

The retrospective study design and sample size were the most important limitations of this study. Furthermore, the placebo effect of MPC cannot be discarded since the control group did not receive inert capsules. Ultrasonography was performed to assess the structural integrity of the healing supraspinatus because it is an objective method and cheaper compared to MRI; and performing a second-look arthroscopy or tissue biopsy is only possible for patients who need a second procedure.

CONCLUSION

In vitro studies have shown a positive effect of MPC on collagen synthesis and tenocyte proliferation, partly due to the restoration of the microenvironment of the healing tendon; however, its working mechanism is not yet fully understood. The decreased lesion prevalence after cuff repair, as shown in this study, and the clinically positive effect on tendinopathies that were not treated surgically are promising. However, there are not enough data in the literature to make a definitive decision.

However, as the growing number of food supplement products and the increasing interest of patients are considered, this study remains important because it provides preliminary information to guide prospective randomized controlled studies with large sample sizes on the MPC.

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Footnote

Ethics Committee Approval: The protocol was approved by the Gazi University Clinical Research Ethics Committee. (decision number: 101, date: 22.02.2016).

Informed Consent: All participants provided written informed consent for their participation.

Authorship Contributions

Surgical and Medical Practices: R.B., U.K., Concept: R.B., M.A.T., Design: R.B., T.A., S.K., U.K., Data Collection or Processing: R.B., T.A., Analysis or Interpretation: R.B., T.A., Literature Search: B.A., M.Ö., U.K., Writing: R.B.

Conflict of Interest: No conflicts of interest were declared by the authors.

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ORIGINAL ARTICLE

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Effect of Diabetes Self-management Education in Diabetics after Myocardial Infarction: A Randomized Controlled Trial

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Abstract

Objective: This study aimed to investigate the impact of an education program on diabetes self-management among individuals with type 2 diabetes (T2D) who had experienced an acute myocardial infarction (AMI).

Methods: This randomized controlled trial was conducted at a training and research hospital in Turkey, which also functions as a cardiology specialty center. The hospital features two coronary intensive care units and three cardiology departments. Data collection took place between January 15 and June 15, 2023. In total, 102 patients with T2D who had undergone AMI were selected and randomly assigned to either the intervention and control groups. The intervention group received individualized diabetes education through two sessions, each lasting approximately 15 minutes. Diabetes self-management levels were assessed at baseline and again one month after the educational intervention. This study followed the consolidated standards of reporting trials reporting guidelines.

Results: At the 1-month follow-up, the intervention group demonstrated significantly higher diabetes self-management scores compared with the control group ($p<0.001$). Intra-group analysis further indicated a substantial improvement in the intervention group's post-education self-management scores compared with their pre-education scores ($p<0.001$).

Conclusion: The educational program significantly improved diabetes self-management among patients with T2D following AMI. Nurse-led educational intervention is an effective approach that can be seamlessly integrated into routine patient care for this population.

Keywords: Diabetes, education, myocardial infarction, patient, self-management

INTRODUCTION

Type 2 diabetes (T2D) is a metabolic and chronic disorder (1). T2D is a significant and important health problem with an increasing prevalence worldwide (2). It is estimated that there are 537 million adults with diabetes globally, and this number may rise to 783 million by 2045 (3). High health expenditures and productivity losses due to diabetes and its complications can negatively impact national economies (4). To reduce these losses, it is crucial to control blood glucose levels in patients with diabetes and prevent complications (5).

Cardiovascular complications can develop in individuals with T2D if glycemic control is not achieved (6). Insulin resistance and insulin deficiency contribute to the development of atherosclerosis in blood vessels (7), and prolonged high blood sugar levels accelerate this process (8). Consequently, atherosclerosis in coronary vessels can lead to acute myocardial infarction (AMI) (9). Therefore, T2D is considered a significant risk factor for AMI (10,11).

AMI is the most serious and fatal cardiovascular disease (CVD) (12,13). Myocardial infarction (MI) is the primary cause of death

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among patients with T2D (14). It has been reported that the risk of AMI is individuals with T2D is twice as high as in those without diabetes (15). Diabetes is commonly found among patients hospitalized due to AMI, with approximately 30% of treated cases being patients with diabetes (10). The rate of patients hospitalized with suspected MI who present to the emergency department again with a suspicion of MI within 1 year was reported to be 0.059 (16). The risk of MI recurrence at some point in their lives for patients with T2D who have a history of MI is greater than 40% (10,17). Diabetes self-management is a crucial concept for ensuring glycemic control and reducing the risk of complications in individuals with T2D (5). Diabetes self-management strategies can help lower the risk of long-term complications for people with diabetes (18). Through these strategies, individuals with diabetes can make informed decisions about their treatment and care and incorporate these decisions into their daily lives (19). There is a significant relationship between T2D management level and the occurrence of cardiovascular events (20). Diabetes self-management is known to be effective in reducing the risk of cardiovascular complications in individuals with T2D (21-23). Current guidelines recommend that individuals with T2D receive diabetes education to improve their self-management (5,10). It has been reported that structured patient education improves diabetes self-management compared to routine information (24,25). The literature indicates that diabetes self-management education supports blood sugar control, utilization of health services, and implementation and maintenance of healthy lifestyle behaviors (19,21). However, no study has examined the effect of patient education on diabetes self-management in individuals with T2D who have experienced AMI.

METHODS

Aim and Design

The aim of this study was to examine the effects of a patient education program on diabetes self-management in patients with T2D who have experienced AMI. The impact of the patient education program on diabetes self-management was evaluated during a 1-month follow-up period (0-1 month). The study hypotheses were as follows:

H0: The patient education program does not affect the diabetes self-management of patients with T2D who have experienced AMI.

H1: The patient education program increases the diabetes self-management of patients with T2D who have experienced AMI.

This study was a prospective, randomized controlled trial. It recruited 102 patients with T2D who had experienced AMI between January and June 2023. Patients in the intervention group received approximately 30 minutes of individual diabetes education, delivered in two sessions, each lasting about 15 minutes. The patient information form was administered at baseline. The T2D self-management scale was administered to the patients as a pretest and again 1 month later as a posttest. The relevant EQUATOR guideline, the CONSORT checklist, was used to report this study, and the ClinicalTrials.gov registration number was obtained (NCT05954819 registered).

Study Setting

The study was carried out in a training and research hospital that also serves as a cardiology specialty hospital, with 2 coronary intensive care units (ICUs) and 3 cardiology services. The ICUs and services are located close together. The coronary ICUs have a total capacity of 66 beds, while the cardiology services have a total capacity of 72 beds. Each unit features a central corridor, with single rooms on both sides equipped with automatic doors. The units are equipped with a central monitoring system that allows nurses to monitor each patient. Each patient receives treatment in a single room. The hospital is a cardiology specialty facility, and the admission rate of patients to ICUs due to heart attacks is high. To reduce patient admission to the coronary ICUs, patients who received treatment and stabilized after AMI were transferred to the cardiology services.

Participants

The sample of the study consisted of 465 patients with T2D who received AMI treatment at a hospital in İstanbul, Turkey. Inclusion criterias were being voluntary and 18 years and older, being patients with T2D and hospitalized for AMI, and no psychiatric or communication problems. Patients treated with sedative or narcotic analgesics or who were intubated were excluded.

Sample Size and Randomization

Power analysis was performed using G*Power 3.1.7 software. The sample size was determined based on data from a comparable study in the literature (26). Drawing on findings from a study that examined the impact of an educational intervention on diabetes self-management, the required sample size was estimated to be 34 participants per group (assuming a two-tailed alpha of 0.05, a power of 0.80, and a medium effect size of 0.40). To account for potential dropouts, we aimed to include at least 51 participants in each group. A total of 102 eligible and willing participants were randomly assigned to groups using an online random number generator. Block randomization was applied, with participants grouped into blocks based on age and gender and then randomly allocated to each block. No participants

withdrew from the study, and the final sample consisted of 51 participants in each group (Figure 1).

Data Collection Tools

The patient information form and the T2D self-management scale were used for data collection.

Patient Information Form

This form was created by researchers to determine patients' personal and disease-related characteristics. It consisted of 11 items covering demographic features (e.g., educational levels, marital status, employment status) and clinical characteristics (e.g., history of AMI, duration of diabetes, treatment methods).

T2D Self-Management Scale

The T2D Self-management scale, developed by Koc (27), consists of 19 items and 3 subscales: Healthy lifestyle behaviors (11 items), blood sugar management (4 items), and use of health services (4 items). The scale has a 5-point likert-type rating system ranging from "Never-1 point" to "Always-5 points". All items are positive. A high score on the scale indicates high-level diabetes self-management (26). In our study, the internal consistency coefficient of the scale was found to be 0.96.

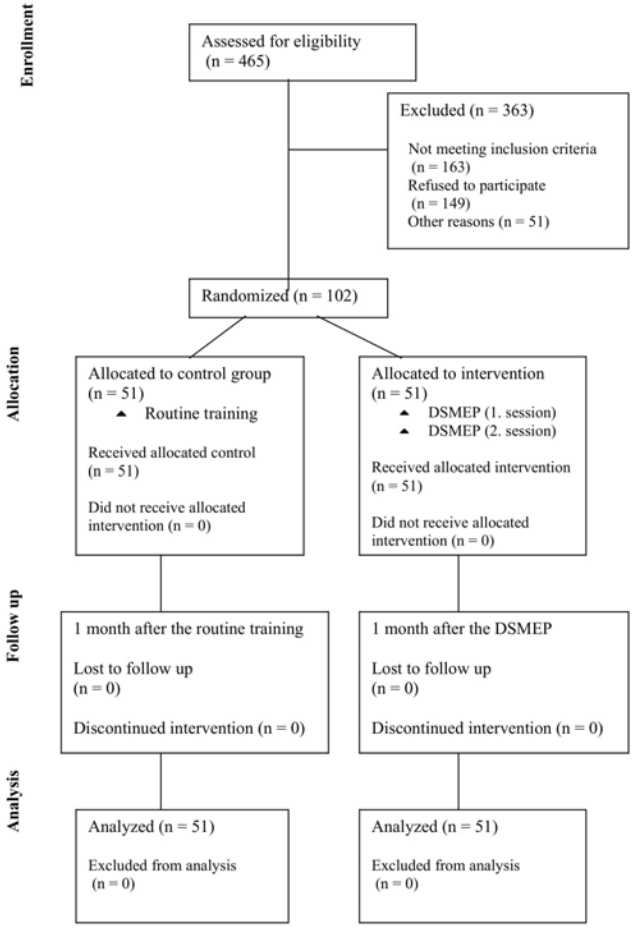

Figure 1. CONSORT participant flow diagram
DSMEP: Diabetes self-management education program

Diabetes Self-management Education Program

The program was developed by researchers through a literature review and in accordance with Pender's health promotion model (Table 1). The training program was structured under three headings: "T2D and diabetes management", "the relationship between diabetes and MI", and "healthy lifestyle behaviors and their importance for improving health". During the training, written and visual materials were used to enhance patient motivation.

