BIOLOGICA NYSSANA
16 (1) June 2025: 247-257
DOI: 10.46793/BiolNyss.16.1.19K

Different types of crystalluria in patients with bone and joint tissue pathology: Hematological and biochemical profiles

Original Article

Pavlo Grigorovich Kravchun
Department of Internal Medicine No. 2, Clinical Immunology and Allergology named after academician L.T. Malaya
Inna Pavlivna Dunayeva
Department of Internal Medicine No. 2, Clinical Immunology and Allergology named after academician L.T. Malaya
Frida Solomonivna Leontyeva
Sytenko Institute of Spine and Joint Pathology, National Academy of Medical Sciences of Ukraine
Olena Dmytrivna Povelychenko
Sytenko Institute of Spine and Joint Pathology, National Academy of Medical Sciences of Ukraine
Valentyna Yuriivna Dielievska
Department of Internal Medicine No. 2, Clinical Immunology and Allergology named after academician L.T. Malaya
valentinka_1987@ukr.net (corresponding author)

Received: December 26, 2024
Revised: March 03, 2025
Accepted: March 17, 2025

Abstract:
Crystalluria, as a sign of dysmetabolic nephropathy, has been associated with bone and joint tissue pathology. The aim of the study was to reveal the structure of crystalluria in patients with bone and joint tissue pathology and to investigate the characteristics of biochemical parameters according to the type of dysmetabolic nephropathy. In this study, common blood analyses and biochemical parameters were investigated. Individuals with bone and joint tissue pathology demonstrated prevalence of hyperoxaluria (59%) with less frequency of uraturia (25.7%) and phosphaturia (15.1%). Hyperoxaluria was associated with high incidence of ligamentum ruptures and bone fractures (21.6%). The patients with hyperoxaluria showed presence of eosinophilia, increased levels of platelets, leukocytes, erythrocyte sedimentation rate, C-reactive protein and serum alkaline phosphatase, whereas the patients with uraturia demonstrated decreased level of platelets and increased level of serum glucose, uric acid and creatinine. Patients with phosphaturia demonstrated increased serum alanine aminotransferase. The results presented in this paper revealed the differences in biochemical parameters of patients with different types of crystalluria, suggesting the necessity of its control to improve the prognosis of the treatment of patients with bone and joint tissue pathology.

Key words:
calcium, joint, oxalates, urates, urea

Apstrakt:
Različiti tipovi kristalurije kod pacijenata sa patologijom koštano-zglobnog tkiva: Hematološki i biohemijski profili
Kristalurija, kao znak dismetaboličke nefropatije, povezuje se sa patologijom koštano-zglobnog tkiva. Cilj ove studije bio je da se utvrdi struktura kristalurije kod osoba sa patologijom koštano-zglobnog tkiva i da se ispitaju karakteristike biohemijskih parametara u zavisnosti od tipa dismetaboličke nefropatije. U ovoj studiji analizirane su rutinske analize krvi i biohemijski parametri. Kod osoba sa patologijom koštano-zglobnog tkiva preovlađivala je hiperoksalurija (59%), a ređe su zabeležene uraturija (25.7%) i fosfaturija (15.1%). Hiperoksalurija je bila povezana sa visokim udelom ruptura ligamenata i preloma kostiju (21.6%). Pacijenti sa hiperoksalurijom imali su eozinofiliju, povećane vrednosti trombocita, leukocita, brzine sedimentacije eritrocita, C-reaktivnog proteina i serumske alkalne fosfataze. S druge strane, pacijenti sa uraturijom pokazali su snižene vrednosti trombocita i povišene vrednosti glukoze u serumu, mokraćne kiseline i kreatinina. Kod pacijenata sa fosfaturijom primećene su povišene vrednosti alanin-aminotransferaze u serumu. Rezultati predstavljeni u ovom radu ukazuju na razlike u biohemijskim parametrima pacijenata sa različitim tipovima kristalurije, što sugeriše potrebu za njenom kontrolom radi poboljšanja prognoze lečenja osoba sa patologijom koštano-zglobnog tkiva.

Ključne reči:
zglob, kalcijum, oksalati, urati, urea

Introduction

Dysmetabolic nephropathies are a group of diseases characterized by an interstitial process in the kidneys with crystalluria due to metabolic disorders (Colaci et al., 2024). Crystalluria may be transient (monotonous diet or enzyme disorders) and permanent (chronic diseases, metabolic disorders). The factors contributing to the formation of crystals include a high concentration of salts in urine, weak water regime, use of medications, urinary tract infection and digestive disorders (Shastri et al.,

2023). The formation of crystals in body fluids in dysmetabolic nephropathies contributes to the development of bone and joint tissue pathology.

The urinary syndrome in dysmetabolic nephropathy is characterized by the presence of urates, phosphates, oxalates, leukocyturia, erythrocyturia and proteinuria (Timo et al., 2023). Crystalluria and urolithiasis occupy one of the leading places in the structure of metabolic diseases. Thus, 8–15% of the population of Europe and North America suffer from urolithiasis (Verdesca et al., 2011; Qian et al., 2022). The enzymes involved in glyoxylate metabolism have been related to primary hyperoxalurias (Moya et al., 2024). The oxalate metabolism is associated with coagulation system. Thus, F1 fragment of prothrombin is excreted in urine and precipitates into calcium oxalate crystals, acting as inhibitor of calcium crystallization in urine (Grover et al., 1999). People with hyperoxaluria have demonstrated increased serum level of glycoproteins and chondroitin sulfates (Hesse et al., 1991). Uraturia patients are characterized by accumulation of monosodium urate crystals in joint tissue, causing inflammation (Han et al., 2024). High serum uric acid has been found to be associated with hypercoagulation, endothelial dysfunction and inflammation. The uric acid correlated with thromboembolism and left atrial thrombosis in systemic diseases, metabolic syndrome and arterial hypertension (Chen et al., 2016; Liu et al., 2022). In high concentrations, uric acid has been shown to predispose to type 2 diabetes mellitus due to the increased production of reactive oxygen species that reduce blood glucose uptake (Wardhana et al., 2018; Wang et al., 2022). The role of phosphorus in aminotransferase activity has been also discussed (Zechner et al., 2021). Meanwhile, the association of oxalates, uric acid and phosphates with bone and joint tissue pathology has been scarcely studied.

The aim of the study was to analyze the incidence and the structure of crystalluria in patients with bone and joint tissue pathology and to investigate the serum biochemical parameters in every type of crystalluria.

