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Vitamin D deficiency in Egyptian and Yemeni primary knee osteoarthritis patients: Relation to physical function and radiographic severity

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ABSTRACT

Aim of the work: To investigate the relationship between serum 25(OH)D (25-hydroxyvitamin D) level and primary knee osteoarthritis (KOA) in Egyptian and Yemeni patients, and to demonstrate its impact on physical function and radiographic severity.
Patients and methods: This study included 82 KOA patients; (41 Egyptian, 41 Yemeni), together with 80 controls; (40 Egyptian, 40 Yemeni). Serum 25(OH)D level was measured using enzyme-linked immunosorbent assay. Physical function was evaluated using 6-minute walk test (6MWT), Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score and chair stand test (CST). Knee radiographic grading was based on Kellgren-Lawrence (KL) scale.
Results: The mean age of Egyptian and Yemeni patients was 53.4 ± 7.1 and 56.2 ± 7.5 years respectively. Serum 25(OH)D level was significantly decreased in Egyptian (13.3 ng/ml;5.3–39.6) and Yemeni (9.5 ng/ml; 3.8–49) KOA patients compared to their corresponding controls (27.7 ng/ml; 12.8–51.4 and 20.9 ng/ml; 8–45.5; $p < 0.001$ each) and was the only significant predictor of KOA in Egyptian ($p < 0.0001$) and Yemeni ($p = 0.001$) patients. Yemeni patients exhibited significantly lower 25(OH)D compared to Egyptian patients ($p = 0.008$) with a significant increase in smoking ($p = 0.002$) and niqab wearing ($p < 0.001$). Serum 25(OH)D level significantly negatively correlated with radiographic grading in Egyptian ($p = 0.03$) and Yemeni ($p = 0.02$) patients. Regression analysis showed no relationship between 25(OH)D levels with WOMAC, 6MWT or CST; the relation was significant with KL grading in Egyptian ($p = 0.01$) and Yemeni ($p = 0.005$) patients.
Conclusion: There is an association between vitamin D deficiency and primary KOA especially to the radiographic severity but not to physical function in Egyptian or Yemeni primary KOA patients.

1. Introduction

Primary knee osteoarthritis (KOA) is a chronic degenerative joint disease [1]. It is characterized by gradual degradation and loss of articular cartilage, abnormal subchondral bone growth, and inflammation of the synovium [2]. Pain, stiffness, and limitation of physical function are the major clinical symptoms of KOA [3].

Vitamin D deficiency has been long speculated to be a profound risk factor for the occurrence and progression of primary KOA [4]. Vitamin D has multiple biological functions on cartilage, bone and muscle via vitamin D receptors (VDRs) [5]. Insufficient levels of vitamin D affect osteoblastic activity, and articular cartilage turnover [6]. Vitamin D acts through controlling the matrix metalloproteinase (MMP) and prostaglandin E2 secretion; moreover vitamin D affects the production of proteoglycans which are necessary for maintaining cartilage health [7].

There is contradictory data linking serum 25-hydroxyvitamin D [25(OH)D] level with functional status and radiographic severity in osteoarthritis. The associations of vitamin D deficiency to cartilage loss, knee osteophytes, decline in physical performance [8] and radiographic KOA severity [9] have been reported. On the other hand, others reported that the level of serum 25(OH)D seems not to be related to cartilage loss, functional limitation, or to the radiographic severity [10].

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This worked aimed to determine the value of serum 25(OH) D level as a predictor of primary KOA and to assess its influence on physical function and radiographic severity of KOA patients.

