



Investigating the 25(OH) Vitamin D Levels and Impacts of Urinary Tract Infection in Geriatric Hematogenous Septic Arthritis Patients

Geriyatrik Hematojen Septik Artritli Hastalarda 25(OH) Vitamin D Düzeyleri ve İdrar Yolu Enfeksiyonunun Etkilerinin Araştırılması

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Abstract

Objective: Our study aimed to determine the serum level of 25(OH) vitamin D in geriatric hematogenous septic arthritis and to assess the potential presence of urinary tract infections in the same cohort.

Method: The study included 22 patients diagnosed with septic arthritis and 25 individuals selected to match the control group's age and gender distribution. Inclusion criteria for patients diagnosed with septic arthritis were the presence of monoarthritis, age over 60, swelling and pain in the joint, high C-reactive protein (CRP) levels, purulent joint fluid, and the presence of more than 50,000 neutrophils per mm³ in the joint fluid or within the joint culture. In both the septic arthritis and control groups, a comprehensive assessment encompassed hemogram, CRP, whole blood biochemistry, complete urinalysis, urine culture, and 25(OH) vitamin D tests for comparative analysis.

Results: In the patient group, 25(OH) vitamin D levels were significantly lower than the control group ($p<0.05$). Urine analysis revealed a notably higher leukocyte count in the patient group compared to the control group ($p<0.05$). In addition, the patient group exhibited significantly lower blood albumin levels in contrast to the control group, along with a significant decrease in hemoglobin levels ($p<0.05$). There was no significant difference in urine culture distribution between the patient and control groups ($p>0.05$).

Conclusion: Our study has identified a notable correlation between severe vitamin D deficiency and hematogenous septic arthritis among elderly individuals. Furthermore, evidence of bacteriuria and pyuria emerged in the complete urinalysis of some subjects. These findings support our belief that certain instances of hematogenous geriatric septic arthritis may arise as a consequence of urosepsis.

Keywords: Geriatric, sepsis, septic arthritis, urinary tract infection, vitamin D

Öz

Amaç: Çalışmamızın amacı geriyatrik hematojen septik artritlerde 25(OH) vitamin D serum seviyesini saptamak ve aynı hastalarda idrar yolları enfeksiyonu olup olmadığını araştırmaktır.

Yöntem: Çalışmaya septik artrit tanısı almış 22 hasta ve kontrol grubu olarak benzer yaş ve cinsiyet dağılımı gösteren 25 denek dahil edilmiştir. Septik artrit tanısı konmuş olan hastalarda dahil edilme kriterleri monoartrit olması, 60 yaş üstü olması, eklemde şişlik ve ağrı olması, C-reaktif protein (CRP) yüksekliği, eklem sıvısının pürülan karakterde olması, eklem sıvısında mm³'te 50000 üzerinde nötrofil olması ya da eklem kültüründe üretilmiş olması olarak belirlenmiştir. Hem septik artrit hem de kontrol grubundan, karşılaştırma yapmak için hemogram, CRP, tam kan biyokimya, tam idrar tahlili, idrar kültürü, 25(OH) vitamin D tetkikleri istenmiştir.

Bulgular: Olgu grubunda 25-(OH) vitamin D serum seviyeleri değeri kontrol grubundan anlamlı ($p<0,05$) olarak daha düşüktü. Olgu grubunda idrarda lökosit sayısı değeri kontrol grubundan anlamlı ($p<0,05$) olarak daha yüksekti. Olgu grubunda kandaki albümin değeri kontrol grubundan anlamlı ($p<0,05$) olarak daha düşüktü. Olgu grubunda hemogloblin değeri kontrol grubundan anlamlı ($p<0,05$) olarak daha düşüktü. Olgu grubu ve kontrol grubu arasında idrar kültürü dağılımı anlamlı ($p>0,05$) farklılık göstermemiştir.

Sonuç: Yaşlı bireylerdeki hematojen nedenli septik artritlerde ciddi D vitamini eksikliği ile beraber bir kısmında da tam idrar tahlilinde bakterüri ve piyüri saptanmıştır. Hematojen geriyatrik septik artritlerin bir kısmının ürosepsis sonucunda geliştiğini düşünüyoruz.