Study Procedures

Researchers visited the coronary ICUs daily to identify patients. We informed the patients about the aim and scope of the study and obtained their informed consent. Next, the patients were randomly assigned to the intervention and control groups. Patients in the control group also participated in the diabetes self-management education program (DSMEP) after the study was concluded. Interviews were conducted with each patient without interrupting treatment or follow-up. First, the demographic and clinical information of all patients were obtained. The control group received routine clinical information provided by physicians and clinical nurses. DSMEP

Table 1. Content of the educational intervention

Content	Explanation
Meeting patients and entering the training program	- The content of the training program was introduced. - The patients' current health status and needs, personal characteristics, experiences, and beliefs about health behaviors were evaluated.
Diabetes and self-management	- Information was given about diabetes, symptoms, complications and prevention of diabetes, healthy nutrition, regular exercise, blood sugar monitoring, drug treatment, and the importance of diabetes management.
Diabetes and myocardial infarction relationship	- Information was given about the macrovascular effects of diabetes, definition, symptoms, and risk factors of myocardial infarction, which is a macrovascular chronic complication of diabetes.
Healthy lifestyle behaviors and their importance for improving health	- Information about healthy nutrition, regular exercise, blood sugar and blood pressure monitoring, compliance with medication, adequate sleep, avoiding smoking/tobacco use, avoiding stress, and regular health check-ups. - Patients were allowed to evaluate themselves (perception of their health status, values, beliefs). - Health goals were explained to the patients.

was administered to the intervention group patients by one of the researchers on the day of the first interview. This program was carried out in 2 sessions with intervals of 3-4 hours. The total training duration was 30 to 40 minutes. After the first meeting, each patient was contacted during the discharge process, and an appointment date was scheduled for outpatient clinic check-up one month later, in accordance with the hospital's routine procedures. A second interview was held with each patient who arrived on the appointment date in a predetermined outpatient clinic room following their routine checkup. In this interview, posttest data from the study were collected using the diabetes self-management scale.

Statistical Analysis

Data were analyzed using SPSS version 21.0. The chi-square test was used to compare the frequency distribution between the two groups and the homogeneity of categorical variables. The independent t-test was used to compare the mean scores obtained from the T2D self-management scale. The data were analyzed with a significance level of $p<0.05$ and a 95% confidence interval.

Ethical Considerations

Institutional permission was obtained from the İstanbul Provincial Health Directorate Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital. Ethical approval was granted by the Social and Human Sciences Research Ethics Board of İstanbul University-Cerrahpaşa (decision number: 2022/476, date: 06.12.2022). Permission to use the scales was obtained from their authors all participants were informed about the objectives of the study and specific requirements for their involvement. In accordance with ethical principles, written informed consent was obtained from patients who voluntarily agreed to participate. Anonymity and confidentiality were strictly maintained. Data were collected in accordance with the principles of the Declaration of Helsinki.

RESULTS

The mean age of patients was 58.68±9.76 years , ranging from 33 to 75 years. The proportion of male patients (80.4%) was greater than that of female patients (19.6%). Approximately 80.5% of patients had graduated from primary and secondary school. Most patients (87.3%) were married. Most patients were receiving oral antidiabetic drug therapy (71.6%) and had not received diabetes education (85.3%). There was no statistically significant difference between the intervention and control groups in terms of demographic and clinical characteristics ($p>0.05$) (Table 2). The pretest T2DSMS scores of the intervention (48.35±11.94) and control (49.86±12.66) groups were similar. The posttest score of the intervention group (72.49±8.06) was significantly higher than that of the control group (46.84±11.80) ($p<0.001$). The effect size between pretest and posttest scores was 2.369. An intragroup comparison of the T2DSMS scores showed that the mean posttest score of the intervention group was significantly higher than the pretest score ($p<0.001$) (Table 3). Additionally, at the end of the study, it was observed that the smoking cessation rate among all patients increased. Notably, 56% of the patients in the experimental group who received planned patient education quit smoking, compared to 14% of the control group patients who received routine information from healthcare professionals. Although the smoking cessation rate was higher in the experimental group, the difference between the groups was not statistically significant ($p>0.05$).

Table 2. Demographic and clinical characteristics of patients (n=102)

	Intervention group (n=51)		**Control group (n=51)**			
Characteristics	**Mean (SD)**		**Mean (SD)**		**Test**	**p[a]**
Age (years)	58.51 (9.91)		58.84 (9.70)		t= -0.172	0.864
BMI (kg/m^2)	28.36 (3.96)		27.50 (4.06)		t= 1.082	0.282
	n	**%**	**n**	**%**	**χ^2**	**p[b]**
Gender					0.249	0.618
Female	11	21.6	9	17.6		
Male	40	78.4	42	82.4		
Marital status					2.204	0.138
Married	47	92.2	42	82.4		
Single	4	7.8	9	17.6		

Table 2. Continued						
	Intervention group (n=51)		Control group (n=51)			
Characteristics	Mean (SD)		Mean (SD)		Test	p[a]
Education level						
Primary school	24	47.1	35	68.6	4.909	0.179
Secondary school	9	17.6	5	9.8		
High school	12	23.5	7	13.7		
University	6	11.8	4	7.8		
Employment status						
Employed	15	29.4	21	41.2	1.556	0.459
Unemployed/retired	36	70.6	30	58.8		
Income status						
High	7	13.7	3	5.9	2.300	0.317
Moderate	33	64.7	39	76.5		
Low	11	21.6	9	17.6		
History of AMI						
Yes	19	37.3	26	50.9		
No	32	62.7	25	49.1	1.949	0.163
Cigarette smoking status						
No	14	27.5	14	27.5	0.919	0.632
Yes	25	49	21	41.2		
Recently quit smoking	12	23.5	16	31.3		
Duration of DM (years)						
0-10	32	62.7	32	62.7		
≥11	19	37.3	19	37.3	1.000	0.581
Treatment method						
Diet	2	3.9	0	0.0		
Oral antidiabetic drug	36	70.6	37	72.5		
Insulin	6	11.8	8	15.7		
Mix	7	13.7	6	11.8	2.376	0.498
Diabetes education history						
Yes	7	13.7	8	15.7		
No	44	86.3	43	84.3	0.078	0.780

[a]Independent samples t-test, [b]χ^2 test, p≤0.05
AMI: Acute myocardial infarction, BMI: Body mass index, DM: Diabetes mellitus, SD: Standard deviation, t: Independent-samples t-test, χ^2: Chi-square test

Table 3. Comparison of T2DSMS score (n=102)					
	Intervention group (n=51)	Control group (n=51)	Test		95% CI, Lower-Upper
Scale	Mean±(SD)	Mean±(SD)	t	p	
T2DSMS					
Pretest	48.35±11.94	49.86±12.66	-0.620	0.537	-6.34 to 3.32
Posttest	72.49±8.06	46.84±11.80	12.816	<0.001	21.68 to 29.62
t[a]	-16.405	6.593			
p	<0.001	<0.001			
Effect size (d)	2.369				
95% CI, Lower-Upper	-27.09 to -21.18	2.10 to 3.94			

[a]Paired samples t-test, p<0.001
CI: Confidence interval, SD: Standard deviation, t: Independent-samples t-test, T2DSMS: Type 2 diabetes self-management scale

DISCUSSION

This randomized controlled experimental study analyzed the effects of a diabetes education program based on Pender's health promotion model on diabetes self-management among patients with T2D who experienced AMI. The strength of our study lies in the fact that the intervention was based on a patient education model and included follow-up data. A total of 102 patients were recruited for the study. Two sessions of DSMEP were conducted, 3-4 hours apart, and the patients were followed up for 1 month. The present study found that DSMEP was an effective method for increasing the levels of diabetes self-management among patients with T2D who have experienced AMI. These findings confirmed the hypothesis.

Our findings were similar to those of other studies that primarily involved patients with diabetes and collected data through face-to-face interviews. One study examined the effect of diabetes education on self-management in patients with T2D and found that their diabetes self-management improved significantly after 3 months (26). Similarly, a study investigating the relationship between patients' participation in structured diabetes education programs and their self-management behaviors reported that those who participated in such education had higher levels of self-management (28). The study found a significant relationship between self-management behaviors and participation in a DSMEP. In a review of interventions aimed at encouraging healthy lifestyle behaviors in individuals diagnosed with T2D, it was reported that interventions including patient education led to positive improvements in blood pressure and cholesterol levels, as well as in diet and physical activity behaviors (29). The needs of individuals with diabetes are not limited to achieving adequate glycemic control; they also include increasing awareness, acquiring sufficient knowledge, developing self-care skills to prevent diabetes-related complications, and participating in diabetes self-management (30). It is essential for nurses to offer counseling services tailored to the specific learning needs of their patients (31). In a study examining the knowledge of patients with T2D regarding possible cardiovascular complications and their relationship with diabetes self-management, it was reported that patients did not have sufficient knowledge regarding CVD risk (32). In individuals with cardiovascular risk have cardiovascular risk factors, behavioral counseling aimed at motivating healthy eating and exercise may provide moderate benefits in reducing the risk of CVD (33). Improvements in healthy lifestyle behaviors of patients who have experienced MI can be observed within the first 3 months after the heart attack (34). It is especially emphasized that smoking cessation can prevent the risk of developing secondary CVD (35). Cardiovascular complications can be significantly reduced through optimal management of cardiovascular risk factors and smoking cessation in adults with diabetes (36). Patient education may improve healthy lifestyle behaviors to prevent secondary cardiovascular complications (37). Therefore, a holistic evaluation of individuals with T2D who have AMI, along with the implementation of a planned training program under nurse leadership, can make significant contributions to improving patient health.

