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Serum 25-Hydroxy Vitamin D and Uric Acid Levels as Predictors of Disease Severity and Functional Impairment in Women with Knee Osteoarthritis

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Abstract

Background: The most frequent type of arthritis is osteoarthritis; it typically develops slowly and is more frequently observed in older adults. Osteoarthritis mainly affects weight-bearing joints but other can also affected joints. The purpose of the study was to explore the associations between serum of 25-hydroxy vitamin D (25(OH)D) and serum uric acid (SUA) with serum lipid profiles and inflammatory cytokines in women with KOA and to scrutinize the prognostic potential of serum 25(OH)D and SUA.

Methods: The study involved 50 elderly obese females with KOA and the control group of 50 healthy women. Assessment of KOA severity by Kellgren-Lawrence score was performed and functional disability was scored. Blood samples were analysed to assess 25(OH)D and inflammatory cytokines, SUA, lipid profile, and calcium.

Results: We found significant differences in most of the laboratory findings between KOA patients and controls. Decreased serum 25(OH)D and increased SUA were linked with more severe KOA. Serum 25(OH)D and SUA can differentiate between mild and moderate-to-severe KOA. Both were correlated with functional impairment.

Conclusions: We concluded robust associations between vitamin D deficiencies, high SUA levels with increased serum lipids and inflammatory cytokines along with increased functional impairment and disease severity in women with KOA. Serum 25(OH)D and SUA can serve as simple reliable prognostic tools in the prediction of KOA severity.

Introduction

Osteoarthritis (OA) is a prevalent joint disease affecting millions worldwide in both developed and developing countries. Ageing is associated with articular tissues alterations that enhance the development of OA. Albeit ageing and OA are closely related, both are independent processes [1–3]. Knee osteoarthritis (KOA) is an extreme form of osteoarthritis that results in restricted joint movement, knee pain, and deformities. It poses a significant financial burden on healthcare systems and has a profound impact on patients and their families [4] KOA is a complex health condition influenced by various factors, including aging, hereditary factors, inflammation, trauma, and obesity. These multiple factors contribute to the development of KOA and its associated symptoms, making it a multifaceted condition to manage and understand [5]. Previous studies have highlighted the significant role of obesity or being overweight as a contributing factor in the development of KOA. Individuals who are obese have a higher likelihood of developing KOA compared to those who are not overweight, signifying the obesity as a potential risk [6]. Numerous studies have established a meaningful correlation between decreased serum levels of 25(OH)D and KOA [7,8]. A study involving elderly patients with idiopathic KOA revealed that 63% of them had vitamin D deficiency, which negatively affected their functional capacity. Additionally, individuals with lower levels of 25(OH)D were more susceptible to knee pain and experienced accelerated radiographic deterioration in the affected joint [9,10]. Vitamin D deficiency is prevalent, particularly among the elderly, and it may contribute to the progression of KOA by promoting inflammation and oxidative stress in the body. Inadequate vitamin D levels are believed to contribute to the development and advancement of KOA, as the body's inflammatory responses are crucial in this disease. Elderly has a limited ability to generate vitamin D secondary to sunlight exposure, and there may also be decreased vitamin D intake or absorption from the diet, with a subsequent greater risk of vitamin D deficiency associated with KOA [11].

There is a strong association between obesity and a greater risk of low vitamin D. Several factors contribute to this relation, including poor absorption in the gut, inadequate sun exposure, insufficient hydroxylation in fat tissue, and the sequestration of vitamin D in fat tissue. These factors collectively contribute to a greater probability of vitamin D deficiency in obese individuals [10,12].