Anahtar kelimeler: Geriyatrik, idrar yolları enfeksiyonu, sepsis, septik artrit, vitamin D



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Introduction

With advancing age, people become more susceptible to infections due to the weakening of their immune systems. Aging disrupts acquired immunity because of T-cell dysfunction and impaired cytokine-mediated inflammatory response (1). One common infection that affects the elderly is urinary tract infections (UTIs), which can lead to septicemia or sepsis (2). Another serious infection that is prevalent among the geriatric population is septic arthritis, which can sometimes be mistaken for acute exacerbation of osteoarthritis, leading to its underdiagnosis. The etiology of septic arthritis encompasses both exogenous and endogenous factors.

Exogenous causes involve invasive interventions such as intra-articular injections and joint arthroplasty (3-5). In contrast, endogenous causes occur as a result of hematogenous spread. The prevalence of diseases such as osteoarthritis and diabetes mellitus, in addition to diseases such as Alzheimer's and dementia, which reduce self-care in the elderly, paves the way for septic arthritis (2,5). In the elderly, septic arthritis most commonly affects the knee joint. Researchers have found a link between UTIs and the development of septic arthritis in older adults (2).

Furthermore, studies have suggested that vitamin D plays a crucial role in maintaining a healthy immune system and reducing the risk of infections. Vitamin D, functioning as a hormone, is primarily synthesized via exposure to ultraviolet sunlight. Vitamin D plays an important role in bone hemostasis, prevention of some cardiovascular diseases, stimulation of insulin secretion, and the regulation of the immune system and inflammatory processes (6,7). Individuals with vitamin D deficiency are prone to infection and sepsis (8,9). Vitamin D plays an important role in the regulation of immunomodulatory function through the presence of vitamin D receptors in most immune cells (10). Low vitamin D levels have been associated with an increased risk of infections and inflammatory diseases (3).

Given this context, our current study is geared toward evaluating vitamin D levels in elderly patients with UTIs and septic arthritis, to understand its potential impact on their conditions. This research endeavor holds significance in highlighting the importance of detecting and managing UTIs among geriatric patients, in addition to emphasizing the potential advantages of maintaining optimal vitamin D levels to prevent and manage infections. Understanding the relationship between UTIs, septic arthritis and vitamin

D can help healthcare professionals provide better care and improve outcomes for their elderly patients.

Materials and Methods

This retrospective, cross-sectional study was carried out at University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital between 2020 and 2021. Our study involved 22 patients aged 60 and above, diagnosed with septic arthritis, as well as a control group comprising 25 individuals sharing similar age and gender characteristics. The control group was selected from patients who visited the outpatient orthopedic clinic.

Inclusion criteria for patients diagnosed with septic arthritis were the presence of monoarthritis, age over 60, swelling and pain in the joint, high C-reactive protein (CRP) levels, purulent joint fluid, and the presence of more than 50,000 neutrophils per mm³ in the joint fluid or within the joint culture. Patients afflicted with rheumatologic disorders, chronic renal failure, septic arthritis following prior joint surgery, recent intra-articular injections, or localized skin infections near the joint were excluded from the study. Only septic arthritis cases thought to be of hematogenous origin were included in the study. Joint fluid was taken from all septic arthritis patients under sterile conditions and sent to the laboratory for neutrophil count, aerobic and anaerobic cultures, and Gram-staining. Synovial fluid and urine were inoculated on aerobic chocolate, blood agar, and anaerobic blood agar plates, then incubated for seven days aerobically at 37 °C with 5% CO₂ and anaerobically at 37 °C.

Before the initiation of empirical antibiotic therapy, all patients suspected of having septic arthritis underwent comprehensive diagnostic evaluations, including complete urinalysis, urine culture, 25(OH) vitamin D levels, whole blood biochemistry, hemogram, sedimentation, CRP, lung PA X-ray, and electrocardiography. Consultations with infectious diseases, internal medicine, cardiology, chest diseases, and anesthesia and reanimation departments were sought for all patients suspected of septic arthritis. Patients in the control group underwent hemogram, CRP, whole blood biochemistry, complete urinalysis, urine culture, and 25(OH) vitamin D tests. In both groups, serum vitamin D levels were measured using the electrochemiluminescence immunoassay method.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional

Review Board. All study participants provided informed consent before participating in the study. The confidentiality and privacy of the participants were ensured throughout the study.

Statistical Analysis

Taking into consideration the frequency of vitamin D deficiency and urinary tract infection in elderly septic patients in the literature, the study's sample size was determined through power calculations involving both qualitative and quantitative data, with a statistical power of over 80% and a margin of error of 5%. Mean, standard deviation, median, minimum, maximum, frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for the comparison of the quantitative data, while the chi-square test was employed for the comparison of the qualitative data. The SPSS v.28.0 software was employed in all statistical analyses.