Unlike other studies, this study was conducted within a limited time frame. Taken together, these studies demonstrate the benefits of DSMEPs in improving the disease self-management behaviors of patients with T2D, thereby preventing chronic complications of diabetes, which supports our findings. We believe that a diabetes education program based on Pender's health promotion model can be an effective intervention for improving disease self-management not only in patients with T2D but also in other patients with diabetes who have vascular complications. We were unable to find any studies on disease self-management in patients with T2D who have experienced AMI. The aim of our study was to examine the effects of a patient education program on diabetes self-management in this patient group. In conclusion, we found that planned patient education is an effective approach for improving disease self-management in patients with T2D who have experienced AMI.

Study Limitations

This study, which was designed within a randomized controlled trial framework, is the first study in our country to comprehensively investigate the effect of an education program on diabetes self-management in individuals with T2D who have experienced AMI. However, this study has several limitations. Because this study was conducted in a single center, it is recommended that the study be repeated in multiple centers. Additionally, in our study, education was provided to the patients, and patient interviews were conducted by the principal investigator. Therefore, the findings may be biased. However, one of the researchers had no prior clinical relationship with the patients included in the study, potentially reducing the risk of bias or coercion. The fact that diabetes self-management outcomes were not evaluated based on hemoglobin A1c levels is a limitation of this study. Another limitation was that the follow-up period after training was only 1 month.

CONCLUSION

In conclusion, this study revealed that the patient education program had a positive effect on diabetes self-management in patients with T2D who experienced AMI. We recommend

conducting large-scale intervention studies in different hospitals and intensive care settings to evaluate effective teaching methods for self-management education in patients with T2D who have experienced AMI.

This study is the first to focus on increasing diabetes self-management in patients with T2D who have experienced AMI treated in a cardiology specialty hospital in Turkey, and to investigate the effectiveness of an education program. The findings may be useful for planning interventions to improve diabetes self-management behaviors in such patients. Diabetes self-management among patients with T2D who experienced AMI was significantly enhanced through the patient education program. A nurse-led educational program is considered an effective intervention that can be integrated into regular patient care for these patients. Our study results may raise awareness among intensive care nurses about the holistic evaluation of disease self-management in patients with T2D who experienced AMI. Additionally, it may encourage intensive care nurses to seek diabetes education for patients with T2D in ICUs. Further studies by other researchers could help confirm our findings.

Footnote

Ethics Committee Approval: Ethical approval was granted by the Social and Human Sciences Research Ethics Board of İstanbul University-Cerrahpaşa (decision number: 2022/476, date: 06.12.2022).

Informed Consent: We informed the patients about the aim and scope of the study and obtained their informed consent.

Authorship Contributions

Surgical and Medical Practices: Z.K., Concept: Z.K., A.E., Design: Z.K., A.E., Data Collection or Processing: Z.K., Analysis or Interpretation: Z.K., A.E., Literature Search: Z.K., A.E., Writing: Z.K., A.E.

Conflict of Interest: No conflicts of interest were declared by the authors.

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ORIGINAL ARTICLE

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The Importance of Coagulation Parameters in Predicting Preterm Birth

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Abstract

Objective: A large proportion of neonatal deaths not related to congenital anomalies are attributed to preterm births. The aim of this study was to compare the coagulation parameters in pregnant women with premature uterine contractions (PUC) who have preterm births with those who have term births and to determine the role of these coagulation parameters in predicting preterm delivery.

Methods: Seventy-two pregnant women with PUC who applied to the Department of Obstetrics and Gynecology at the Okmeydanı Training and Research Hospital, University of Health Sciences, were included in the study. The coagulation parameters of 36 women who had preterm births were compared with those of 36 women who had term births. In analysing the findings of the study, statistical analyses were performed using IBM SPSS Statistics 22 (IBM SPSS, Turkey). The data were analyzed using Shapiro-Wilks, one-way, ANOVA, Tamhane's T2 test, and Student's t-test etc.

Results: The activated partial thromboplastin time (aPTT) was significantly shorter in the preterm birth group (25.64±3.24 seconds) compared to the term birth group (26.153±2.49 seconds). International normalized ratio (INR) and prothrombin time (PT) levels were similar in both groups and subgroups. Fibrinogen levels were lower in the preterm birth group (397.56±54.67 mg/dL) compared to those who delivered at term (409.78±65.06 mg/dL). Fibrinogen levels were significantly lower in the preterm labor subgroup (388±50.72 mg/dL) compared to the preterm premature rupture of membranes (PPROM) subgroup (431±58.09 mg/dL).

Conclusion: In this study, it was observed that the aPTT values in the preterm birth group were significantly shorter compared to the term birth group. Fibrinogen levels were found to be lower in the preterm birth group compared to those who delivered at term. Within the preterm labour subgroup, fibrinogen levels were significantly lower than those in the PPROM subgroup. INR and PT levels were similar across both groups and subgroups. The aPTT values were also similar between the preterm labour and PPROM subgroups.

Keywords: Premature uterine contractions, preterm birth, preterm labour

INTRODUCTION

Despite advancements in the fields of medicine and technology, preterm births, which constitute approximately 7-8% of all births, continue to be significant causes of perinatal morbidity and mortality. A large majority (75%) of non-congenital anomaly-related neonatal deaths are attributable to preterm births. Most of these premature birth cases (75-80%) occur due to spontaneous preterm labor (PE) and preterm premature rupture of membranes (PPROM), while the remaining 20-25% are due to maternal and fetal problems and are recorded as indicated preterm births (1,2).

The pathophysiological mechanisms underlying preterm birth have been associated with various factors, such as decidual bleeding, excessive uterine stretching, and hormonal changes. Among these, hormonal changes triggered by fetal or maternal stress have also been noted. However, the exact mechanism of

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these pathological processes has not been clearly explained. Moreover, numerous factors that increase the risk of preterm birth have been identified. The threat of PE, defined as the onset of contractions without cervical changes, is more common than the incidence of actual PE.

Premature uterine contractions (PUC) are defined as uterine contractions occurring before 37 weeks of gestation without cervical dilation that may or may not result in preterm birth. PUC affects approximately 10-12% of pregnancies, but only a fraction of these cases lead to PE. Studies have indicated that up to 33% of pregnant women observed for PUC can be discharged after 48 hours of observation without intervention (1). However, the false-positive rate of diagnosing the risk of PE in women with PUC is high, reaching up to 20-40%. On the other hand, about 40% of preterm birth cases are complicated with PPROM, whereas only 18% of untreated pregnancies result in early labor (3).

Despite advances in medical sciences that have significantly reduced the incidence of many obstetric complications, there has been no reduction in the frequency of PE and PPROM cases despite innovations and developments in obstetrics. Indeed, over the last decade, PE cases have increased by 15% (1,4). In this context, studies have been conducted aimed at a more accurate diagnosis of PE by detecting certain biochemical markers that could be used in predicting preterm birth. These studies have focused on the analysis of various biochemical markers in blood, saliva, and cervicovaginal secretion (5-7).

Pregnancy creates a known prothrombotic condition. During this period, there is a decrease in anticoagulant and fibrinolysis activity along with an increase in procoagulant factor levels. The hypercoagulation observed during pregnancy intensifies on the basis of acquired or hereditary thrombophilia, paving the way for various pregnancy complications. Furthermore, changes in coagulation parameters during pregnancy, such as tissue plasminogen activator, factors V, factor VII, activated partial thromboplastin time (aPTT), and prothrombin time (PT), have been supported by studies indicating their association with PE (4,6).

The primary objective of this research was to compare the coagulation parameters of pregnant women who experience PUC and have preterm births with those who have term births and to determine the role of these coagulation parameters in predicting preterm birth. Specifically, we aim to identify specific coagulation parameters that can serve as reliable biomarkers for early preterm birth prediction, thereby improving clinical outcomes and providing better targeted interventions for at-risk pregnancies. Additionally, this study seeks to elucidate the underlying mechanisms linking coagulation abnormalities with PE and delivery, contributing to a broader understanding of preterm birth pathophysiology.

METHODS

This prospective observational study was conducted with the approval of the Health Sciences University Okmeydanı Health Application and Research Center Clinical Research Ethics Commitee, under the (decision number: 611, date: 14.03.2017).

Criteria for participation in the study were as follows:

• Healthy women aged between 17 and 44 with singleton pregnancies diagnosed with PUC between 28 and 34 weeks of gestation who had preterm births for the study group.

• Healthy women aged between 17 and 44 with singleton pregnancies diagnosed with PUC between 28 and 34 weeks of gestation who had term births for the control group.

• Patients who agreed to participate and signed the informed consent form.

• No detection of fetal anomalies during the second trimester ultrasonography screening performed between 18-22 weeks of gestation.

• Maternal hemoglobin (Hb) levels above 10 g/dL.

Exclusion criteria: Reasons for excluding participants from the study are listed as follows:

Maternal factors:

• Susceptibility to thrombophilia.

• The initiation of tocolytic treatment prior to presentation.

• History of sexual intercourse within the last 24 hours.

• Placenta previa totalis.

• Placental abruption.

• History of vaginitis during pregnancy.

• Diagnosed coagulation disorder.

• Multiple pregnancies.

• The presence of active infection.

• Signs and symptoms of intraamniotic infection.

• Vaginal bleeding.

Fetal factors:

• Fetal distress: Clinical and laboratory indicators of decreased fetal oxygenation.

• Stillbirth: Fetus death at advanced stages of gestation.

• Fetal anomalies incompatible with life: Structural or genetic anomalies that prevent the fetus from surviving post-birth.

• Presence of intrauterine growth restriction (IUGR) ıntrauterine growth restriction-The fetus weighing less than expected at the gestational age.

• Polyhydramnios-excessive amniotic fluid.

The study population consisted of women who were diagnosed with PUC between the 28th and 34th weeks of gestation and who had preterm births as well as women diagnosed with PUCs during the same gestational weeks but who had term births. This population was divided into two main groups for analysis. Participants included in the study were categorized into two groups based on their time of delivery: those who gave birth at 37 weeks of gestation and later were classified into the term group, and those who delivered between 28 and 36 weeks of gestation were classified into the preterm group. A total of 72 pregnant women, 36 from each group, were included in the study. The preterm birth group was further subdivided into two subgroups based on the diagnoses of PE and PPROM.

• Group: Healthy pregnant women with PUC between 28-34 weeks who had preterm births (n=36) (Preterm birth group)

• Subgroup 1a: Preterm premature membrane rupture group (n=8)

• Subgroup 1b: PE group (n=28)

• Group: Healthy pregnant women with PUC between 28-34 weeks who had term births (n=36) (Term birth group).