Hyperuricemia is a condition with an excess of uric acid production or a decrease in its excretion. It is reported that hyperuricemia is prevalent in approximately 19% to 25% of the general population, with a higher incidence observed in males than females [13]. Additionally, hyperuricemia is associated with various health problems and metabolic disorders, including metabolic syndrome [14]. Scientific research has revealed that elevated SUA in the body can expedite the onset and advancement of OA by disrupting molecular communication and altering the response to inflammatory substances [15]. In the progression of OA, inflammatory mediators are fundamental contributors in controlling the NF-kB and MAPK signalling pathways. This regulatory process ultimately leads to damage and breakdown of articular cartilage [16,17]. When the balance between pro-inflammatory/inflammatory distorted, joint degeneration can develop. Anti-inflammatory cytokines can slow the progression of KOA. Interleukins (IL-1, IL-6, IL-15, IL-17, and IL-18), along with tumour necrosis factor-alpha (TNF-α), are the primary cytokines responsible for initiating inflammation in KOA [18]. Interleukin-4 (IL-4), insulin-like growth factor (IGF), interleukin-10 (IL-10), and transforming growth factor are the most major mediators in this process [19,20]. Moreover, it has been demonstrated that TNF-α can trigger inflammation in synovial tissue and cause damage to cartilage by upregulating the expression of cadherin-11 [21]. Individuals with KOA have been found to have higher levels of immune-stimulating cytokine IL-7 in their inflamed tissues, which is linked to the clinical features of the condition [22]. Several studies have demonstrated that interleukin-4 (IL-4) has a potent protective effect on cartilage. IL-4 can inhibit monocyte cytokine synthesis and release. When the balance between inflammatory/anti-inflammatory cytokines interrupts the knee joint function and structure, it can lead to abnormal metabolism in the articular cartilage, ultimately resulting in damage to the typical structure of the knee joint [23,24].

Accordingly, the purpose of the study was designed to explore the association between serum levels of 25(OH)D and uric acid with serum levels of lipids and inflammatory cytokines (TNF-α, IL-7, and IL-4) in obese elderly women with KOA as the primary outcome while the secondary outcome was to scrutinize the prognostic role of serum levels of 25(OH)D and uric acid in the prediction of KOA severity.

Methods

Study design and participants

This was a case-control observational study, with patient recruitment taking place at the Rheumatology Clinic of the King Faisal Medical Complex in Taif, Saudi Arabia. The study period spanned from January to June 2023. The patients' group included 50 obese women with KOA. The patients aged between 50 to 75 years.

The diagnosis of KOA was made according to the classification criteria of the American College of Rheumatology [25]. The control subjects were 50 healthy age-matched women who reported no previous history of any rheumatic or joint diseases as well as they were undergoing routine check-ups.

The exclusion criteria included patients with bone fractures, persistent infections, and rheumatologic/joint disorders.

Assessment of KOA severity and functional impairment

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to assess the functional impairment of KOA. The WOMAC is a 24-item questionnaire, and its total score ranged from 0 to 96. The higher scores mean a more functional impairment of KOA patients [26]. The severity of disease in both knee joints of each patient was assessed radiographically using the Kellgren–Lawrence score. The severity ranging from very mild (grade 1) to severe (grade 4). The patients' disease severity is attributed to the more severe knee joint [27]. Other details from patients' history and physical examination were extracted from their medical records.

Blood samples collection and processing

Ten-millilitre fasting blood sample were drawn from all the study subjects and divided into two tubes: ethylenediaminetetraacetic acid (EDTA) and plain tubes. EDTA samples were used for erythrocyte sedimentation rate (ESR) assessment using the Westergren method [28]. Enzymatic colorimetric techniques were used to measure the samples' serum uric acid, calcium, and serum lipids, 25(OH)D, TNF-α, IL-7, IL-4, LDH, and C-reactive protein (CRP) were measured using enzyme-linked immunosorbent assay (ELISA) kits available commercially.

Statistical analyses

Numerical variables were expressed as mean ± standard deviation (SD) or median (interquartile range) according to the distribution normality. The normality of distribution assumption was tested by Shapiro-Wilk test while the assumption of equality of variance assumption was tested by Leven's test. Qualitative variables were summarized by number and percentage. The receiver operating characteristic (ROC) curve was utilized to determine the prognostic role of serum levels of 25(OH)D and uric acid in KOA severity prediction. Differences were considered statistically significant at a P-value less than 0.05. The Statistical Package for the Social Sciences (SPSS®) software, Version 26 was used for all statistical analyses. All statistical comparisons were two-tailed.

Results

A total of 50 healthy women and 50 women with KOA were enrolled in this study. The median age of the control women was 55 years (IQR 52-59.3 years) and that of women with KOA was 55 years (IQR 52-58.8 years), respectively. Women with KOA had statistically significantly higher BMI, serum levels of uric acid, TC, TG, LDL, ESR, CRP, TNF-α, and IL-7 (P<0.001 each) and LDH (P=0.04) than the controls. Serum levels of 25(OH)D, Ca^{2+}, HDL, and IL-4 were significantly lower in patients with KOA compared with the controls (P<0.001 each), Table 1.