Materials and Methods

The examined patients

A total of 728 patients (382 female, 346 male), aged 32 to 81 years, with bone and joint tissue pathology (including coxarthrosis, gonarthrosis, ligament ruptures, and bone fractures) treated at the Sytenko Institute of Spine and Joint Pathology were included in the study following institutional ethical approval. Among them, 66 patients exhibited crystalluria and signs of dysmetabolic nephropathy and were assigned to the study group. This group was further divided into Group I: patients with hyperoxaluria (n=39), Group II: patients with uraturia (n=17), and Group III: patients with phosphaturia (n=10). An additional 61 patients with bone and joint tissue pathology but without crystalluria were included as the control group. Results were compared between the crystalluria subgroups and the control group.

Clinical examination of the patients included objective examination of organs and systems. Ultrasound investigation of kidneys, complete urinalysis and serum biochemical analysis were performed, and revealed the presence of echo-positive formations as a sign of crystals.

Microscopic examination of crystals

The crystals were observed under MicroMed XS -3330 microscope at ×400 magnification. The salt excretion from the 24-hour urine collection was investigated (**Fig. 1**). Increased oxalates excretion (more than 1 mg/kg/day) was revealed in patients with hyperoxaluria. Patients with uraturia showed increased urinary excretion of uric acid and calcium (uric acid level in urine: more than 4.0 mmol/l, and calcium: more than 7.5 mmol/l). High phosphorus excretion (more than 33 mmol/l) was detected in patients with phosphaturia.

Urea

The content of urea (by color reaction with diacetylmonooxime, Langenfeld et al., 2021) was performed with a spectrophotometer. The reaction between diacetyl monoxime and urea, in the presence of sulfuric acid, phosphoric acid, thiosemicarbazide, and ferric chloride, produces a chromophore whose absorbance was measured at a wavelength of 520 nm.

Creatinine

Concentration of creatinine was detected using commercial kit (Felicit diagnostics) by color Yaffe reaction (Toora et al., 2002), where 1 ml of working solution was added to 0.25 ml of serum, afterwards the optical density of analyzed sample and standard sample was measured after 30 seconds (E2 and E2) and 90 seconds (E3 and E4) accordingly at wavelength of 505 nm. Creatinine concentration was calculated using formula:

$$\text{Creatinine concentration} = \text{Concentration of calibrator sample} \times (E3-E1)/(E4-E2)$$

Total protein

4.0 ml of monoreagent (pyrrogalol red 50 mmol/l, sodium molybdate) were added to 0.08 ml of serum and incubated for 10 minutes at room temperature in dark conditions. The optical density of the test

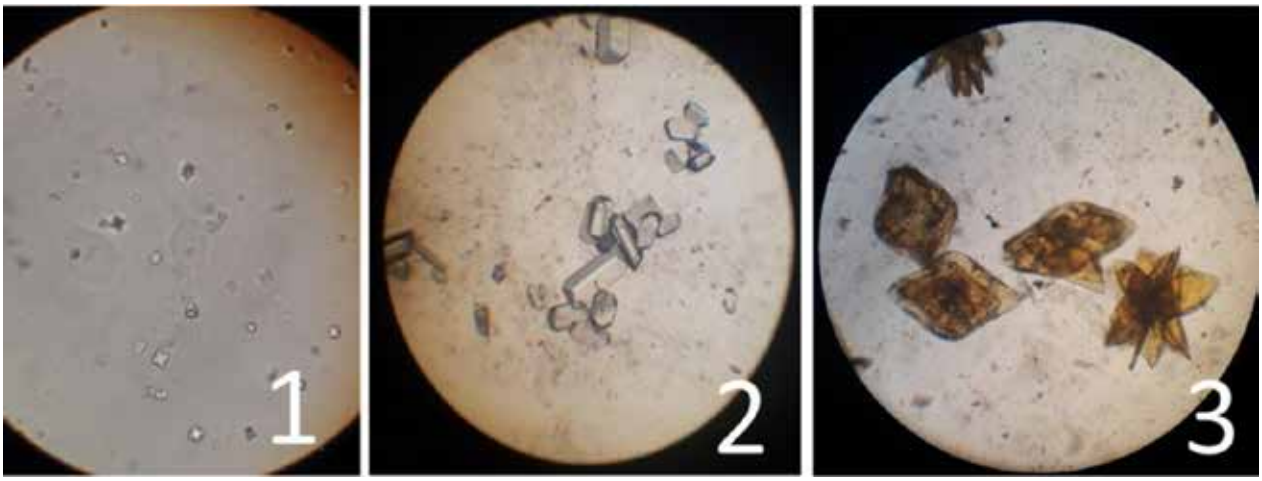

Fig. 1. Microscopic appearance of oxalates (**1**), phosphates (**2**), and urates (**3**).

sample (E test) and the calibration sample (E calibration) was measured against a blank sample. The concentration of total protein was calculated by formula:

C=E test: E calibration × 1000 mg/l

Calcium, glycoproteins, and chondrotin sulfates

Total calcium (complexonometric method with murexide indicator; Ritgen U, 2023), glycoproteins (according to the method of Steinberg and Docenko; Shtenberg OP et al., 1962), and chondroitin sulfates (measured by the Nemeth-Csok method in Sluckiy's modification; De Jong et al., 1989) were analyzed in patients with bone and joint tissue pathology using the respective procedures.

B-lipoproteins

B-lipoproteins were measured using a commercial kit (CORMAY LDL DIRECT, Poland) and analyzed spectrophotometrically at a wavelength of 630 nm, following the manufacturer's instructions and the method described by Alan (2006). A total of 900 µl of Reagent 1 was mixed with 9 µl of serum and incubated for 5 minutes at 37 °C. Subsequently, 300 µl of Reagent 2 was added to the mixture, followed by an additional 5-minute incubation at 37 °C.

Uric acid

A mixture of 2.4 mL of distilled water, 0.3 mL of serum, 0.15 mL of catalyst solution, and 0.15 mL of sodium tungstate was incubated for 10 minutes at room temperature, then centrifuged for 10 minutes at 2000 rpm. 1.0 ml of the centrifugate was added to 0.5 ml of sodium carbonate solution and 0.3 ml of phosphotungsten reagent, incubated for 30 minutes at room temperature. The optical density was measured spectrophotometrically at a wavelength of 650 nm.

Aspartate aminotransferase activity

Aspartate aminotransferase (Ast) was detected spectrophotometrically on Multiparametric Photocolorimetric biochemical analyser ALIZE (Lisa-bio, France) by the dinitrophenylhydrazine method (Huang, X.-J., et al., 2006). Substrate-buffer solution (0.25 ml) was added to the blood serum (0.05 ml) and incubated for 60 minutes at 37 °C. 0.25 ml of 2,4 dinitrophenylhydrazine was added and incubated for 20 minutes at room temperature. 0.4 M sodium hydroxide solution (2.5 ml) was added and incubated for 10 minutes at room temperature. The optical density of the test sample for aspartate aminotransferase was measured against a control sample on a photometer at a wavelength of 500-560 nm.