For subgroup 1a, the diagnosis of membrane rupture was made during a sterile speculum examination by observing active amniotic fluid flow from the cervical canal. Additionally, the intense fluid discharge noted in patient reports and detected in the vaginal area during speculum examination along with a decrease in amniotic fluid observed during ultrasonographic examination assisted in diagnosing PPROM. Subgroup 1b, the PE group, consisted of pregnant women who showed at least four regular uterine contractions within 20 minutes with a cervical length below 30 mm and cervical dilation of at least 2 cm. All participants' privacy was prioritized; personal identification details, consultation dates, contact details, professions, lifestyles, educational levels, age, height, weight, body mass index (BMI), number of pregnancies (gravida), number of births (parity), number of miscarriages (abortus), number of living children, and obstetric history (risk of preterm birth, early birth, cervical insufficiency, cerclage history, stories about assisted reproduction techniques, threat of miscarriage) were meticulously recorded. Additionally, the date of the last menstruation, first trimester ultrasonography results and the latest ultrasonography findings, as well as vaginal examination results, were carefully documented. Details such as the babies' birth weights, dates of birth, conditions of admission to neonatal intensive care, first- and fifth-minute Apgar scores, and the use of tocolytic agents were also recorded. Gestational age was determined based on the last menstrual period and was confirmed confirmed with first trimester ultrasonography findings. In all pregnant women experiencing PUC, standard blood counts, liver and kidney function tests, C-reactive protein (CRP), coagulation tests, D-dimer, and complete urine tests were performed at presentation, and the results were recorded. For the coagulation tests, blood samples were collected in sterile tubes containing 3.2% sodium citrate, centrifuged at 4000 g for 10 min. The resulting fresh plasma samples were used to calculate fibrinogen, PT, aPTT, and international normalized ratio (INR) values. For the D-dimer test, purple-cap sterile tubes were used, and analysis was performed using the AQT 90 device. In necessary cases, tocolytic agents and steroids were administered to the preterm birth and PPROM subgroups. Details such as weeks of birth, weight, and type of delivery were recorded for participants who gave birth in our clinic. For patients who gave birth outside our clinic, the same information was obtained through telephone interviews. Demographic characteristics of all groups, Hb, platelet (PLT), activated aPTT, PT, INR, fibrinogen, and D-dimer levels were compared and analyzed.

Statistical Analysis

During the evaluation of the findings of this study, statistical analyses were performed using IBM SPSS Statistics 22 (IBM SPSS, Turkey). In the evaluation of the study data, the Shapiro-Wilk test was used to assess whether the parameters conformed to the normal distribution. For the analysis of quantitative data, the one-way ANOVA test was used for comparisons between groups in which parameters showed normal distribution, and Tamhane's T2 test was chosen to identify groups that demonstrated differences. For comparisons between two groups, Student's t-test was applied for parameters that exhibited normal distribution, whereas the Mann-Whitney U test was used for those that did not. The comparison of qualitative data employed Fisher's Exact test and the Continuity (Yates) Correction. The relationships between parameters that conformed to the normal distribution were assessed using Pearson's correlation analysis. The significance level was set at $p<0.05$.

RESULTS

This study was conducted between January 15, 2017, and April 15, 2018, on a total of 72 female participants aged between 17 and 44. The mean age of the participants was determined to be 28.86 (standard deviation: 6.77). Within the scope of the research, participants were divided into two main groups: "preterm birth" and "term birth", each consisting of 36 women. Furthermore, the preterm birth group was subdivided into two detailed subgroups: PE and PPROM.

Statistically significant differences were observed between the groups, with the mean age of the preterm birth group being significantly lower than that of the term birth group (p=0.010; p<0.05). Similarly, the average BMI of the preterm birth group was also significantly lower compared to the term birth group (p=0.000; p<0.05). The average gestational week of pregnancies in the preterm birth group was significantly lower compared to the term birth group (p=0.008; p<0.05). However, no statistically significant difference was found in the number of pregnancies (gravida) between the preterm and term birth groups (p>0.05). Additionally, the parity (number of births) values for the preterm birth group were significantly lower than those of the term birth group (p=0.017; p<0.05). No significant statistical differences were found between the preterm and term groups in terms of occupational distribution and education levels (p>0.05). The detailed data and findings are comprehensively presented in Table 1 below.

The average weight of newborns in the preterm birth group was found to be statistically significantly lower compared to the term birth group (p=0.000; p<0.05). However, no statistically significant difference was observed between the preterm and term birth groups in terms of gender distribution ratios and modes of delivery (both p>0.05). Conversely, the rates of Apgar scores (an assessment indicating the newborn's health status) being 7 or above at 1 and 5 minutes were significantly lower in the preterm group compared with the term group; while this rate was 58.3% in the preterm group, it was 86.1% in the term group (p=0.018; p<0.05). The detailed findings are presented in Table 2.

In the preterm birth group, the mean Hb level was determined to be 11.55±1 g/dL, which was statistically significantly lower compared to the mean of 12.26±1.04 g/dL in the term birth group (p=0.004; p<0.05). aPTT values were measured as 25.64±3.24 seconds in the preterm birth group, whereas in the term group, this value was found to be 26.153±2.49 seconds, indicating that aPTT was significantly shorter in the preterm group (p<0.05). However, there was no statistically significant difference between the two groups in terms of INR, PT, PLT count, D-Dimer, and fibrinogen levels (p>0.05). Furthermore, no significant difference was observed between the groups in terms of CRP, white blood cell (WBC) distribution ratios, and recovery rates (p>0.05). Although fibrinogen levels were lower in the preterm birth group at 397.56±54.67 mg/dL compared with the term birth group, the fibrinogen level in the term birth group was recorded as 409.78±65.06 mg/dL. D-dimer values were measured as 1013.06±927.93 ng/mL in the preterm birth group and 879.42±583.4 ng/mL in the term birth group, but these differences were not statistically significant (p>0.05). The detailed findings are presented in Table 3.

When examining preterm birth cases, the average weight of newborns in the PE group was determined to be 2314.93±365.26 kg. This value was significantly higher when compared to the average weight of 1916.88±500.31 kg in the PPROM group (p=0.017; p<0.05). No statistically significant differences were found between the PE and PPROM groups in terms of cervical

Table 1. Evaluation of demographic data between groups

	Preterm group	Term group	Total	p
Age	26.83±6.43	30.89±6.58	28.86±6.77	**0.010**[1]
BMI (kg/m^2)	23.18±2.19	26.72±0.90	24.95±2.44	**0.000**[1]
Gestational week (weeks)	32.04±1.63	32.92±1.00	32.48±1.41	**0.008**[1]
Gravida number (median)	2.3±1.51	2.64±0.87	2.47±1.23	0.065[2]
Parity number (median)	0.92±1.05	1.36±0.72	1.14±0.92	**0.017**[2]
Occupation (%)				0.733[3]
Housewife	30 (83.3)	32 (88.9)	62 (86.1)	
Educational status (%)				0.733[3]
High school or less	30 (83.3)	32 (88.9)	62 (86.1)	

Values indicated with p<0.05 are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Continuity (Yates) Correction
BMI: Body mass index

length, week of birth, or average gestational age ($p<0.05$). Similarly, no significant statistical difference was found in the distribution of tocolysis applications between the two groups ($p>0.05$). However, the rate of normal spontaneous delivery (NSD) in the PE group was 67.9%, whereas that in the PPROM group was 25%, and this difference was found to be statistically significant ($p=0.046$; $p<0.05$). Looking at the rates of admission to the intensive care unit, 57.1% of the PE group was admitted compared to 100% of the PPROM group. This indicates that the intensive care admission rate for the PE group was significantly lower than that for the PPROM group ($p=0.033$; $p<0.05$). The related findings are detailed in Table 4. According to the data

Table 2. Evaluation of study parameters between groups

	Preterm group	Term group	Total	p
Newborn weight (g)	2226±425.62	3445±526.93	2836±776.66	**0.000**[1]
Weeks of gestation	33.78±1.82	38.82±1.2	36.32±1.96	**0.000**[1]
Gender (%)				0.631[3]
Female	65.5%	63.9%	59.7%	
Male	34.4%	36.1%	40.3%	
Mode of delivery				0.813[3]
NSD	58.3%	58.2%	55.6%	
Sectio	41.7%	47.2%	44.4%	
1st and 5th minute Apgar scores (%)				**0.018**[3]
>7	58.3%	68.6%	67.2%	
<7	41.7%	31.9%	32.8%	
Intensive care admission (%)				**0.010**[3]
None	63.3%	66.7%	50.0%	
Present	66.7%	33.3%	50.0%	

Values indicated with $p<0.05$ are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Continuity (Yates) Correction
NSD: Normal spontaneous delivery

Table 3. Evaluation of hematological parameters between group

	Preterm group	Term group	Total	p
Hemoglobin (g/dL)	11.55±1.34	12.61±1.04	11.98±1.08	**0.004**[1]
PLT (10^3Ul)	230.56±57.24	267.39±53.28	248.77±60.06	0.125[1]
aPTT (sn)	25.65±4.23	26.13±2.49	25.88±2.98	0.013[1]
INR	0.99±0.08	0.97±0.1	0.99±0.09	0.483[1]
PT (sn)	11.72±0.86	11.78±1.1	11.74±0.98	0.901[1]
Dimer (ng/dL)	676.65±789	706±878.92	693±810.67	0.679[2]
Fibrinojen (mg/dL)	103±23.79	293±58.34	296±70.05	0.879[1]
Feritin (ng/mL)	397.55±24.67	498.76±30.65	448.67±35.98	0.891[1]
CRP (mg/dL)	0.78±0.96	0.89±1.06	0.83±1.02	0.896[2]
WBC (10^3/µL)				
<12.000	22 (61.1%)	20 (55.6%)	42 (58.3%)	0.811[3]
>12.000	14 (38.9%)	16 (44.4%)	30 (41.7%)	0.811[3]
Recovery				
None	21 (58.3%)	20 (55.6%)	41 (56.9%)	0.000[3]
Present	15 (41.7%)	16 (44.4%)	31 (43.1%)	0.000[3]

Values indicated with $p<0.05$ are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Continuity (Yates) Correction
PLT: Platelet, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time, CRP: C-reactive protein, WBC: White blood cell

presented in Table 5, no statistically significant differences were found between the PE and PPROM groups within the preterm birth group in terms of Hb, PLT, aPTT, INR, PT, and D-dimer levels (p>0.05). However, fibrinogen levels averaged 388±50.72 in the PE group compared to 431±58.09 in the PPROM group, and this difference was statistically significant (p=0.048; p<0.05). Additionally, no statistical significance was found between the PE and PPROM groups regarding CRP distribution rates, WBC distribution rates, and recovery rates (p>0.05).