According to the severity of KOA, women with KOA were stratified radiographically by the Kellgren–Lawrence score into mild, moderate, severe, (grade I, II, and III, respectively). Patients with grades II and III Kallgren scores had significantly lower serum 25(OH)D levels than grade I patients (P=0.012 and P<0.001, respectively). Similarly, serum 25(OH)D levels were significantly lower in grade III patients than grade II patients (P=0.007). Patients with grades II and III Kallgren scores had significantly lower serum HDL levels than grade I patients (P=0.006 and P<0.001, respectively). Patients with grades I and II Kallgren scores had significantly lower serum LDL levels than grade III patients (P=0.008 and P=0.03, respectively). Compared to patients with grade I, patients with grade III had significantly higher ESR, CRP and TNF-α levels (P<0.001, P=0.029, and P=0.002, respectively). While patients with grade III had significantly higher IL-7 levels than patients with grade II (P=0.006), Table 2.

We found that serum level of 25(OH)D was inversely correlated with TC (P<0.001), TG (P=0.013), LDL (P=0.010), ESR (P<0.001), CRP (P=0.006), TNF-α (P<0.001), IL-7 (P=0.004) and was positively correlated with HDL (P<0.001), Table 3. Moreover, SUA was positively correlated with TC, TG, LDL, ESR, CRP, TNF-α, IL-7 (P<0.001, each) and was inversely correlated with HDL (P<0.001) existed, Table 3.

Regarding WOMAC scores, patients with grades II and III Kallgren scores had significantly higher WOMAC scores than grade I patients (39.73±7.78, 69.75±15.18 vs 18.11±7.22, respectively, P<0.001), Figure 1a. Additionally, WOMAC scores were inverse correlated with serum (25(OH)D) levels (P<0.001), Figure 1b. In contrast, WOMAC scores were positively correlated with serum SUA levels (P<0.001), Figure 1c.

The ROC curve analysis revealed that serum (25(OH)D) levels can excellently differentiate between moderate-to-severe (grades II and III) KOA women and those with mild KOA (grade I), an AUC of 0.955. [(95% confidence interval (CI): 0.872 to 1.0, P<0.001)]. The optimal sensitivity and specificity were (96.77% and 94.74%, respectively at a cutoff expression value<26.5 ng/mL), Figure 1d. Similarly, SUA can differentiate

Initial characteristics and laboratory findings	Healthy participants *n*=50	KOA patients *n*=50	*P*-value
Age (years)	55(52-59.3)	55(52-58.8)	0.88†
Body mass index (kg/m²)	23.65(19.8-27.2)	49.88(42.65-54.65)	<0.001†
25-hydroxy vitamin D (ng/mL)	38.65(32.65-43.65)	25(17.82-29.25)	<0.001†
Calcium (mg/dL)	10.17(9.01-11)	8.88(7.75-9.33)	<0.001†
Serum uric acid (mg/dL)	4.33(3.22-5.98)	8.86(7.78-9.89)	<0.001†
Serum lipids Total cholesterol (mg/dL)	152(123-174)	228(213-262)	<0.001†
Triglycerides (mg/dL)	143(118-187)	218.7(209.2-237.9)	<0.001†
High-density lipoprotein cholesterol (mg/dL)	72.19±10.16	39.24±10.56	<0.001‡
Low-density lipoprotein cholesterol (mg/dL)	71.5(65-81)	206(159.8-217.2)	<0.001†
Inflammatory biomarkers Erythrocyte sedimentation rate (mm/hr)	8.56(9.55-10.01)	30(23.95-35)	<0.001†
C-reactive protein (mg/L)	4.6(3.22-6.46)	24.15(21-28)	<0.001†
Tumor necrosis factor-alpha (pg/mL)	4.0±1.45	78.45±9.6	<0.001‡
Interleukin-7 (pg/mL)	0.32(0.15-0.52)	6.63(5.74-7.57)	<0.001†
Interleukin-4 (pg/mL)	173.3(137.5-210.5)	45.95(34.84-53.87)	<0.001†
lactate dehydrogenase (mg/dL)	199(149-209)	215(18-232)	0.04†

Data are mean±standard deviation or median (interquartile range).
Bold values donate significant differences at *P*-value<0.05
†Mann-Whitney *U* test
‡ Independent samples-t test
Table 1: Initial characteristics and laboratory findings of the study participants.