Determination of enzyme activity was carried out according to the calibration schedule. The difference in optical densities of the test and control samples was noted on the ordinate axis, and the corresponding value of enzyme activity was found on the abscissa axis.

Alanine aminotransferase activity

1 ml of working solution (substrate solution and coenzyme-enzyme reagent) was mixed with 0.1 ml of serum. The optical density was measured at a wavelength of 340 nm after 1 (E1) and 3 (E2) minutes. The difference in extinction (E2-E1)/3 was calculated.

Urinalysis

The urinalysis was carried out according to the methods listed in Urinalysis: approved guideline (Rabinovitch et al., 2009) and included estimation of pH (pH meter, OMEGA Engineering inc.), specific gravity (Lab World urinometer, UK), leukocytes, presence of bacteria, erythrocytes (under MicroMed XS -3330 microscope), and glucose in the urine sample.

The renal function was evaluated by calculation of glomerular filtration rate (GFR) (CKD-EPI, 2021) using the following formula:

eGFR (mL/min/1.73 m²) = 142 x min (creatinine/k, 1) α × max (creatinine/k, 1) 1.200 × 0.9938age × 1.012 (if female)

where k is 0.7 for women and 0.9 for men; α is 0.241 for women and 0.302 for men (Kirsztajn et al., 2024).

Ethical consent

The study was approved by the Ethical committee of Kharkiv National Medical University (protocol N 21, 24.07.23). Informed consent was obtained from all the participants. The study adhered to the ethical guidelines of the Declaration of Helsinki.

Statistical evaluation

Statistical analysis was performed using the software Statistica 10.0 (Stat Soft Inc., USA). All measurements were performed in triplicate and the data are presented as average ± standard deviation (SD) (for normally distributed data). The significance of the differences was determined using Student's t-test for parametric data. P values less than 5% were accepted as positive in the tests. Correlation analysis was performed using Spearman's correlation test.

Results and discussion

Crystalluria was detected in 9% (n=66) of patients with bone and joint tissue pathology (n=728). In accordance with the study objective, the study group (n=66) comprised patients with bone and joint tissue pathology who exhibited crystalluria. This group was further subdivided into three subgroups: patients with hyperoxaluria (Group I, n=39), uraturia (Group II, n=17), and phosphaturia (Group III, n=10). Patients with bone and joint tissue pathology but without crystalluria (n=61) were included as the control group.

According to the international KDIGO guidelines, Group II exhibited a lower glomerular filtration rate (GFR) (44.52±1.31 ml/min/1.73 m²) compared to the control group (86.34±2.30 ml/min/1.73 m²), Group I (83.22±1.91 ml/min/1.73 m²), and Group III (85.10±2.01 ml/min/1.73 m²).

Patients with hyperoxaluria

Hyperoxaluria was the most frequently observed type of crystalluria among individuals with bone and joint tissue pathology, identified in 39 patients (59%).

Individuals with hyperoxaluria showed a high incidence of ligament ruptures and bone fractures (21.6%), a finding that has also been reported by other researchers (Büscher et al., 2024). However, there is no clear evidence in the literature linking the severity of bone disease directly to oxalate levels (Ben-Shalom et al., 2021). Hage et al. (2008) reported that dense and radiolucent metaphyseal bands, vertebral osteocondensations, and renal osteodystrophy are characteristic signs of oxalosis. Although considerable progress has been made in understanding the pathophysiological mechanisms underlying hyperoxaluria, the diagnosis of oxalate-related bone disease is often delayed, and the prognosis remains poor (Demoulin et al., 2022).

Patients with hyperoxaluria demonstrated significantly elevated levels of leukocytes (by 34.2%), eosinophils (by 75%), erythrocyte sedimentation rate (ESR) (by 90%), and platelets (by 21.8%) in the complete blood count compared to the control group (p<0.05) (**Tab. 1**).

The increased levels of leukocytes and ESR suggest that disturbances in oxalate metabolism are accompanied by inflammatory processes, possibly due to bacterial involvement. The presence of pathogenic bacteria in calcium oxalate stones has been previously reported, and such bacteria are known to accelerate crystal growth (Cooper et al., 2008). Conversely, the beneficial bacterium *Oxalobacter formigenes* has been shown to interact with the intestinal mucosa and enhance oxalate secretion (Nazzal et al., 2021).

The erythrocyte sedimentation rate (ESR) is a known marker of inflammation severity, and some researchers have reported an association between hyperoxaluria and inflammatory responses (Guo et al., 2020). In Europe, a group of scientists formed the European Hyperoxaluria Consortium to advance research and collaboration in this field (Bernd et al., 2009).

The increased platelet count observed in patients with hyperoxaluria may be explained by a compensatory response of the bone marrow, as oxalic acid has been reported to exhibit anticoagulant properties (National Center for Biotechnology Information, 2025). Oxalate dysmetabolism, often resulting from low serum glycine levels, has been associated with disrupted redox homeostasis, inflammation, atherosclerosis, and cytopenia. Furthermore, dysregulated oxalate metabolism has been implicated as a contributing factor in the development of thrombosis and atherosclerosis (Liu et al., 2021). Therefore, the elevated platelet levels detected in patients with hyperoxaluria may indicate a predisposition to thrombotic events.

To date, no prior studies have reported an association between hyperoxaluria and elevated eosinophil counts.

Biochemical analysis revealed that individuals

Table 1. Clinical blood parameters in patients with bone and joint tissue pathology presenting with hyperoxaluria, uraturia, and phosphaturia

Variables	Hyperoxaluria (n=39)	Uraturia (n=17)	Phosphaturia (n=10)	Control group (n=61)
	(mean±SD)			
Erythrocytes (10^{12}/l)	4.46±0.35	5.02±0.44	4.82±0.4	4.84±0.42
Hemoglobin (g/l)	130.62±11.5	143.6±14.2	141.7±13.7	140.25±13.5
Platelets (10^9/l)	334.67±21.4*	213.6±15.63*	270.63±17.8	274.22±19.1
Leukocytes (10^9/l)	8.08±0.85*	5.79±0.6	6.8±0.74	5.96±0.63
ESR (mm/h)	19.07±3.2*	10.66±1.8	11.24±2.1	10.1±1.7
Eosinophils (%)	3.5±0.6*	2.2±0.43	2.25±0.43	2.0±0.41
Segmented neutrophils (%)	58.7±7.2	59.34±7.56	57.08±6.54	53.33±6.1
Lymphocytes (%)	26.85±3.74	27.5±3.85	32.18±4.2	28.33±4.0
Monocytes (%)	8.21±0.78*	7.78±0.74	4.83±0.32	5.0±0.6

ESR: erythrocyte sedimentation rate; *p<0.05 compared to control group

with hyperoxaluria had a 23.8% higher serum alkaline phosphatase level compared to the control group (**Tab. 2**). Elevated alkaline phosphatase, a known marker of osteomalacia, may help explain the high frequency of ligament ruptures and bone fractures observed in this study. The increased serum alkaline phosphatase levels in hyperoxaluric individuals are consistent with previous findings (Bchir et al., 2022).