Results

The age distribution of patients exhibited no significant difference between the patient and control groups ($p>0.05$). Furthermore, the gender distribution among patients demonstrated no significant difference between the case and control groups ($p>0.05$). In the patient group, the 25(OH) vitamin D levels were significantly lower than the control group ($p<0.05$) (Figure 1). Urine analysis revealed a notably higher leukocyte count in the patient group compared to the control group ($p<0.05$) (Figure 2). Conversely, the urinary erythrocyte count didn't manifest any considerable distinction between the patient and control groups ($p>0.05$). In addition, the patient group

exhibited significantly lower blood albumin levels in contrast to the control group, along with a significant decrease in hemoglobin levels ($p<0.05$). The CRP value in the patient group exceeded that of the control group, signifying a significant disparity ($p<0.05$). There was no significant difference in urine culture distribution between the patient and control groups ($p>0.05$) (Table 1). The mean leukocyte count per mm^3 in the joint fluid of septic arthritis patients reached 81,077, as indicated in Table 2.

Discussion

Our investigation unveiled a noteworthy prevalence of 25(OH) vitamin D deficiency alongside frequent occurrences of bacteriuria within the urinary tract of patients afflicted with hematogenous geriatric septic arthritis. Moreover, this patient cohort exhibited a significant reduction in mean hemoglobin and serum albumin levels when compared to the control group.

In the guideline for diagnosis and treatment of metabolic bone diseases published in 2012 by the Turkish Society of Endocrinology and Metabolism, 25(OH) vitamin D was evaluated in four categories based on serum concentration: significant deficiency for serum 25(OH)D levels <10 ng/mL, deficiency for levels between 11-20 ng/mL, insufficiency for levels between 21-30 ng/mL, and normalcy for levels >30 ng/mL. Remarkably, the serum vitamin D level in septic arthritis patients reached a mere 7.3 ng/mL, while it was observed that the mean vitamin D levels within the control group, albeit lower than the patient group, were significantly higher. Vitamin D deficiency (≤ 30 ng/mL) or insufficiency (≤ 20 ng/mL) is known to be associated with an increased risk of infection (11,12). Furthermore, vitamin D levels in septic patients in all age groups are lower than in other patients without sepsis (13,14).

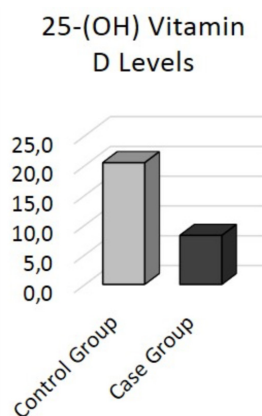


Figure 1. Serum vitamin D levels in the control and septic arthritis group

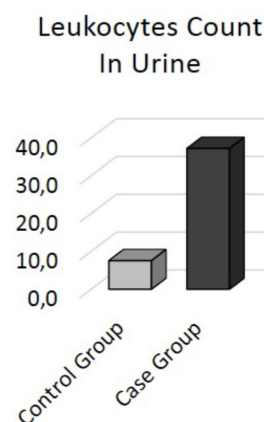


Figure 2. Mean leukocyte count in the urine of the control and septic arthritis groups

Table 1. Comparison of the 25(OH) vitamin D, albumin, CRP, and hemoglobin levels, and complete urinalysis and urine culture outcomes of both septic arthritis and control groups

Mean ± SD/n-%	Control group		Patient group		p
	Median	Mean ± SD/n-%	Median	Mean ± SD/n-%	
Age	71.9±7.3	71.0	74.9±7.8	74.0	0.208*
Gender	Female	19, 76.0%	11, 50.0%		0.064†
	Male	6, 24.0%	11, 50.0%		
Albumin levels in blood	4.0±0.4	4.1	3.3±0.57	3.3	0.000*
CRP	5.1±5.1	3.6	162±65.0	167.0	0.000*
Hemoglobin	12.3±1.8	12.5	11.3±1.8	11.7	0.044*
25(OH) vitamin D	20.4±13.3	17.0	8.2±3.5	7.3	0.000*
Leukocyte count in urine	7.6±17.9	2.0	37.2±137.9	3.0	0.047*
Erythrocyte count in urine	3.5±4.8	1.0	12.6±33.6	3.5	0.067*
Bacteria count in urine	3.4±13.7	0.0	10.6±23.3	0.0	0.050*
Urine culture					
(-)	22, 88.0%		15, 68.2%		0.098†
(+)	3, 12.0%		7, 31.8%		
<i>Escherichia coli</i>	3, 12.0%		5, 22.7%		
<i>Candida albicans</i>	0, 0.0%		1, 4.5%		
<i>Proteus mirabilis</i>	0, 0.0%		1, 4.5%		