Discussion

Preterm birth is a critical complication that can lead to death and serious health issues for both the mother and the newborn. The observed shortening of aPTT in the preterm birth group may be explained by mild increases in coagulation factors, such as von Willebrand factor (vWF) and Factor VIII activity. These changes contribute to the hypercoagulable state observed in pregnancy. Furthermore, elevated levels of coagulation factors such as Factor VII and Factor XI, which were not measured in this

Table 4. Evaluation of study parameters between preterm action and PPROM groups in the preterm birth group

	Preterm labor group	PPROM group	Total	p
Newborn weight (g)	2314.93±365.16	1916.88±500.31	2226.47±425.62	**0.017**
Cervical length (mm)	24.11±7.81	29.25±6.39	25.25±7.74	0.098[1]
Weeks of gestation	34.04±1.57	32.88±2.42	33.78±1.82	0.113[1]
Pregnancy week (week)	32.24±1.51	31.36±1.97	32.04±1.63	0.181[1]
Form of tocolysis	N8 (61.5%)	6 (75%)	14 (66.7%)	0.656[2]
Method of tocolysis	A5 (38.5%)	2 (25%)	7 (33.3%)	0.656[2]
Mode of delivery	NSD 19 (67.9%)	2 (25%)	21 (58.3%)	**0.046[2]**
Mode of delivery	Sectio 9 (32.1%)	2 (25%)	7 (33.3%)	**0.046[2]**
Intensive care admission				**0.033[2]**
None	12 (94.2%)	0 (0%)	12 (63.3%)	
Exists	16 (65.7%)	8 (100%)	24 (66.7%)	

Values indicated with p<0.05 are statistically significant
[1]Student t-test, [2]Fisher's Exact Test
PPROM: Preterm premature rupture of membranes

Table 5. Evaluation of laboratory parameters between preterm labor and pprom groups in the preterm birth group

	Preterm labor group	PPROM group	Total	p
Hemogram (g/dL)	11.52±0.97	11.65±1.18	11.55±1.0	0.748[1]
PLT (10^3/µL)	231.71±67.92	225±64.62	230.22±66.35	0.845[1]
aPTT (sn)	25.79±33	25.1±31.4	25.64±32.4	0.602[1]
INR	0.98±0.06	1.02±0.12	0.99±0.08	0.309[1]
PT (sn)	11.7±0.62	11.78±11.49	11.72±0.86	0.896[1]
Dimer (ng/mL)	109046±1040	74213±15355	101306±92793	0.435[2]
Fibrinojen (mg/dL)	388±50.72	431±58.09	397.56±54.67	**0.048[1]**
CRP (mg/dL)	0 26 (92.9%)	5 (62.5%)	31 (86.1%)	0.064[3]
WBC (/mm^3) n (%)				0.683[3]
<12.000	18 (64.3%)	4 (50%)	22 (61.1%)	
>12.000	10 (35.7%)	4 (50%)	14 (38.9%)	
Benign n (%)				0.694[3]
None	17 (60.7%)	4 (50%)	21 (58.3%)	
Exist	11 (39.3%)	4 (50%)	15 (41.7%)	

Values indicated with p<0.05 are statistically significant
[1]Student t-test, [2]Mann-Whitney U Test, [3]Fisher's Exact Test
PPROM: Preterm premature rupture of membranes, PLT: Platelet, aPTT: Activated partial thromboplastin time, INR: International normalized ratio, PT: Prothrombin time, CRP: C-reactive protein, WBC: White blood cell

study, could also play a role. These factors, although not directly causing PE, may signal an increased thrombotic tendency in patients with preterm birth. Although these changes are subtle, they could be clinically significant, particularly in high-risk populations in whom thromboembolic events are a concern. Therefore, the identification of women at risk of preterm birth experiencing PUC is both challenging and essential. Early diagnosis, which is crucial for treating and preventing preterm birth, can be easily achieved in cases associated with PPROM, whereas it is more challenging in cases with a closed cervix and intact membranes. Moreover, uncertainties regarding whether preterm birth will occur and the necessity of a special treatment regimen that could have adverse effects on both the mother and the baby lead to dilemmas in treatment implementation. Furthermore, no low-cost, non-invasive, and universally reliable indicator that can be integrated into daily practice to predict spontaneous preterm birth.

Studies have suggested a relationship between hypercoagulability during pregnancy and pregnancy complications, such as preterm birth have been found (6,4,8,9). In a study conducted by Hrubaru et al. (10) in 2023, it was found that Hb levels below 12.0 g/dL, PT below 12.5 seconds, aPTT values below 25 seconds, and D-dimer levels above 250 ng/mL were significant determinants of preterm birth (10). Keren-Politansky et al. (3) showed that in women experiencing PUC and undergoing preterm birth, PT and activated aPTT values were significantly shorter compared with women with term births and PUC. Although anemia has been identified as a significant marker of preterm birth, a recent meta-analysis showed no significant association between anemia during pregnancy and the risk of preterm birth (11). In our study, it was found that the mean Hb level was statistically significantly lower in the preterm birth group than in the term group. Additionally, in another study, it was stated that anemia is mostly due to normocytic normochromic variation and has a prevalence rate of more than 50%; however, the type of anemia was not examined in our study (12). Furthermore, in our study, it was observed that aPTT duration was statistically significantly shorter in women with preterm births and PUC than in women with term births and PUC, while no significant difference was detected between the two groups in terms of PT values. In the comparison between the PE and PPROM groups, no statistically significant difference was found in terms of aPTT and PT. Short PT and activated aPTT are global tests used to assess the coagulation system and are associated with the risk of venous thromboembolism (9,3). A possible explanation for the shorter aPTT duration detected in women with preterm births could be mild increases in vWF antigen and Factor VIII activity in this group. Additionally, high levels of coagulation factors such as factors VII, Factor XI, and Factor IX, which are known to increase during pregnancy but were not measured in our study, could also contribute to the shortening of PT and aPTT durations. The relatively small groups may have made it difficult to obtain statistically significant results for some parameters. Nevertheless, global coagulation tests, including PT and aPTT, have demonstrated a tendency toward hypercoagulability; however, while no difference was found in terms of PT between the study and control groups, a difference was observed in terms of aPTT. Although these coagulation parameters have the potential to differentiate the clinical conditions of pregnant women, their exact cutoff values have not yet been determined.

To the best of our knowledge, this study is one of the few that comprehensively examined the coagulation process in women experiencing PUC. A pioneering study suggested that shortened PT and aPTT could predict early contractions that might subsequently lead to preterm birth. In our study, when comparing women with preterm births to those with term births, the preterm group had shorter aPTT values, whereas there was no difference between the two groups in terms of PT values. In a study by Erez et al. (13) tissue factor (TF) and tissue factor pathway inhibitor (TFPI) were analyzed in pregnant women without PUC in the term period and those with preterm births, revealing that women with preterm births had higher TF activity and lower TFPI concentrations. The analysis results by Erez et al. (13) focused solely on patients with PUC, and no difference in TF and TFPI concentrations was observed between term and preterm patients. In this context, the findings obtained by Erez et al. (13) are consistent with the results of our study. The final stage of coagulation involves the formation of fibrin clots from fibrinogen via thrombin. Except for a published study, no other study has compared fibrinogen levels at the same gestational weeks between women experiencing PUC who deliver preterm and term births. In our study, matching was performed according to gestational age. This is particularly important given the significant increase in fibrinogen concentration in the second and third trimesters; without this matching, bias could occur in the results. In the study by Keren-Politansky et al. (3) it was observed that fibrinogen concentration in the study group was slightly higher than in the control group, but the difference was not statistically significant. In our study, although fibrinogen levels were slightly lower in the study group than in the control group, the difference was not statistically significant. However, among the subgroups of women with preterm births, fibrinogen levels in the PE group were found to be statistically significantly lower compared to the PPROM

group. Despite the significant differences in aPTT and fibrinogen levels, the clinical relevance of these findings remains uncertain. Shortened aPTT and lowered fibrinogen levels might indicate increased thrombotic risk; however, further studies are required to determine the cutoff points that can predict preterm birth with high accuracy. The variations in these parameters suggest the involvement of a complex pathophysiological mechanism in PE, which warrants more detailed exploration.

This may indicate different mechanisms at play in PE: potentially less thrombogenic activity in cases with intact membranes and increased thrombogenic activity in PPROM cases. However, further comprehensive research is needed to confirm this hypothesis. Considering the significant impact of hypercoagulability on the pathogenesis of PE, more pronounced alterations in the coagulation profile are expected in women exhibiting more intense PE. Indeed, a study by Catov et al. (14) demonstrated that levels of the thrombin-antithrombin complex, a sensitive indicator of coagulation activation, increased linearly and dose-dependently with the risk of PE. This study, which used aPTT values as an indicator of the time from PUC onset to the appearance of clinical signs until delivery, did not find a relationship between these parameters. This suggests that an approach based on the measurement of delay times may not be ideal for quantitatively estimating the activation of preterm birth. Therefore, additional research is needed to determine the most appropriate method for quantitatively evaluating the degree of preterm birth activation (15).

Although it is known that D-dimer levels increase with gestational age during pregnancy, there is a lack of comprehensive, enlightening, and robust studies on this topic. In a study by Kline et al. (15) which started with 50 cases and ended with 18 cases, it was reported that the average plasma D-dimer concentration was 430 ng/mL in the preconceptional period, 579 ng/mL in the first trimester, 832 ng/mL in the second trimester, and 1159 ng/mL in the third trimester. Another study conducted by Francalanci et al. (16) found that plasma D-dimer concentrations increased with gestational age and D-dimer levels in the second and third trimesters were significantly different compared to non-pregnant healthy women. In a study by Haznedaroğlu et al. (17) investigating hemostatic markers in preterm birth, they found that D-dimer levels in the group with preterm birth differed significantly from both the D-dimer levels of the healthy pregnant and the unhealthy women group (17). Additionally, in a study by Yazıcıoğlu et al. (18) examining serum D-dimer levels during the first admission between women hospitalized due to threatened PE who subsequently had preterm births and women who had term births, significant differences were found (18). In our study, although the D-dimer values of the preterm birth group (1013.06±927.93 ng/mL) were higher compared to the term birth group (879.42±583.4 ng/mL), no statistically significant difference was detected between the two groups in terms of D-dimer values.