B-lipoprotein levels did not differ significantly between groups, with mean values of 80.42±6.4 units in the hyperoxaluria group and 74.0±5.1 units in the control group.

During periods of active oxalate excretion, individuals with hyperoxaluria demonstrated a 17.3% increase in serum alanine aminotransferase (ALT) and a 77% increase in C-reactive protein (CRP) levels (**Tab. 3**). The elevated ALT may reflect liver cell damage, potentially due to cholestasis and the concomitant rise in alkaline phosphatase.

Table 2. Biochemical parameters in patients with bone and joint tissue pathology presenting with hyperoxaluria, uraturia, and phosphaturia

Variables	Hyperoxaluria (n=39)	Uraturia (n=17)	Phosphaturia (n=10)	Bone fractures (n=17)	Control (n=61)
			(mean±SD)		
Glucose (mmol/l)	5.3±0.24	6.4±0.3*	5.05±0.17	5.97±0.27*	5.1±0.2
Total protein (g/l)	75.7±7.13	74.55±6.7	74.3±6.63	77.7±7.4	75.88±7.2
Calcium (mmol/l)	2.4±0.15	2.42±0.17	2.3±0.11	2.39±0.13	2.43±0.18
Alt (un/l)	24.96±1.6	29.83±1.7*	32.14±2.4*	23.32±1.56	22.97±2.2
Ast (un/l)	29.35±1.77	34.66±2.54*	33.6±2.41*	26.82±1.64	27.28±1.7
Alph(un/l)	394.7±26.2*	302.42±17.4	-	-	318.27±20.1
Urea (mmol/l)	4.05±0.48	6.31±0.8*	4.55±0.7	4.41±0.6	4.21±0.57
Creatinine (mcmol/l)	95.33±13.1	164.3±17.2*	89.33±12.4	88.22±11.5	91.32±12.73
Thymol probe (units)	2.34±0.2	2.56±0.24*	2.06±0.15	2.64±0.27*	1,97±0.11
Uric acid (mcmol/l)	361.4±20.6	442.0±25.2*	-	-	351.2±17.4

p<0.05 compared to control group. **Alt**: alanine aminotransferase; **Ast**: aspartate aminotransferase; **Alph**: alkaline phosphatase

Table 3. Dynamics of biochemical parameters during active oxalate excretion in patients with hyperoxaluria

Variables	Present oxalate excretion (n=19)	Absent oxalate excretion (n=20)
	(mean±SD)	
Calcium (mmol/l)	2.37±0.25	2.34±0.22
Alt (un/l)	27.4±1.24*	23.42±1.1
Ast (un/l)	29.21±1.4	26.87±1.2
CRP (mg/l)	62.74±11.7*	35.7±7.2
Alph (un/l)	345.67±26.8	334.56±22.1

$p<0.05$

Correlations

Correlation analysis in patients with hyperoxaluria revealed a strong positive association between serum glucose and B-lipoproteins (r=0.74). Serum total protein levels were significantly correlated with chondroitin sulfates (r=0.68) and calcium (r=0.87) (**Tab. 4**), consistent with previous studies reporting a relationship between total protein and serum calcium levels. Calcium concentration was inversely correlated with thymol turbidity test results (r=-0.69) and positively correlated with chondroitin sulfates (r=0.55).

Table 4. Correlation analysis of biochemical parameters in patients with hyperoxaluria

Variables	Calcium	Ast	Alt	RBC	Hb	ESR
Glucose		-0.6		-0.85	-0.6	0.57
Total protein	0.87			0.2	0.38	-0.82
ESR				-0.55	-0.48	
CRP				-0.38	-0.38	0.64
Calcium		-0.56	-0.3			

Ast: aspartate aminotransferase; **Alt**: alanine aminotransferase; **Blp**: B-lipoproteins; **RBC**: erythrocytes; **Hb**: hemoglobin; **CRP**: C-reactive protein; **ESR**: erythrocyte sedimentation rate. Only correlations with $p<0.05$ are shown

Urine specific gravity demonstrated strong positive correlations with serum glucose (r=0.77) and B-lipoproteins (r=0.94) ($p<0.05$). Serum glucose also showed moderate correlations with total protein (r=0.30) and eosinophils (r=0.20) ($p<0.05$), while creatinine was negatively correlated with glucose (r= -0.65). A strong inverse correlation was observed between neutrophil count and total protein (r= -0.87) ($p<0.05$).

In patients with hyperoxaluria, serum calcium levels were inversely correlated with ALT, AST, thymol turbidity test results, and CRP. In contrast, the control group (without dysmetabolic nephropathies) showed a direct correlation between serum calcium and thymol probe (r=0.57), CRP (r=0.36), ALT (r=0.16), and AST (r=0.12)($p<0.05$). These findings indicate that, in hyperoxaluria, reduced serum calcium levels are associated with systemic inflammation.

Patients with uraturia

Among individuals with bone and joint tissue pathology, uraturia was observed less frequently, in 17 patients (25.7%). The platelet count in patients with uraturia was 22.6% lower compared to the control group ($p<0.05$). This reduction may reflect a compensatory response of the bone marrow, possibly due to the stimulatory effect of uric acid on prothrombotic factors. Our findings are consistent with previous studies reporting an association between elevated serum uric acid and reduced platelet count, as demonstrated by regression analyses in individuals with hypertension (Tayefi et al., 2018; Țăpoi et al., 2021; Weng et al., 2023).

Serum creatinine levels in the uraturia group were significantly higher, by 81.3%, compared to the control group (165.5±27.4 µmol/l vs. 91.32±12.73 µmol/l; $p<0.05$), indicating impaired renal function. Previous research has shown that uric acid exerts a detrimental effect on kidney function.