SD: Standard deviation, *Mann-Whitney U test, †chi-square test, CRP: C-reactive protein, significant p-values are written in bold

Table 2. The number of leukocytes per mm³ in the joint fluid, the distribution of the bacteria grown in culture, and blood sedimentation averages in septic arthritis patients

	Patient group	
	Mean ± SD/n-%	Median
Sedimentation	66.2±27.2	65.5
Leukocyte count in joint fluid	81,077±55,301	59,401
Joint fluid culture		
(-)	16, 72.7%	
(+)	6, 27.3%	
<i>Staphylococcus aureus</i>	2, 9.1%	
<i>Enterococcus faecalis</i>	1, 4.5%	
<i>Escherichia coli</i>	1, 4.5%	
<i>Staphylococcus haemolyticus</i>	1, 4.5%	
<i>Streptococcus dysgalactiae</i> ssp. <i>equisimilis</i>	1, 4.5%	

SD: Standard deviation

Vitamin D's multifaceted role in regulating monocyte activation, attenuating inflammatory responses triggered by pathogens such as bacteria, viruses, and fungi, its bactericidal properties, facilitation of phagocytosis, and induction of B and T-cell proliferation and differentiation, have all been well-documented (9,15). In addition, the synthesis of cathelicidin, a strong antimicrobial peptide

synthesized from neutrophils in the epithelia of the respiratory, bladder, and gastrointestinal tract, is stimulated by vitamin D (6). Notably, previous studies have shown that patients with low vitamin D levels have longer hospital stays and higher mortality rates than patients with normal vitamin D levels (7,12,16,17). In our study, the average hospitalization period of the patients ranged from 3 to 6 weeks, with one unfortunate fatality during this period.

The realm of sepsis reveals genitourinary infections as the second most prevalent cause. Furthermore, among the elderly, UTIs claim the position of the second most common ailment after respiratory tract infections (1). In addition, asymptomatic bacteriuria emerges as a prevalent occurrence within this demographic. In our study, while 20% bacteriuria was observed in the urine in the control group, the rate escalated to 50% in the septic arthritis group. The geriatric populace confronts various factors contributing to this trend, encompassing advanced age, the burden of diseases that impede cellular immunity, and complications stemming from conditions like dementia, stroke, and Parkinson's disease that instigate incontinence within the urinary bladder and intestines (18,19).

In females, estrogen deficiency within this age group causes vaginal and urinary incontinence, and thus bacterial flow into the sterile urinary tract. In addition,

the deficiency further disrupts the protective colonization of *Lactobacillus* bacteria in the vagina, which normally suppresses the growth of pathogenic bacteria (20). On the male front, prostatic hypertrophy causes post-void urinary retention, predisposing them to chronic prostatitis. On the other hand, a chronically inflamed prostate causes recurrent UTIs by forming stones that trap bacteria (21). Thus, our findings postulate that the recurrence of UTIs in the elderly causes sepsis and paves the way for septic arthritis development.

While one or more leukocytes were observed in the urine of all but one of the septic arthritis patients, there were no leukocytes in the urine of six participants in the control group. Pyuria, denoting the emergence of leukocytes surpassing 10 HPF (high-power field) in urine, was identified in eight septic arthritis patients, as opposed to four from the control group. Although there was no difference in microscopic hematuria (erythrocyte count ≤ 50 HPF) in both groups, one patient in the septic arthritis group had gross hematuria. Nonetheless, it's crucial to acknowledge that the presence of asymptomatic bacteriuria, pyuria, and microscopic hematuria alone does not suffice for a UTI diagnosis (2). Antibiotic treatment is not recommended in asymptomatic bacteriuria because of multidrug-resistant bacteria growth and high recurrence rate (2,22). Nonetheless, we underscore the significance of vigilant monitoring via complete urinalysis, as changes in its content may be a precursor to sepsis. The diagnosis of UTI is mostly made in the presence of major symptoms such as dysuria or fever. McGeer et al. formulated diagnostic criteria for UTIs, encompassing indicators such as dysuria, fever, flank pain, suprapubic pain, chills, gross hematuria, new urinary incontinence, changes in urinary characteristics (hematuria, increased pyuria, altered odor, etc.), cognitive and functional decline, and delirium. While dysuria or fever is sufficient alone for the diagnosis of UTI among these criteria, the authors stipulated that at least three of the other criteria should be present in non-catheterized patients in the absence of these two criteria (2,23). Notably, upon investigating the medical histories of septic arthritis patients, it emerged that a subset of them reported dysuria-related complaints.