Maternal anemia during pregnancy is widely accepted to be associated with fetal outcomes such as fetal IUGR, preterm birth, and low birth weight, as well as maternal complications like preeclampsia, eclampsia. In our study, maternal Hb level was defined with a lower limit of 10 mg/dL. However, the average Hb levels were significantly lower in the group with preterm births compared to the group with term births. These findings highlight the potential importance of iron supplementation in preventing preeclampsia and preterm birth. Another study reported a higher likelihood of anemia during pregnancy in young mothers; our study is supportive of these findings (19). In a study by Hawrryshyn et al. (20) it was reported that if the serum CRP level is above 1.5 mg/dL, there is an increased likelihood of delivery within 7 days. However, in our study, no difference was observed among the different groups in terms of CRP values. On the other hand, in another study conducted by Yuan et al. (21) the role of maternal peripheral blood leukocytes in preparing for activation during both term and preterm delivery was indicated. However, in our study, no difference was detected in terms of WBC among any of the groups. The strengths of our study lie in its original and prospective design, matching between the study and control groups, and detailed examination of the coagulation profile of each participant.

Study Limitations

However, the limitations of the study include the relatively small size of the study arms. Although power analyses indicated that 30 patients in each arm were sufficient for a Type I (α) error of 5%, larger studies with more patients may be able to detect subtle changes in the coagulation profile identified in the current study but did not reach statistical significance. Additionally, such studies may contribute to determining the cutoff value for aPTT that distinguishes between patients experiencing PUC who deliver preterm and those who successfully maintain pregnancy until term or allow for the use of plasma fibrinogen levels in predicting PE and PPROM.

All parameters evaluated in this study, including Hb and coagulation parameters, can be measured during routine pregnancy follow-up visits and used as a non-invasive method to identify women at high risk of early delivery. Another potential application is the monitoring of women who are already at high risk of early delivery because of pre-existing medical conditions

or past history. Regular measurement of these parameters during prenatal visits could facilitate early detection of changes indicating an increased risk of preterm birth. These findings could prompt healthcare providers to recommend closer monitoring or early intervention (10).

CONCLUSION

Our study revealed significantly shorter aPTT values in the preterm birth group compared to the term birth group. In the group experiencing preterm birth, lower fibrinogen levels and higher D-dimer levels were observed compared with the term group; however, these findings were not statistically significant. In the preterm action subgroup, fibrinogen levels were significantly lower compared to the PPROM subgroup. Additionally, the mean age of women experiencing preterm birth was statistically significantly lower compared to women delivering at term. Currently, there is no reliable marker for predicting spontaneous preterm birth that can be used in clinical practice. Further research is needed to determine the clinical value of specific coagulation factors and values of aPTT, fibrinogen, and D-dimer levels that could predict preterm birth. The significantly lower levels in the group experiencing preterm birth compared to the term birth group emphasize the importance of iron supplementation during pregnancy. Developing low-cost and effective tests and treatment methods aimed at reducing and delaying preterm birth will contribute to better patient care and ultimately reduce neonatal mortality and morbidity rates.

Footnote

Ethics Committee Approval: Health Sciences University Okmeydanı Health Application and Research Center Clinical Research Ethics Commitee, under the (decision number: 611, date: 14.03.2017). Criteria for participation in the study.

Informed Consent: Patients who agreed to participate and signed the informed consent form.

Authorship Contributions

Surgical and Medical Practices: E.İ.K., B.C., Concept: E.İ.K., B.C., Design: E.İ.K., B.C., Data Collection or Processing: E.İ.K., B.C., Analysis or Interpretation: E.I.K., B.C., Literature Search: E.İ.K., B.C., Writing: E.İ.K., B.C.

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ORIGINAL ARTICLE

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The Effect of Radial Translation Deformity on Functional Results after the Conservative Treatment of Distal Radius Fracture

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Abstract

Objective: Radial translation in the radiographic evaluation of distal radius fractures has recently been mentioned in the literature. The aim of this study was to evaluate the effect on clinical results of radial translation deformity following conservative treatment of radius distal fractures.

Methods: The radial translation value in the normal population was calculated by evaluating the bilateral wrist radiographs of 278 healthy individuals in the control group. The study group, a retrospective evaluation was made of 447 patients diagnosed with a distal radius fracture and treated with plaster casting. At the final follow-up examination, the wrist radiographs, DASH score, visual analog pain score (VAS), the presence of ulnar-side wrist pain, and Ballotman test results were evaluated.

Results: On the 206 wrist radiographs of the control group, the mean radial translation value was 43.6%±8.2% (range: 25-66%). The mean difference between the right and left wrist measurements of the same patients was found to be 3.94%±1.64%. The study group included 108 patients. In patients with a radial translation difference between the two wrists of >3.94%±1.64%, the DASH and VAS were significantly high ($p<0.001$). On physical examination, distal radioulnar joint instability was determined in 78% of these patients.

Conclusion: The development of radial translation deformity after plaster cast treatment of a distal radius fracture was seen to have a negative effect on functional outcomes. Therefore, evaluation and correction of this parameter are important in the treatment of distal radius fractures.

Keywords: Radial translation, instability, distal radius fracture, deformity

INTRODUCTION

Of all the fractures in the skeletal system, 5-10% are in the forearm, and almost 75% of forearm fractures are seen at the distal radius (1). Radius distal fractures constitute approximately 16% of all the fractures seen in the emergency department (2). The parameters of ulnar variance, volar tilt, and radial inclination have long been used in the radiographic evaluation of distal radius fractures. More recently, radial translation, as another parameter, has started to be mention in the literature (1-3). Radial translation is an extremely new entity defined as a shift of the distal radius in the radial direction compared to the proximal fragment (1,4). In studies conducted to date, the effect of radial translation deformity on distal radioulnar joint (DRUJ) instability was evaluated (1,2,5). However, the effects of the radial translation value on the functional results and DRUJ stability have not yet been fully clarified. The aim of this study was to evaluate the effect on clinical results of radial translation deformity developing after conservative treatment of radius distal fractures.

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METHODS

A control group was formed from a retrospective evaluation of the bilateral wrist posteroanterior (PA) and lateral radiographs obtained from patients aged 18-70 years who presented at the Orthopedics and Traumatology Polyclinic of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital between 01.01.2014 and 01.01.2021. Patients were excluded from the study if the radiographs had not been taken in an appropriate position (6) or if the patient had a history of wrist fracture or any radiocarpal pathology in the operated wrist. Informed consent was obtained from all participants in compliance with the ethical guidelines prior to their inclusion in the study. The wrist radiographs were examined using the PACS. To perform radiographic measurements, a universally licensed application was used which has a four-point angle function and a virtual ruler. To ensure the accuracy and consistency of the measurements, the radiographs were electronically calibrated with an integral standard marker in the PACS. The radial translation values of all patients were calculated using this system. First, a line was drawn on the PA radiograph from the ulnar cortex of the radius toward the distal. A line was then drawn parallel to the distal radial joint line in the longest axis of the coronal plane of the lunatum, and the point at which this line crossed the first line was identified. The length of this line on the radial side was labelled (a), and the length on the ulnar side was labelled (b) (Figure 1). The radial translation value was calculated using these lines (1,5). A retrospective evaluation was performed on the bilateral wrist radiographs of patients aged 18-70 years who were diagnosed with distal radius fracture and treated with plaster casting in the same center between 15.02.2017 and 15.02.2020. Patients were excluded if they had a fracture other than type 2R3A2 or 2R3A3 according to the association of osteosynthesis classification, if they underwent surgery because of reduction loss during follow-up, had any concomitant carpal bone fracture or ulna fracture (except ulna styloid fracture), or if the ulnar positive variance on the final follow-up images was >4mm and the radial inclination and volar tilt measurements were not within the normal limits (7). The study group was formed of patients with at least 1 year of follow-up and bilateral wrist radiographs obtained in the appropriate position at the final follow-up examination.

The patients were evaluated using the presence of ulnar-side wrist pain, Ballotman test results, and DASH and visual analogue pain scores at the final follow-up. In the Ballotman test, the presence of crepitus and pain was evaluated as DRUJ instability (4). In radiographic examination, the parameters of volar tilt, radial inclination, radial translation, and ulnar variance were measured.

Approval for the study was granted by the Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital Health Practice and Research Center Clinical Research Ethics Committee (decision number: 1980, date: 08.03.2022).

Statistical Analysis

All radiographs were evaluated by 3 observers. To determine the inter-observer agreement of the measurements obtained from the same point, the intraclass correlation coefficients (ICC) were calculated. The mean right and left measurements in the dependent groups and whether or not the differences between them were statistically significant were analyzed using the t-test. The significance of the difference between the right and left measurements in repeated measurements was examined by variance analysis. In the independent groups of variables, the difference between the mean values according to the groups was examined with the t-test. Categorical variables were analyzed using the chi-square test. The obtained data were statistically analyzed using SPSS vn. 20.0 software. The results were stated in a 95% confidence interval. A value of $p<0.05$ was accepted as statistically significant.

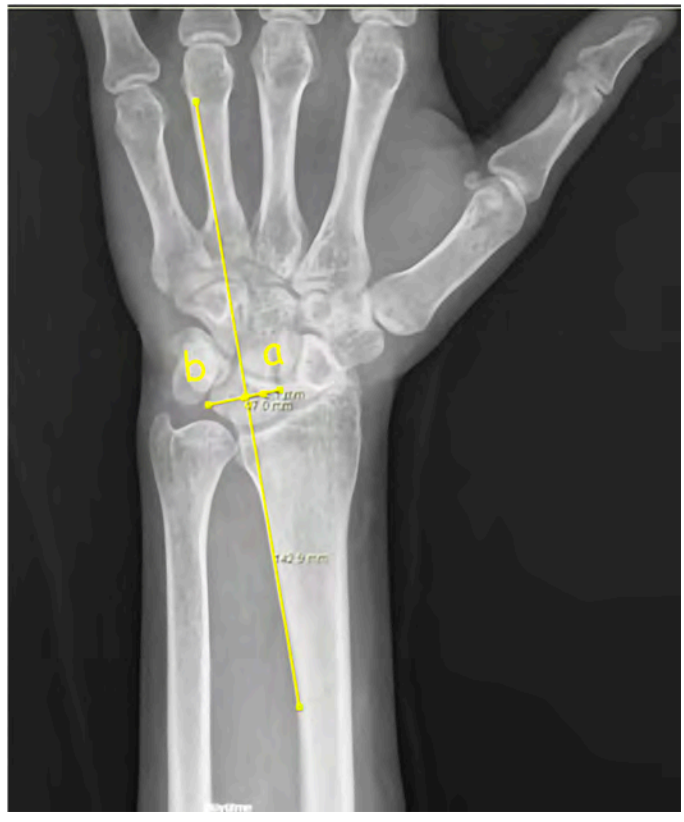

Figure 1. Radial translation value calculation: [a / (a+b)] x 100

RESULTS

Control Group Results

The wrist radiographs of 278 patients were evaluated, and 103 patients who met the study criteria were included in the study. The demographic characteristics of the control group are presented in Table 1.