This group also exhibited increased serum glucose levels (by 25.4%), and uric acid levels (by 25.9%) compared to controls ($p<0.05$). Elevated glucose in individuals with uraturia suggests that uric acid may be involved in disorders of carbohydrate metabolism. Hyperuricemia and liver dysfunction have been reported in association with diabetes, insulin resistance, obesity, and dyslipidemia. High serum uric acid levels have also been found in patients with diabetes mellitus, showing a positive correlation with glycated hemoglobin A1c. Previous studies confirm that hyperuricemia, hyperuricosuria, and urate nephropathy are common in individuals with diabetes.

Furthermore, uric acid is structurally related to alloxan, a known diabetogenic compound. Experimental studies have shown that alloxan administration can induce "uric acid diabetes" (Wang et al., 2021; Gapparova et al., 2023). Therefore, the increased serum glucose observed in individuals

with uraturia in this study supports existing evidence suggesting that elevated uric acid contributes to carbohydrate dysmetabolism (Yang et al., 2023).

The levels of glycoproteins in individuals with hyperoxaluria (0.71±0.11 g/l) and uraturia (0.78±0.13 g/l) did not differ significantly from the control group (0.65±0.10 g/l). Similarly, chondroitin sulfate levels were comparable across groups: 0.207±0.032 g/l in hyperoxaluria, 0.187±0.020 g/l in uraturia, and 0.190±0.020 g/l in controls.

Patients with phosphaturia

Phosphaturia was the least frequently observed type of crystalluria among individuals with bone and joint tissue pathology, detected in only 10 patients (15.1%). This group demonstrated a 22% increase in serum aspartate aminotransferase (AST) levels compared to the control group ($p<0.05$).

Correlation analysis in the phosphaturia group revealed only minor abnormalities. Serum calcium levels correlated weakly with chondroitin sulfates (r=0.25), while both alanine aminotransferase (ALT) and AST showed a moderate correlation with glycoproteins (r=0.66). Chondroitin sulfate levels were also weakly associated with total protein (r=0.25) and glycoproteins (r=0.25) ($p<0.05$).

Patients with bone fractures exhibited increased serum glucose levels by 17% and thymol turbidity values by 34% ($p<0.05$).

This study aimed to investigate differences in biochemical parameters among patients with bone and joint tissue pathology based on the type of crystalluria, and to compare these findings to a control group. Additionally, the potential association between crystalluria type and bone or joint complications was explored.

Bone and joint tissue pathology remains a leading cause of morbidity and mortality, particularly in aging populations. Identifying and managing risk factors is therefore essential for prevention and treatment. Numerous risk factors have been implicated in the development of such pathologies, including elevated blood glucose, kidney disease, obesity, and dyslipidemia (İzki et al., 2024). Kidney dysfunction has also been associated with vascular wall changes, leading to decreased arterial elasticity (Sarısoy et al., 2024). However, the role of dysmetabolic nephropathy in bone and joint pathology remains poorly defined.

Crystalluria, characterized by increased urinary excretion of oxalates, urates, and phosphates, has been associated with disorders of connective tissue metabolism, which may contribute to degenerative and dystrophic changes in bones and joints (Burlaka et al., 2021). The "calcium paradox," whereby endothelial cells adopt osteoblast-like characteristics and sequester calcium crystals, has been proposed as a contributing factor in bone fragility and calcinosis (Seker et al., 2024).

This study therefore sought to determine the incidence and structural distribution of crystalluria in patients with bone and joint tissue pathology and to analyze biochemical profiles according to the type of crystalluria (hyperoxaluria, uraturia, phosphaturia). Crystalluria was present in 9% of the 728 patients with bone and joint tissue pathology. Among these, hyperoxaluria was the most common form (59%), followed by uraturia (25.7%) and phosphaturia (15.1%).

Hyperoxaluria has been linked to gastrointestinal disorders such as chronic gastritis, biliary tract dysfunction, duodenal ulcers, chronic enterocolitis, and Crohn's disease (Basoglu et al., 2023), as well as joint dysfunction and oxalate osteopathy (Horta-Baas et al., 2013; Hassona et al., 2024). Several studies have reported skeletal abnormalities in patients with hyperoxaluria (Bacchetta et al., 2016). An inverse relationship between dietary calcium intake and the risk of stone formation has also been observed. Notably, elevated serum alkaline phosphatase in individuals with hyperoxaluria has been linked to low-calcium diets. The ratio of ionized to bound calcium is influenced by serum albumin levels (Lalayiannis et al., 2024), and our study confirmed a strong correlation between total protein and calcium levels (r=0.87, $p<0.05$). Low dietary calcium intake contributes to bone demineralization, and individuals with kidney stones are at increased risk for osteoporotic fractures. Other studies have confirmed a correlation between low calcium intake and reduced bone mineral density (Joshi et al., 2015). Supplementation with calcium and lactose has been shown to elevate serum calcium and alkaline phosphatase levels (Yang et al., 2024).

Studies examining the association between serum uric acid and bone mineral density have produced conflicting results. Some report a positive association between uric acid levels and bone density (Ibrahim et al., 2021; Kim et al., 2023; Li et al., 2023), while others have found that increased uric acid may reduce the risk of osteoporosis (Lin et al., 2019). At physiological levels, uric acid may offer protection against bone fractures. However, in cases of hyperuricemia and gout, uric acid is associated with increased bone resorption and fracture risk (Yan et al., 2017). Some researchers have identified a significant negative correlation between serum uric acid and trabecular bone score (Kuwabara et al., 2023).

Uric acid has also been associated with altered liver enzyme profiles, including elevated ALT levels. High uric acid concentrations may disrupt

antioxidant defenses and contribute to liver damage (Anothaisintawee et al., 2017). Increased levels of both ALT and uric acid have been linked to a higher incidence of metabolic syndrome.

Importantly, this study revealed significant differences in platelet counts depending on the type of crystalluria. Patients with hyperoxaluria had significantly higher platelet counts compared to those with uraturia ($p<0.05$).

Phosphaturia has been associated with skeletal abnormalities, osteopenia, and osteoporosis (Benson et al., 2022). Excessive phosphate excretion in urine may result in hypophosphatemia due to reduced intestinal absorption. Renal phosphate waste may be secondary to elevated parathyroid hormone levels or the use of loop and thiazide diuretics. Phosphaturia is linked to decreased bone strength and typically presents with a low urinary calcium-to-creatinine ratio and a serum calcium × phosphorus product below 30 (Mitri et al., 2012).