Urine cultures of septic arthritis patients yielded *Escherichia coli* in five cases, *Proteus mirabilis* in one, and *Candida albicans* in another (Table 1). In the control group, *E. coli* grew in three cultures. The most isolated microorganism in UTI is *E. coli*, and its prevalence is reported to be 53% in the literature (24), followed by *Proteus*

at 15% and *Klebsiella* at 14% (24,25). The causative pathogen was cultured in 28% of the joint fluid of septic arthritis patients, with *Staphylococcus aureus* being the prevailing microorganism (Table 2). For all age groups, *Staphylococcus aureus* ranks as the most prevalent cause of septic arthritis (5). Other produced microorganisms were *Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus haemolyticus*, and *Streptococcus dysgalactiae* ssp. *equisimilis* (Table 2). All of these bacteria produced in the joint fluid can cause urosepsis in the elderly (26-28). The physiological balance of the urinary tract's flora is known to deteriorate with age, potentially leading to polymicrobial infections (2). Microorganisms such as *Staphylococcus epidermitis*, *Streptococcus faecalis*, non-pathogenic *Neisseria* species, *Corynebacterium*, as well as *Candida* fungi can be found in the urinary tract flora.

There may be a significant relationship between the serum level of vitamin D in the elderly and the risk of UTI, similar to observations in children (29). In addition, there are studies related to the fact that vitamin D may be effective in the management of UTI infection through different mechanisms (30,31). It has been shown that tightly bound proteins play an important role in preventing bacterial invasion of the epithelial barrier, and that vitamin D supplementation can strengthen the bladder lining and restore bladder epithelial integrity (30). In addition, vitamin D acts as a local immune response mediator in UTIs (32). In a randomized clinical trial, the subjects who received vitamin D3 (20,000 IU per week) for five years showed better prevention against UTIs (33).

In this present study, septic arthritis patients experienced joint involvement predominantly in the right knee (12 cases), followed by the left knee (seven cases), right ankle (two cases), and right shoulder (one case). Notably, septic arthritis patients exhibited lower albumin and hemoglobin levels compared with the control group (Table 1). In addition, due to the presence of comorbidities in these patients, the duration of emergency surgery was prolonged in some instances. While emergency arthroscopic saline flushing and debridement were performed in merely six out of the 22 patients, others underwent emergency aspiration and flushing via the lateral suprapatellar portal, performed at the bedside. Patients who underwent bedside emergency washing at the bedside were subject to follow-up involving serum CRP level and neutrophil count in the joint fluid and clinical examination. Patients displaying a less rapid healing response during follow-up were subjected to late arthroscopic washing and debridement.

Study Limitations

There were several limitations in our study, including the limited number of cases, the omission of procalcitonin investigation in septic arthritis patients, and the culturing of causative microorganisms in joint fluid in only a minority of cases.

Conclusion

Our study has identified a notable correlation between severe vitamin D deficiency and hematogenous septic arthritis among elderly individuals. Furthermore, evidence of bacteriuria and pyuria emerged in the complete urinalysis of some subjects. These findings support our belief that certain instances of hematogenous geriatric septic arthritis may arise as a consequence of urosepsis. This situation should be considered when choosing antibiotics for treatment and supplementing with vitamin D.

Ethics

Ethics Committee Approval: Granted by University of Health Sciences Turkey, İstanbul Bağcilar Training and Research Hospital Clinical Research Ethics Committee of (12, 22, 2022-subject 2022/12/11/048).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ç., E.B., Concept: S.Ç., En.B., O.B., Design: S.Ç., O.B., Data Collection or Processing: E.B., En.B., Analysis or Interpretation: E.B., En.B., O.B., Literature Search: S.Ç., E.B., Writing: S.Ç.

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