On the 206 wrist radiographs of the control group, the mean radial translation value was determined to be 43.6%±8.2% (range: 25%-66%) (Figure 2). The mean difference between the right and left wrist measurements of the same patients was found to be 3.94%±1.64%.

Study Group Results

A total of 447 patients were evaluated in the study group, of which 339 did not meet the study criteria, leaving a total of 108 patients included in the study analyses. The demographic characteristics of the patients are presented in Table 2. The mean follow-up period was 21 months (range, 13-47 months). An ulna styloid fracture was found to accompany the radial distal fracture in 45% of the patients. The study group patients were separated into two subgroups; Group A included 28 patients with ulnar positive variance of 2-4 mm, and Group B included the remaining 80 patients. Using the mean difference between the right and left wrist radial translation values (3.94%±1.61%), the groups were separated into two groups. Patients with a difference above the mean value were named Group 1 and those with a value below the mean value, Group 2. The t-test was applied to determine whether or not the mean difference between the radial translation values of the A and B group patients was statistically significant. The mean radial translation difference was found to be 6.81 for the Group A patients and 1.41 for the Group B patients. The difference between the two groups was determined to be statistically significant ($p<0.001$). When all patients were examined according to age, the mean age was determined to be 48.1 years in Group 2 (n=94) and 59.7 years in Group 1 (n=14). Using the t-test, the difference in mean age between the two groups was found to be statistically significant ($p<0.001$). The mean difference in the radial translation values was found to be 1.62 in the patients aged ≤50 years, and statistically significantly higher at 3.53 in patients aged >50 years ($p<0.05$) (Table 3). The radial translation deformities of all patients based on the age group of 50 years are shown in Table 3. The mean ages of the patients was determined to be 59.7 years in Group A-1 and 45.8 years in Group A-2. When examined with the t-test, this difference between the groups was statistically significant ($p<0.05$). The presence of DRUJ instability was evaluated statistically in the Group A patients. DRUJ instability was determined in 4 (28.5%) patients in Group 2 and in 11 (78%) patients in Group 1. The difference between the two groups was

Table 1. Demographic statistics of control group patients

Control group		
Mean age (years)		42.5
Gender	Male	45.6% (n=47)
	Female	54.4% (n=56)
Age groups	20-29 yrs	16.5% (n=17)
	30-39 yrs	27.2% (n=28)
	40-49 yrs	31.1% (n=32)
	50-59 yrs	13.6% (n=14)
	60-70 yrs	11.7% (n=12)
Total	103	

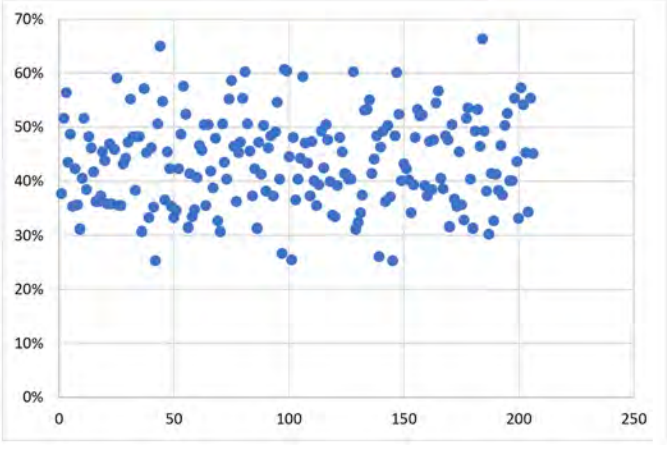

Figure 2. Distribution of the radial translation values

Table 2. Demographic statistics of study group patients

Study group		
Mean age (years)		49.6
Gender	Male	45.5% (n=48)
	Female	55.5% (n=60)
Side	Right	43% (n=62)
	Left	57% (n=46)
Total	108	

Table 3. Evaluation of patients according to age

		<50 years	≥50 years
Total patients (n)		41	67
A group	Group 1	9 (22%)	14 (20.9%)
	Group 2	0	5 (7.5%)
B group		32 (78%)	48 (71.6%)
Translation difference		1.62±1.25	3.53±4.47

statistically significant ($p<0.001$). The effect of the DASH score on translation deformity in Group A patients was examined with the Independent Samples t-test. The DASH score was determined to be statistically significantly higher in the Group 1 patients than in Group 2 ($p<0.001$) (Table 3). A significant difference was determined between these 2 groups in respect of the visual analog pain score, evaluated with the t-test, with the mean visual analog pain score of 6.36 of the Group 1 patients seen to be statistically significantly higher than that of the Group 2 patients at 3.57 ($p<0.001$). The relationship between the presence of ulnar-side wrist pain at the final follow-up examination and the translational difference was examined using the Fisher Exact test. There was determined to be a statistically significant correlation between radial translation deformity and ulnar-side wrist pain ($p<0.05$). The level of agreement between the measurements obtained by the 3 observers was determined with the ICC, and there was observed to be a high level of agreement (>95%) between all the measurements.

DISCUSSION

The results of this retrospective study demonstrated that the mean radial translation value in the normal population was 43.6%±8.2% (range: 25%-66%), and the mean difference between the right and left wrist measurements of the same patients was found to be 3.94%±1.64%. The DASH and visual analog scale pain scores were significantly higher in patients with a high radial translation difference than in those with lower values. The parameters of ulnar variance, volar tilt, and radial inclination have long been used in the radiographic evaluation of distal radius fractures (8). Recently, another parameter has entered the literature (1-3). In a 2008 study by Rapley et al. (9) this new parameter, which was overlooked or not diagnosed, was named ulnar translation. In 2011, Fujitani et al. (2) evaluated DRUJ instability and named this parameter radial translation. This name was subsequently accepted by different authors (1,3,5,10). Two different techniques have been defined in literature for the measurement of radial translation (1,2). In articles published in 2011 by Fujitani et al. (2) radial translation was calculated using the longest distance between the sigmoid notch and the ulnar head on PA radiographs. However, interobserver reliability was not tested in this study. The parameter of Fujitani et al. (2) increased awareness of the possibility of DRUJ instability based on radiographs obtained before reduction and presented a specific guide for the evaluation of the reduction of radial distal fractures. As the measurement this method is complex and intraoperative evaluation is difficult, Ross et al. (1) recommended another measurement method in 2014. Using this method, the authors evaluated 100 normal wrist radiographs and found the mean radial translation rate to be 45.48%±9.6% (range, 25-73.68%). This method was used in the current study, and the mean radial translation value in normal wrists was found to be 43.6%±8.2% (range: 25-66%). Although the mean radial translation values obtained in these two studies were very close to each other, the range of values in both studies was extremely broad. This greatly limits the use of the mean radial translation value alone. Ross et al. (1) stated that the comparison of the radial translation value with the contralateral wrist measurement provided a more reliable result, but did not state any value related to this comparison. In the current study, the mean difference between the left and right wrist measurements was found to be 3.94%±1.64%, and evaluations were made according to this value. It is thought that this value could be more clearly defined in future studies with a larger population. Dario et al. (11) showed that volar tilt and ulnar variance were the primary radiographic parameters necessary for restoration to achieve the desired functional outcome in distal radius fractures. However, radial translation was not included in the radiological parameters evaluated in this study (11). In the current study of patients treated with plaster casting, there was found to be radial translation deformity in 50% of those with positive ulnar variance. Considering that this deformity could have an effect on the clinical results, it was not thought to be appropriate to evaluate the effect of ulnar positive variance on the results without evaluating radial translation. The DASH and visual analog pain scores were found to be significantly low in patients with positive ulnar variance and no radial translation compared to the patients with radial translation ($p<0.001$). When the complaints of patients with positive ulnar variance were evaluated, a there was seen to be a statistically significant negative effect. According to these results, the radial translation can be evaluated as having a negative effect on the functional results.

Although distal radius fractures are seen in every age group, the frequency is increased at older ages. However, it has been shown in the literature that impairments in the radiographic parameters of patients of advanced age have a lesser effect on functional outcomes (12). In the current study, there was seen to be a significantly greater probability of radial translation deformity developing in patients aged >50 years compared with those aged <50 years ($p<0.05$). Further studies are needed to clarify whether the effect of this deformity on the functional results in older patients is different from that of younger patients. There are many factors involved in DRUJ stability, primarily bone anatomy, joint capsule, radioulnar ligaments, triangular fibrocartilage complex,

ulnocarpal ligaments, intraosseous membrane, and pronator quadratus muscle (4,12,13). It is accepted that impairment of the anatomic relationships between these structures can lead to DRUJ instability (4). DRUJ instability causes ulnar-side wrist pain, weakness, and loss of forearm rotation (2,14,15). Previous studies on the clinical effects of radial translation have focused on DRUJ instability. Omokawa et al. (10) found that of all the parameters on wrist PA radiographs, only the radial translation rate (with DRUJ gap length measurement) provided guidance for DRUJ instability which could develop. Ross et al. (1) reported that not correcting residual radial translation deformity could lead to DRUJ instability, which can present with the need for surgery. In the current study, DRUJ instability was observed in 78% of patients with radial translation deformity. There were some limitations to this study, primarily the retrospective design, and although interobserver reliability was statistically evaluated, intraobserver reliability was not evaluated. More analyses in future studies with larger cohorts are would be useful in the determination of the threshold value of the measurement parameter. Many different methods have been reported in the literature on the evaluation of DRUJ instability, so standardization of the methods used is extremely difficult. A further limitation could be said to be that when classifying the ulnar positive variance parameter in the measurements made, patients with an ulnar positive variance of 2-4 mm were included in the same group, and this may have had an effect on the functional results.

CONCLUSION

In conclusion, the results of this study demonstrated that when evaluating distal radius radiographs, the radial translation value should be carefully analyzed in addition to widely used parameters such as volar tilt, ulnar variance, and radial inclination. Functional impairment and DRUJ instability can develop in patients with radial translation deformity. Therefore, it is important that this parameter is evaluated and corrected in the treatment of distal radius fractures.