Initial characteristics and laboratory findings	Kallgren scores			*P*-value
	Grade I *n*=19	Grade II *n*=15	Grade III *n*=16	
Age (years)	55(52-59)	54(52-56)	58.5(52.25-66.5)	0.28†
Body mass index (kg/m²)	51.57±8.76	46.68±12.69	47.47±9.48	0.24‡
25-hydroxy vitamin D (ng/mL)	32(28-34.64)	25(21-25.77)[a]	17.01(14.25-17.98)[ab]	<0.001†
Calcium (mg/dL)	8.8(7.12-9.21)	9.25(8.31-9.42)	8.74(7.84-9.24)	0.35†
Serum uric acid (mg/dL)	7.93(6.87-8.88)	8.98(8.56-9.65)	9.89(8.97-11.09)[a]	0.001†
Serum lipids Total cholesterol (mg/dL)	218(211-261)	231(216-242)	236.5(217.25-301.5)	0.11†
Triglycerides (mg/dL)	216(198-233)	216.8(204-238.3)	231.25(212.38-265.025)	0.24†
High-density lipoprotein cholesterol (mg/dL)	46.63±8.49	36.73±7.77[a]	32.81±10.08[a]	<0.001‡
Low-density lipoprotein cholesterol (mg/dL)	195(159-210)	200(151-216.5)	231.25(212.38-265.03)[ab]	0.005†
Inflammatory biomarkers Erythrocyte sedimentation rate(mm/hr)	26(22.55-30)	29(24-36)	35(31.25-38.75)[a]	0.001†
C-reactive protein (mg/L)	22.97±4.21	25.09±4.85	27.41±5.66[a]	0.038‡
Tumor necrosis factor-alpha (pg/mL)	73.12±9.40	76.46±7.63	83.82±8.72[a]	0.003‡
Interleukin-7 (pg/mL)	6.77(4.9-7.33)	5.88(5-6.65)	7.77(6.45-8.13)[b]	0.007†
Interleukin-4 (pg/mL)	41.76±15.16	45.98±11.66	43.64±14.90	0.69‡
lactate dehydrogenase (mg/dL)	195.9(149.2-231.8)	216.5(153.8-237.2)	216.5(195.4-231.32)	0.76†

Data are mean±standard deviation or median (interquartile range).
Bold values donate significant differences at *P*-value<0.05
†Kruskal Wallis *H* test
‡ One-way analysis of variance (ANOVA) test
[a] significant vs grade I, [b] significant vs grade II by Kruskal Wallis *H* test followed by Dunn's post hoc multiple comparison test or Tukey post hoc test following a one-way ANOVA test at *P*-value <0.05.
Table 2: Initial characteristics and laboratory findings of KOA patients stratified according to the severity.

Lipid and inflammatory biomarkers		Serum lipids				Inflammatory biomarkers					
		TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	LDH (mg/dL)	ESR (mm/hr)	CRP (mg/L)	TNF-α (pg/mL)	IL-7 (pg/mL)	IL-4 (pg/mL)
25(OH)D (ng/mL)	*r*	-0.511	-0.347	0.499	-0.363	-0.159	-0.530	-0.386	-0.588	-0.399	-0.119
	P	<0.001	0.013	<0.001	0.010	0.27	<0.001	0.006	<0.001	0.004	0.41
SUA (mg/dL)	*r*	0.790	0.567	-0.603	0.543	0.099	0.596	0.585	0.751	0.511	0.067
	P	<0.001	<0.001	<0.001	<0.001	0.49	<0.001	<0.001	<0.001	<0.001	0.64

Table 3: Correlation between serum levels of lipid and inflammatory biomarkers, 25(OH)D and SUA.