In summary, this study demonstrated distinct biochemical profiles associated with different types of crystalluria in patients with bone and joint tissue pathology. Hyperoxaluria was associated with inflammation (leukocytosis, elevated ESR), thrombocytosis (increased platelet count), and bile stagnation (elevated alkaline phosphatase). Hyperglycemia was observed in patients with uraturia, underscoring the need for glucose monitoring in this population. Elevated AST levels were found in individuals with phosphaturia. Hyperoxaluria was also associated with an increased risk of bone fractures. While dysmetabolic changes are often difficult to reverse, dietary modifications and appropriate treatment of crystalluria may substantially improve clinical outcomes in patients with bone and joint tissue pathology. Prior studies have shown that even in advanced stages of renal dysfunction, reducing dietary oxalate intake may normalize serum creatinine and urinary markers (Sun et al., 2017).

Conclusion

Hyperoxaluria in individuals with bone and joint tissue pathology was associated with leukocytosis, eosinophilia, and elevated levels of both platelets and serum alkaline phosphatase. In contrast, individuals with uraturia demonstrated increased serum levels of glucose, uric acid, and creatinine, alongside a decreased platelet count. Patients with phosphaturia exhibited elevated serum aspartate aminotransferase (AST) levels. These findings suggest that clinicians should closely monitor leukocyte count, eosinophils, platelet levels, and serum alkaline phosphatase in patients with hyperoxaluria; platelet count, uric acid, glucose, and creatinine in those with uraturia; and AST in patients with phosphaturia during the treatment of bone and joint tissue pathology. The observed differences in platelet levels, elevated in hyperoxaluria and reduced in uraturia, represent a novel finding of this study and warrant further investigation.

Acknowledgements. The authors would like to thank the laboratory staff for their assistance in carrying out the analyses.

References

Alan, H. B. Wu. (2006). *Tietz clinical guide to laboratory tests* (4th ed.). 1857 p.

Anothaisintawee, T., **Lertrattananon, D.**, **Thamakaison, S.**, **Reutrakul, S.**, **Ongphiphadhanakul, B.**, **Thakkinstian, A.** (2017). Direct and indirect effects of serum uric acid on blood sugar levels in patients with prediabetes: A mediation analysis. *Journal of Diabetes Research*, *2017*, 6830671. https://doi.org/10.1155/2017/6830671

Bacchetta, J., **Boivin, G.**, **Cochat, P.** (2016). Bone impairment in primary hyperoxaluria: A review. *Pediatric Nephrology*, *31*, 1–6. https://doi.org/10.1007/s00467-015-3048-z

Başoğlu, I. A., **Karakoyun, B.** (2023). Crohn's disease: Etiology, pathogenesis and treatment strategies. *Marmara Medical Journal*, *36*(2), 249–254. https://doi.org/10.5472/marumj.1307982

Bchir, S., **Salem, M. B.**, **Manaa, R.**, **Aloui, S.** (2022). POS-433 systemic manifest antigens of primary hyperoxaluria in adult patients: A monocentric Tunisian study. *Kidney International Reports*, *7*(2), S193. https://doi.org/10.1016/j.ekir.2022.01.460

Ben-Shalom, E., **Cytter-Kuint, R.**, **Rinat, C.**, **Becker-Cohen, R.**, **Tzvi-Behr, S.**, **Goichberg, J.**, **Peles, V.**, **Frishberg, Y.** (2021). Long-term complications of systemic oxalosis in children: A retrospective single-center cohort study. *Pediatric Nephrology*, *36*(10), 3123–3132. https://doi.org/10.1007/s00467-021-05002-1

Benson, J. C., **Trejo-Lopez, J. A.**, **Nassiri, A. M.**, **Eschbacher, K.**, **Link, M. J.**, **Driscoll, C. L.**, **Tiegs, R. D.**, **Sfeir, J.**, **DeLone, D. R.** (2022). Phosphaturic mesenchymal tumor. *American Journal of Neuroradiology*, *43*(6), 817–822. https://doi.org/10.3174/ajnr.A7513

Hoppe, B., **Beck, B. B.**, **Milliner, D. S.** (2009). The primary hyperoxalurias. *Kidney International*, *75*(12), 1264–1271. https://doi.org/10.1038/ki.2009.32

Burlaka, I. A., **Mityuryayeva, I. O.**, **Shevchenko,**

T. A., **Kovalenko, V. M.**, **Kovalenko, T. M.**, **Kovalenko, M. M.**, **Kovalenko, O. M.** (2021). Clinical, laboratory, instrumental, anamnestic characteristics in children with type I diabetes mellitus and early stage of diabetic nephropathy. *Global Pediatric Health*, *8*, 2333794X211063052. https://doi.org/10.1177/2333794X211063052

Büscher, R., **Pape, L.**, **Büscher, A. K.** (2024). Bone health in children with primary hyperoxaluria type 1 following liver and kidney transplantation. *Frontiers in Pediatrics*, *12*, 1353880. https://doi.org/10.3389/fped.2024.1353880

Chen, S., **Guo, X.**, **Yu, S.**, **Sun, G.**, **Yang, H.**, **Li, Z.**, **Li, L.**, **Zhang, Y.**, **Zhang, W.** (2016). Association between serum uric acid and elevated alanine aminotransferase in the general population. *International Journal of Environmental Research and Public Health*, *13*(9), 841. https://doi.org/10.3390/ijerph13090841

Colaci, C., **Gambardella, M. L.**, **Scarlata, G. G. M.**, **Boccuto, L.**, **Colica, C.**, **Luzza, F.**, **Scarpellini, E.**, **Mendez-Sanchez, N.**, **Abenavoli, L.** (2024). Dysmetabolic comorbidities and non-alcoholic fatty liver disease: A stairway to metabolic dysfunction-associated steatotic liver disease. *Hepatoma Research*, *10*, 16. https://doi.org/10.20517/2394-5079.2023.134

Cooper, M. S., **Gittoes, N. J.** (2008). Diagnosis and management of hypocalcaemia. *BMJ*, *336*(7656), 1298–1302. https://doi.org/10.1136/bmj.39582.589433.BE

De Jong, J.G.N., **Wevers, R.A.**, **Lefeber, D.J.** (1989). Dimethylmethylene blue-based spectrophotometric assay for glycosaminoglycans: application in mucopolysaccharidosis screening. *Clinical Chemistry, 35*(8), 1472–1476. PMID: 2667889

Demoulin, N., **Aydin, S.**, **Gillion, V.**, **Morelle, J.**, **Jadoul, M.** (2022). Pathophysiology and management of hyperoxaluria and oxalate nephropathy: A review. *American Journal of Kidney Diseases*, *79*(5), 717–727. https://doi.org/10.1053/j.ajkd.2021.07.018

El Hage, S., **Ghanem, I.**, **Baradhi, A.**, **Mourani, C.**, **Mallat, S.**, **Dagher, F.**, **Kharrat, K.** (2008). Skeletal features of primary hyperoxaluria type 1, revisited. *Journal of Children's Orthopaedics*, *2*(3), 205–210. https://doi.org/10.1007/s11832-008-0082-4