Footnote

This article is based on Yusuf Yahşi's thesis entitled "Radial Translasyonun Normal Değerinin Belirlenmesi ve Distal Radius Kiriği Tedavisi Sonrasi Fonksiyonel Sonuçlara Etkisi" in 2022 year. Thesis Approval E-48865165-302.14.01-117229.

Ethics Committee Approval: Approval for the study was granted by the Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital Health Practice and Research Center Clinical Research Ethics Committee (decision number: 1980, date: 08.03.2022).

Informed Consent: Informed consent was obtained from all participants in compliance with the ethical guidelines prior to their inclusion in the study.

Authorship Contributions

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

Conflict of Interest: No conflicts of interest were declared by the authors.

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LETTER to the EDITOR

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The Importance of Scaling Earthquake Magnitude and Intensity for Medical Management of Disasters: An Emergency Physician's Perspective

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Keywords: Disaster management, modified mercalli intensity scale, universal disaster severity classification scheme, disaster impact assessment, richter scale, emergency medicine

Dear Editor,

Geologists characterize earthquakes by their magnitude and intensity. Magnitude refers to the total energy produced by the Earth's crust. This energy is measured using a seismograph and converted using the Richter scale. While it is well known that the Richter magnitude scale is a logarithmic scale for estimating the total energy released by an earthquake, it is less commonly known that a one-unit increase on the Richter scale corresponds to a tenfold increase in ground motion and a thirty-twofold increase in energy release (1).

The most used scales for measuring earthquakes are the modified mercalli (MM) intensity scale and the Richter magnitude scale. A comparison of the MM Intensity scale with the Richter scale is provided in Table 1 (2). The main point to consider when interpreting the values in Table 1 is that although the Richter scale values represent magnitude, the roman numerals on the MM intensity scale denote intensity. While measurements above 5.0 on the Richter scale can cause environmental and human damage, those below 2.0 are generally not felt. Foreshocks, smaller tremors preceding major earthquakes, may also occur. Additionally, aftershocks, smaller events following the main earthquake, can also happen and may lead to significant additional damage, as seen in the February 6 Kahramanmaraş earthquake in Turkey, necessitating further local or regional evacuations (3-5).

The level set for disasters also determines the response scale. For example, Turkey called for level 4 aid after the February 6 Kahramanmaraş earthquake (6). These levels of aid calls are developed within the framework of the Turkey Disaster Response Plan (TAMP), and as the level increases, the scope of the call extends from local resources to international aid requests. TAMP classifies disasters into four levels: S1 indicates that local resources are sufficient; S2 is when the scale of the disaster or emergency in a province exceeds the capabilities of that province, necessitating support from neighboring provinces; S3 indicates a need for national-level support; and S4 is when international assistance is required (7).

The primary factors determining the earthquake intensity in these scaling systems are multifaceted. Socioeconomic factors, which reflect the impact on people and property, include the number of deaths, injuries, missing persons, homeless individuals, evacuated people, the total number of affected individuals, and damage cost, encompassing property damage, crop losses, and economic impact. Additionally, power measurement factors, which reflect the strength and intensity

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of the event, encompass parameters such as the magnitude, duration, speed, location, and distance of affected populated areas from the disaster zone. Finally, preparedness factors, which reflect a region's readiness, involve available technology, resources, ability to evacuate areas before they are impacted, mitigation strategies, and response rate.

Throughout history, it has been observed that the naming of destructive events has often taken precedence over their scaling. For instance, in the Oxford dictionary, the term "catastrophe" is used to define "disaster", while "disaster" is used to define both "catastrophe" and "calamity." This cyclical nature of definition has resulted in these terms being used interchangeably to describe the severity and intensity of natural events (8).

In the categorization of natural disasters, it is common to see events with vastly different levels of severity placed in the same category. For example, both the 1998 Mitch hurricane and the 2004 Indian Ocean tsunami were categorized as catastrophes (9). However, when compared with the tsunami, the impact of hurricane Mitch was much smaller: It struck the Caribbean and Central America, resulting in 11,000 deaths, whereas the Indian Ocean Tsunami affected 12 countries across Asia and Africa and caused approximately 230,000 deaths. The root of this problem lies in the lack of a sufficient number of categories to represent the severity of a natural disaster adequately. Consequently, using terms such as emergency, disaster, and catastrophe does not provide enough detail to clearly understand the impact of an event.

To accurately represent the magnitude of a disaster and avoid subjective and inaccurate classifications, the universal disaster severity classification scheme (UDSCS) was developed (9). Table 2 shows the classification of disaster magnitude and color on an international scale. Using the UDSCS, it may be easier to evaluate a city's population and damage, and infrastructure losses caused by a disaster than assessments based solely on property losses, such as homes and other assets. Using the UDSCS, planning decisions can include determining the storage and distribution of essential resources such as food, water, medicine, sanitation supplies, and clothing to the affected area; identifying hospitals to be mobilized and their capacity; and determining where and

Table 1. Comparison of the modified mercalli intensity scale with the richter scale

Richter magnitude	Mercalli intensity	Shaking	Occurrence frequency
0 to 1.9	I	No felt	8000 times per day
2 to 2.9	II	Weak	1000 times per day
3 to 3.9	III	Weak	49000 times per year
4 to 4.9	IV and V	Light-moderate	6200 times per year
5 to 5.9	VI	Strong	800 times per year
6 to 6.9	VII and IX	Very strong-severe-violent	120 times per year
7 to 7.9	X and XI	Extreme	18 times per year
8 to 8.9	XII	Extreme	1 time per year
9.0 and above	-	Extreme	1 time per 20 years

Table 2. Universal disaster severity classification scheme and disasters

UDSCS	Color coding	Descriptive term	Description	Fatality range
0	White	Emergency	Suddenly occurring, causing injuries and fatalities	F<1
1	Blue	Emergency	Suddenly occurring, causing injuries and fatalities	1≤ F<10
2	Dark green	Disaster type 1	Many people severely injured or killed	10≤F<100
3	Light green	Disaster type 2	Many people severely injured or killed	100≤F<1,000
4	Yellow	Calamity type 1	Widespread area damage, severe injuries and fatalities	1,000≤F<10,000
5	Dark yellow	Calamity type 2	Widespread area damage, severe injuries and fatalities	10,000≤F<100,000
6	Red	Catastrophic type 1	Very widespread area damage, affecting a continent	100,000≤F<1m
7	Dark red	Catastrophic type 2	Extremely widespread area damage, affecting multiple continents	1m≤ F<10m
8	Light purple	Cataclysm type 1	Global damage, countless fatalities	10m≤F<100m
9	Dark purple	Cataclysm type 2	Global damage, extreme fatalities	100m≤F<100b
10	Black	Partial or total annihilation	Intercontinental, partial, or total annihilation	100b≤F

UDSCS: Universal disaster severity classification scheme, F: Number of fatalities, m: Million, b: Billion

for how long temporary shelters will be established. By having a comprehensive understanding of disaster severity, emergency response management organizations, disaster managers, first responders, government stakeholders, aid organizations, and nongovernmental organizations can quickly estimate the potential impact of a natural disaster. This allows for the efficient allocation of resources, accelerated mitigation efforts, and expedited recovery processes (10).

When asked why the intensity scale of an earthquake is valuable to an emergency physician, the answer is multifaceted. Foremost among these is that clearly understanding the magnitude of a disaster is crucial for planning every step, from providing aid to managing the response to the disaster (11). These classifications and scales are not only developed for healthcare workers and disaster managers but also for emergency response teams, national/regional/local governments, aid organizations and civil society organizations, reporters and media, the public, insurance managers and assessors, database/information managers, and research communities. For disaster managers and emergency response personnel, these classifications provide a clear understanding of the severity scale of each disaster type by considering expected probabilities based on historical events. The UDSCS facilitates relative comparisons among different disaster levels and ranks natural disasters using a set of criteria, providing a comprehensive disaster picture. This information can be used for proper resource allocation during disasters and for advanced planning.

The initial assessment of a disaster is based on estimates made shortly after the event occurs, and this decision is part of a dynamic process that is frequently updated. For example, in the aftermath of an earthquake, initial assessments are used to determine whether to declare a state of emergency, initiate evacuations, request international aid, or involve military forces in response efforts. In devastating earthquakes, many buildings, including government institutions and even hospitals, sustain damage, often leaving only the ground floors and emergency departments operational. Efforts to mitigate the impacts of earthquakes depend on accurately estimating the disaster's impact on the city and its residents. Timely and accurate assessment of disaster impacts is crucial because lives depend on these decisions. Consequently, emergency departments, as the first point of contact after earthquakes, play a vital role, and the proficiency of physicians in these concepts is of paramount importance. The inconsistent identification of disaster impacts can lead to either excessive or insufficient allocation of resources by disaster managers. Over-allocation of resources can result in significant and critical wastage, while insufficient resources can exacerbate the disaster's impact on public health and its overall severity.

For both preparedness and post-disaster mitigation efforts, disaster managers and health administrators should adopt a standardized disaster scale that reflects the human impact of earthquakes. This strategy offers several advantages. Firstly, activities such as issuing warnings, organizing evacuations, providing public education, and conducting earthquake training and drills can shift public perceptions of earthquake risks. Secondly, these initiatives can engage public interest and foster greater trust in the methods employed by emergency management systems and response teams. Lastly, utilizing uniform terminology can shorten response times to warnings and improve the effectiveness of public responses.

In summary, as Durage stated, "the frequent occurrence and intensity of natural disasters can leave irreversible negative impacts on people. To mitigate the adverse effects of disasters, it is crucial to take preventive measures well in advance, which can either prevent or significantly reduce the impact of such events." By nature, disasters occur suddenly and require rapid decisions and activation. Therefore, in an established emergency management system, the use of appropriate classifications and terminology can facilitate timely warnings and accurate situation reporting to the necessary institutions and organizations in the hierarchy. This approach can minimize deaths and injuries by ensuring prompt and effective response efforts.

In conclusion, clearly defining the link between a disaster and its potential human impact through the use of the UDSCS can significantly improve public awareness, education, and responsiveness to warnings. Communicating the severity of natural disasters using precise terms from the UDSCS can increase the chances of appropriate public reactions and raise awareness of life-threatening situations. Furthermore, this method can minimize confusion, strengthen understanding between the community and response teams, and enhance decision-making processes. It is recommended that these communication strategies be tested before being fully implemented.

Footnote

Informed Consent: Informed consent is not necessary.

Authorship Contributions

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