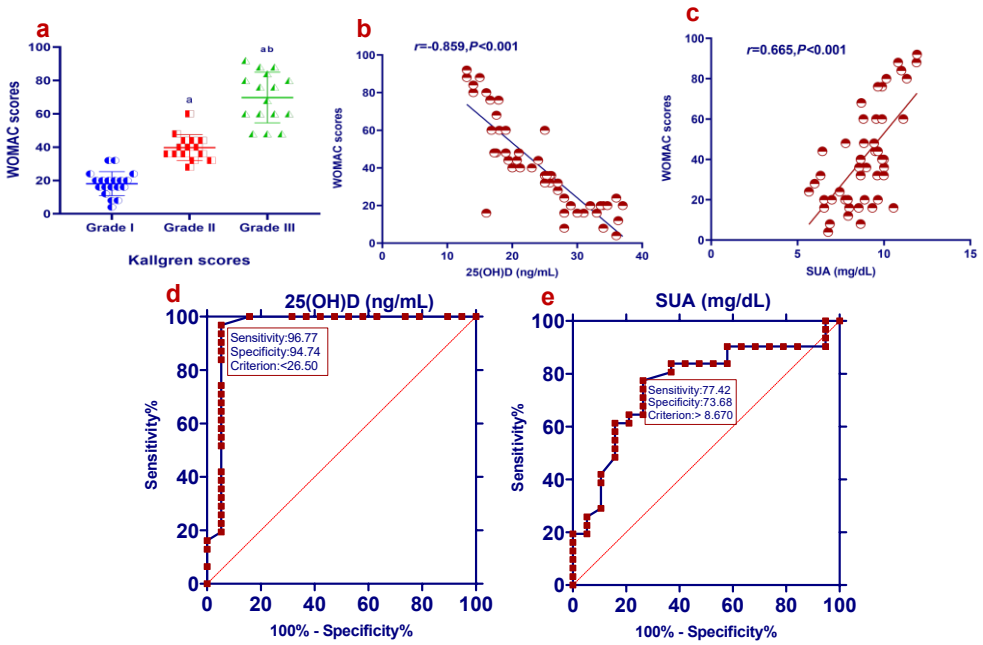

Figure 1.: a Scatter dot plots representing the WOMAC pain scores among KOA women stratified according Kallgren scores. [a] significant vs grade I, [b] significant vs grade II by Games-Howell test following one way Welch's ANOVA, as homogeneity of variances were violated, at *P*-value <0.05.
b Correlation between the Western Ontario and WOMAC scores and 25-hydroxy vitamin D [25(OH)D] in KOA women. *r*, Pearson correlation coefficient
c Correlation between the WOMAC and serum uric acid (SUA) in KOA women. *r*, Pearson correlation coefficient
d The receiver operating characteristic (ROC) curve for 25-hydroxy vitamin D [25(OH)D] in KOA women in the prediction of KOA severity among the involved women.
e The ROC curve for serum uric acid (SUA) in the prediction of KOA severity among the involved women.

between moderate-to-severe (grades II and III) KOA women and those with mild KOA (grade I), with an AUC of 0.760, [(95% (CI): 0.620 to 0.899, *P*=0.002), an accepted discrimination ability. The optimal sensitivity and specificity were (77.42% and 73.68%, respectively at a cutoff expression value>8.67 mg/dL), Figure 1e.

Discussion

Our study proved significant associations between serum levels of 25(OH)D and SUA with serum levels of lipids and inflammatory cytokines in obese elderly women with KOA. In addition, serum levels of 25(OH)D and uric acid can serve as reliable simple reliable prognostic tools in the prediction of KOA severity based on Kellgren scores in those women. However, serum 25(OH)D revealed better prognostic performance compared with SUA.

Synovitis, associated with OA, is incriminated in the severity and progression of pain and structural damage of OA. Moreover, increased inflammatory/immune cells including macrophages and lymphocytes have been evidenced in OA synovium [29].

Hyperuricemia is an inflammatory condition that can cause deleterious health effects such as gout and cardiovascular diseases. High SUA levels can cause joint inflammation and pain secondary to the formation of crystals [30]. Vitamin D deficiency is prevalent, especially among the elderly. The body's inflammatory responses are crucial in developing and advancing KOA. It is believed that insufficient vitamin D levels may contribute to the pathogenesis of OA [11]. Moreover, vitamin D deficiency can induce parathyroid hormone release leading to increase SUA [31].

Functions of vitamin D includes maintaining normal bone homeostasis and enhancing the intestinal absorption of calcium, phosphorous, magnesium, iron, and zinc. In addition, vitamin D has several physiological functions such as control of insulin and glucose secretion and regulation of cardiorenal functions. Moreover, it has anti-inflammatory and immunomodulatory functions [32–36]. In corroboration to the current results, several epidemiological studies have revealed a positive association between vitamin D deficiency and chronic inflammatory disorders, e.g., chronic renal conditions, hepatic inflammatory diseases, inflammatory bowel diseases and rheumatoid arthritis [29,37].

Our findings revealed that CRP and ESR levels are helpful indicators of inflammation and tissue damage in KOA rather than LDH. In addition, they showed higher levels among severe than mild cases. Many studies agree with this observation [38,39].

Coinciding with our findings, Amirkhizi and colleagues [40] in their previous work reported similar findings. We reported that patients with grades II and III Kallgren scores had significantly lower serum 25(OH)D levels than grade I patients. In support, Heidari et al., [41] clarified that the severity of OA is positively associated with vitamin D level. A meta-analysis, conducted by Yu et al., [11] concluded similar results.