Gapparova, G. N., & Utamurodova, N. A. (2023). Clinical and laboratory features of nephropathy in children with diabetes mellitus. *JournalNX – A Multidisciplinary Peer Reviewed Journal*, *9*(2), 116–122. https://doi.org/10.17605/OSF.IO/2SFZG

Grover, P. K., & Ryall, R. L. (1999). Inhibition of calcium oxalate crystal growth and aggregation by prothrombin and its fragments in vitro: Relationship between protein structure and inhibitory activity. *European Journal of Biochemistry*, *263*(1), 50–56. https://doi.org/10.1046/j.1432-1327.1999.00448.x

Guo, S., Wang, M., Yu, Y., Li, Y., & Wang, Y. (2020). The association of erythrocyte sedimentation rate, high-sensitivity C-reactive protein and diabetic kidney disease in patients with type 2 diabetes. *BMC Endocrine Disorders*, *20*(1), 103. https://doi.org/10.1186/s12902-020-00584-7

Han, T., Chen, W., Qiu, X., & Wang, W. (2024). Epidemiology of gout: Global burden of disease research from 1990 to 2019 and future trend predictions. *Therapeutic Advances in Endocrinology and Metabolism*, *15*, 20420188241227295. https://doi.org/10.1177/20420188241227295

Hassona, Y., Hassan, S., Atef, A., Abou-Elezz, A., & Ghallab, N. A. (2024). Primary hyperoxaluria: Description of a new oral finding and review of literature. *Special Care in Dentistry*, *44*(4), 1041–1048. https://doi.org/10.1111/scd.12968

Hesse, A., Wuzel, H., & Vahlensieck, W. (1991). Significance of glycosaminoglycans for the formation of calcium oxalate stones. *American Journal of Kidney Diseases*, *17*(4), 414–419. https://doi.org/10.1016/S0272-6386(12)80634-2

Horta-Baas, G., Vargas-Gutiérrez, C., & Barile-Fabris, L. (2013). Large joint destructive arthropathy and tumoral calcinosis associated to primary oxalosis: Case report and literature review. *Reumatología Clínica*, *9*(3), 181–185. https://doi.org/10.1016/j.reuma.2012.09.009

Huang, X.-J., Choi, Y.-K., Im, H.-S., Yarimaga, O., Yoon, E., & Kim, H.-S. (2006). Aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) detection techniques. *Sensors*, *6*, 756–782. https://doi.org/10.3390/s6070756

Ibrahim, W. N., Younes, N., Shi, Z., & Abu-Madi, M. A. (2021). Serum uric acid level is positively associated with higher bone mineral density at multiple skeletal sites among healthy Qataris. *Frontiers in Endocrinology*, *12*, 653685. https://doi.org/10.3389/fendo.2021.653685

İzki, A. A., Yılmaz, H., & Göksu, H. (2024). Evaluation of balance disorder and associated factors in patients with ankylosing spondylitis. *Marmara Medical Journal*, *37*(3), 332–337. https://

doi.org/10.5472/marumj.1573709

Joshi, S., Clapp, W. L., Wang, W., & Khan, S. R. (2015). Osteogenic changes in kidneys of hyperoxaluric rats. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, *1852*(9), 2000–2012. https://doi.org/10.1016/j.bbadis.2015.06.020

Kim, S., Lee, S., & Kwon, H. (2023). Association between serum uric acid level and bone mineral density in men more than 50 years of age. *Frontiers in Endocrinology*, *14*, 1259077. https://doi.org/10.3389/fendo.2023.1259077

Ibrahim, W. N., Younes, N., Shi, Z., & Abu-Madi, M. A. (2021). Serum uric acid level is positively associated with higher bone mineral density at multiple skeletal sites among healthy Qataris. *Frontiers in Endocrinology*, *12*, 653685. https://doi.org/10.3389/fendo.2021.653685

Lin, K. M., Lu, C. L., Hung, K. C., Huang, Y. C., & Huang, Y. T. (2019). The paradoxical role of uric acid in osteoporosis. *Nutrients*, *11*(9), 2111. https://doi.org/10.3390/nu11092111

Li, Y., Tan, J., Tian, J., Zhao, J., Zhou, Y., & Shi, Y. (2023). Cross-sectional analysis of the correlation between serum uric acid and trabecular bone score: NHANES 2005–2008. *Scientific Reports*, *13*, 21546. https://doi.org/10.1038/s41598-023-48739-5

Kuwabara, M., Fukuuchi, T., Aoki, Y., Uesugi, T., Nakagawa, T., & Kanbay, M. (2023). Exploring the multifaceted nexus of uric acid and health: A review of recent studies on diverse diseases. *Biomolecules*, *13*(10), 1519. https://doi.org/10.3390/biom13101519

Lalayiannis, A. D., Soeiro, E. M. D., Moysés, R. M. A., & Shroff, R. (2024). Chronic kidney disease mineral bone disorder in childhood and young adulthood: A 'growing' understanding. *Pediatric Nephrology*, *39*(3), 723–739. https://doi.org/10.1007/s00467-023-06109-3

Langenfeld, N. J., Payne, L. E., & Bugbee, B. (2021). Colorimetric determination of urea using diacetyl monoxime with strong acids. *PLOS ONE*, *16*(11), e0259760. https://doi.org/10.1371/journal.pone.0259760

Li, Y., Tan, J., Tian, J., Zhou, Y., & Shi, Y. (2023). Cross-sectional analysis of the correlation between serum uric acid and trabecular bone score: NHANES 2005–2008. *Scientific Reports*, *13*, 21546. https://doi.org/10.1038/s41598-023-48739-5

Lin, K. M., Lu, C. L., Hung, K. C., Huang, Y. C., & Huang, Y. T. (2019). The paradoxical role of uric acid in osteoporosis. *Nutrients*, *11*(9), 2111. https://doi.org/10.3390/nu11092111

Liu, L., Shao, Y., Li, X., Sun, J., & Xing, D. (2022). Individual and combined relationship of serum uric acid and alanine aminotransferase on metabolic syndrome in adults in Qingdao, China. *Nutrition, Metabolism and Cardiovascular Diseases*, *32*(12), 2822–2829. https://doi.org/10.1016/j.numecd.2022.08.014

Liu, Y., Zhao, Y., Shukla, Y., Tan, W., Wang, Y., & Tang, H. (2021). Dysregulated oxalate metabolism is a driver and therapeutic target in atherosclerosis. *Cell Reports*, *36*(4), 109420. https://doi.org/10.1016/j.celrep.2021.109420