Furthermore, the current findings showed that vitamin D levels are inversely correlated to CRP and ESR levels in KOA patients. In support, vitamin D deficiency is accompanied by overexpression of the inflammatory markers [42]. The significant positive correlations between SUA levels and CRP and ESR implying that elevated SUA levels may be associated with increased systemic inflammation. Activation of the proinflammatory NF-κB signalling cascade could be induced by hyperuricemia [43]. We found a significant negative correlation between serum 25(OH)D and functional disability in KOA patients existed. This agreed with the previous finding of saturation vitamin D stores may relieve joint pain in case of vitamin D deficiency [44].

Moreover, serum UA >8.67 mg/dL can differentiate moderate-severe KOA from mild cases with less sensitivity and specificity than 25(OH)D (77.42% and 73.68% respectively). An American study of KOA subjects with asymptomatic hyperuricemia showed that SUA levels significantly distinguished patients with disease progression from non-progressors based on radiography over one year period of follow-up [45]. The association of SUA and OA has long been evaluated, and the pathological similarity between gout and OA has been proposed. Aging and obesity are significant predictors shared by both diseases [46–48]. According to Ding and coworkers [49] elevated levels of SUA were positively associated with the most radiographic alterations with KOA in both males and females patients including osteophytes but not joint space narrowing. In contrast to our results, in Korean population-based epidemiological study, SUA was not considered as a significant determinant for KOA progression [50].

According to our findings, vitamin D levels are linked to serum lipid components. Vitamin D positively correlates with serum HDL, whereas TC, TG, and LDL correlate negatively. Several studies supported this result and stated that less vitamin D levels are associated with an atherogenic lipid profile [51,52]. Multiple cardiovascular and metabolic factors can increase the risk of OA, causing metabolic syndrome. This syndrome includes vascular alteration, decreased HDL levels, increased both LDL and TG levels, elevated blood glucose levels and abdominal obesity, creating a low-grade chronic inflammatory condition [53–55]. Raised SUA levels are commonly observed in patients with metabolic syndrome. A former meta-analysis including 32 studies found a bidirectional association between SUA and vitamin D [56,57]. Patients with early OA experienced higher levels of LDL, UA, and CRP and significantly correlated with higher levels of pain intensity and higher disability [58].

An open-label clinical trial enrolled 80 patients with KOA by Divjack et al., [59] demonstrated improved clinical response as assessed by the visual analogue scale pain and WOMAC scores three months following vitamin D administration in those patients. A 3-month oral vitamin D supplementation was associated with decreased serum levels of inflammatory cytokines as TNF-α. UA could stimulate an innate immune response contributing to OA pathology and progression. A randomized controlled trial of Leung and colleagues [60] concluded that low dose colchicine reduced inflammation and high bone turnover but did not cause clinical improvement in most patients.

Overall, these results suggested that metabolic and inflammatory markers are chief players in the pathogenesis of KOA and act as potential targets for novel treatment measures. The findings also indicated the need for early detection and management of serum metabolic and inflammatory changes in patients with KOA to improve outcomes and quality of life as increased UA levels and/or reduced vitamin D levels are linked to worsened functional impairment with KOA.

Our study had some limitations. First, all the enrolled women were obese. Therefore, some laboratory findings might be confounded by the effect of obesity. Second, the lack of the follow-up assessments of the relevant biomarkers and the functional status of KOA patients confers another limitation.

Our results suggest robust associations between vitamin D deficiencies, high SUA levels with increased serum lipids and proinflammatory biomarkers as well as increased progression of clinical symptoms and radiological findings in KOA obese elderly women. In addition, serum levels of 25(OH)D and uric acid can serve as promising simple reliable prognostic tools in the prediction of KOA severity based on radiographic grading in those women. However, the prognostic performance of serum 25(OH)D was superior to SUA.

Ethical Statement

The Scientific Research Ethics Committee at King Faisal Medical Complex approved the study proposal

(Ethical Permission No. 2023-B-1). Informed written consent was obtained from all participants. The study was following the 1964 Helsinki Declaration and its later amendments.

Author Contributions

AFG conceived the study, study design, participated in data collection, blood samples collection, performing the biochemical analyses. The initial draft was written by AFG, EIA, and ON performed data analysis and wrote the original draft. AAA, RAA, NAM, AA, AA, OA, MA, and AFH shared in blood samples collection, performing the biochemical analyses, AHA participated in data collection. All authors contributed to drafting, and reviewing, and approved the final version.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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