Mitri, Z., & Tangpricha, V. (2012). Osteopetrosis, hypophosphatemia, and phosphaturia in a young man: a case presentation and differential diagnosis. *Case Reports in Endocrinology, 2012*, 238364. https://doi.org/10.1155/2012/238364

Moya, F.J., Rodríguez-Perales, S., García-Escudero, R., Nieto-Romero, V., Garcia-Torralba, A., Molinos-Vicente, A., Salido, E., Segovia, J.C., & Garcia-Bravo, M. (2024). Restored glyoxylate metabolism after AGXT gene correction and direct reprogramming of primary hyperoxaluria type 1 fibroblasts. *iScience, 27*(4), 109530. https://doi.org/10.1016/j.isci.2024.109530

National Center for Biotechnology Information. (2025). PubChem Compound Summary for CID 971, Oxalic Acid. Retrieved February 24, 2025, from https://pubchem.ncbi.nlm.nih.gov/compound/Oxalic-Acid

Nazzal, L., Francois, F., Henderson, N., Li, X., & Asplin, J.R. (2021). Effect of antibiotic treatment on Oxalobacter formigenes colonization of the gut microbiome and urinary oxalate excretion. *Scientific Reports, 11*, 16428. https://doi.org/10.1038/s41598-021-95992-7

Qian, X., Wan, J., Xu, J., Liu, C., Zhong, M., Zhang, J., Zhang, Y., & Wang, S. (2022). Epidemiological trends of urolithiasis at the global, regional, and national levels: A population-based study. *International Journal of Clinical Practice, 2022*, 6807203. https://doi.org/10.1155/2022/6807203

Rabinovitch, A., Arzoumanian, L., Curcio, K.M., Dougherty, B., Halim, A. (2009). Urinalysis: approved guideline, 3rd ed. *Clinical and Laboratory Standards Institute*, *29*(4), 41 p.

Ritgen, U. (2023). *Analytical chemistry*. Springer, 308 p.

Sarısoy, Ö., Arıcı, Ş., Demirci Bodur, E., Tezel, O., Alpay, H., Akalın, F. (2024). Is aortic elasticity

associated with hydration status in stage of chronic renal disease in children? *Marmara Medical Journal*, *37*(3), 311–317. doi: 10.5472/marumj.1573657

Seker, A., Gogas Yavuz, D. (2024). Bone mineral density in patients with Cushing's syndrome. *Marmara Medical Journal*, *37*(2), 185–191.

Shastri, S., Patel, J., Sambandam, K.K., Lederer, E.D. (2023). Kidney stone pathophysiology, evaluation and management: core curriculum. *American Journal of Kidney Diseases*, *82*(5), 617–634. doi: 10.1053/j.ajkd.2023.03.017

Shtenberg, O.P. (1962). Determination of glycoproteins in blood serum. *Doctor's Case*, *12*, 43–45.

Sun, Y., Horowitz, B.L., Servilla, K.S., Fair, J.R. (2017). Chronic nephropathy from dietary hyperoxaluria: sustained improvement of renal function after dietary intervention. *Cureus*, *9*(3), e1105. doi: 10.7759/cureus.1105

Țăpoi, L., Șalaru, D.L., Sascău, R., Stătescu, C. (2021). Uric acid—An emergent risk marker for thrombosis? *Journal of Clinical Medicine*, *10*(10), 2062. doi: 10.3390/jcm10102062

Tayefi, M., Hassanian, S.M., Maftouh, M., Moohebati, M., Bahrami, A., Parizadeh, S.M., Mahdizadeh, A., Ghazizadeh, H., Bazeli, J., Heidari-Bakavoli, A. (2018). Relationship between platelet count and platelet width distribution and serum uric acid concentrations in patients with untreated essential hypertension. *BioFactors*, *44*(6), 532–538. doi: 10.1002/biof.1453

Toora, B.D., Rajagopal, G. (2002). Measurement of creatinine by Jaffe's reaction—determination of concentration of sodium hydroxide required for maximum color development in standard, urine and protein free filtrate of serum. *Indian Journal of Experimental Biology*, *40*(3), 352–354. PMID: 12635710

Verdesca, S., Fogazzi, G.B., Garigali, G., Messa, P., Daudon, M. (2011). Crystalluria: prevalence, different types of crystals and the role of infrared spectroscopy. *Clinical Chemistry and Laboratory Medicine*, *49*(3), 515–520. doi: 10.1515/CCLM.2011.078

Wang, X., Zhong, S., Guo, X. (2022). The associations between fasting glucose, lipids and uric acid levels strengthen with the decile of uric acid increase and differ by sex. *Nutrition, Metabolism and Cardiovascular Diseases*, *32*(12), 2786–2793. doi: 10.1016/j.numecd.2022.09.004

Wang, Z., Zhang, Y., Zhang, J., Deng, Q., Liang, H. (2021). Recent advances on the mechanisms of kidney stone formation (Review). *International Journal of Molecular Medicine*, *48*(2), 149. doi: 10.3892/ijmm.2021.4982

Wardhana, W., Rudijanto, A. (2018). Effect of uric acid on blood glucose levels. *Acta Medica Indonesiana*, *50*(3), 253–256. PMID: 30333276

Weng, H., Li, H., Zhang, Z., et al. (2023). Association between uric acid and risk of venous thromboembolism in East Asian populations: a cohort and Mendelian randomization study. *The Lancet Regional Health – Western Pacific*, *39*, 100848. doi: 10.1016/j.lanwpc.2023.100848

Yan, D.D., Wang, J., Hou, X.H., et al. (2018). Association of serum uric acid levels with osteoporosis and bone turnover markers in a Chinese population. *Acta Pharmacologica Sinica*, *39*(4), 626–632. doi: 10.1038/aps.2017.165

Yang, C., Wu, S., Lan, Y., et al. (2023). Association between blood calcium, magnesium, and non-alcoholic fatty liver disease in adults: a cohort-based case-control study. *Biological Trace Element Research*, *201*(10), 4625–4636. doi: 10.1007/s12011-022-03543-6

Yang, R., Ding, N., Qin, J., Peng, H. (2024). The relationship between uric acid and bone mineral density in the intermediate stage of CKD 1–3. *BMC Nephrology*, *25*(1), 219. doi: 10.1186/s12882-024-03650-7

Zechner, C., Adams-Huet, B., Gregory, B., Neyra, J.A., Rule, J.A., Li, X., Rakela, J., Moe, O.W., Lee, W.M. (2021). Hypophosphatemia in acute liver failure of a broad range of etiologies is associated with phosphaturia without kidney damage or phosphatonin elevation. *Translational Research*, *238*, 1–11. doi: 10.1016/j.trsl.2021.07.003