2. Patients and methods

The present study included 82 patients; (41 Egyptian and 41 Yemeni) with primary KOA and fulfilling the American College of Rheumatology (ACR) diagnostic criteria for classification of KOA [11]. Patients were recruited from the Rheumatology outpatient clinic, Kasr Alainy Hospital, Cairo University and Al-Thawra Hospital, Sana'a University and were aged >45 years. 80 age and sex matched healthy individuals were considered as a control group (40 Egyptian and 40 Yemeni). Exclusion criteria included patients with secondary causes of KOA, with diseases that affect serum vitamin D levels (e.g. malabsorption syndrome, liver or kidney diseases), patients taking medications known to affect 25(OH) D level in the previous 3 months (e.g. anticonvulsants, antituberculous drugs, 25(OH) D or its analogs), patients who used glucosamine, chondroitin or intra-articular injections in the previous 3 months. All procedures performed were in accordance with the ethical standards of Kasr Alainy Cairo University Hospitals, Al-Thawra Hospital research committee, and with the 1964 Helsinki declaration ethical standards. Informed consents were provided by the patients.

Demographic characteristics e.g. age, sex and clinical data demonstrating risk factors of vitamin D deficiency (e.g. smoking, niqab wear in women which includes complete covering of the face and body), and body mass indices (BMIs) were recorded [12].

2.1. Laboratory investigations

Fasting venous morning blood samples were obtained from all patients. Ionized calcium (1.1–1.35 mmol/L), serum phosphorous (2.7–4.5 mg/dl), bone-specific alkaline phosphatase (ALP) (40–190 U/L), kidney and liver functions, were measured with the standard auto analyzer. Intact parathyroid hormone (PTH) (reference: 9–94 pg/ml) was measured by the enzyme-linked immunosorbent assay (ELISA) technique (kit provided by IBL international GMBH, Hamburg, Germany with Reference NM59041). Serum 25(OH) D level was assessed using the ELISA technique (kit provided by ORGENTEC Diagnostika GmbH, Mainz, Germany). Serum 25(OH) D deficiency was defined if <20 ng/mL [13].

Physical function was evaluated using the 6 min walk test (6MWT) which measures the distance (in meters) an individual is able to walk in 6 min on a hard, flat surface [14], and chair stand test (CST) which measures the number of chair stand repetitions possible in 30 secondswith higher values representing better performance [14], and Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score which is a questionnaire of 24 items divided into 3 subscales: pain, stiffness, physical function. Sums of the scores for all 3 subscales gives a total WOMAC score [15].

Anteroposterior and lateral weight-bearing knee radiographs were obtained for all patients. Radiographs were graded from I to IV grades according to the Kellgren-Lawrence (K-L) grading scale. Radiographs graded from 0 to 4 Grades. Grades 1 and 2 were considered to be mild while grades 3 and 4 were considered as severe [16].

2.2. Statistical methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, Chi square ($\chi 2$) test was performed. Fisher's exact test was used instead when the expected frequency is <5. Correlations between quantitative variables were done using Spearman correlation coefficient. Multivariatelinear regression analysiswas used to detect independent predictors of physical function. Multivariate logistic regression analysiswas done to detect independent predictors of primary KOA. P values < 0.05 were considered as significant.

3. Results

The demographic characteristics and laboratory investigations of Egyptian, and Yemeni KOA patients and controls are shown in Table 1. The range of the age of the patients and control was 45–75 years. Table 2 shows the differences between Egyptian and Yemeni KOA patients. Serum 2 5(OH)D level was significantly decreased in Egyptian and Yemeni KOA patients compared to controls (p < 0.001 each) (Fig. 1). Serum 25(OH) D level was significantly decreased in Yemeni KOA patients compared to Egyptian KOA patients (p = 0.008). There was a significant increase in smokers' and niqab wearing number in Yemeni patients compared to Egyptian KOA patients (p = 0.002, p < 0.001 respectively). There were no signficant differences between patients with severe and mild KL regarding age or BMIs, however patients with severe KL grading had significantly lower vitamin D compared to those with mild grade in Egyptian (p = 0.05) and Yemeni patients (p = 0.02) (Table 3).

Table 1
Demographic characteristics, laboratory investigations of Egyptian and Yemeni knee osteoarthritis (KOA) patients and controls.

Parameter	Egyptians			Yemeni		
	KOA (n = 41)	Control (n = 40)	p	KOA (n = 41)	Control (n = 40)	p
Age (years)	53.4 ± 7.1	52.2 ± 7.7	0.2	56.2 ± 7.5	53.7 ± 8.1	0.07
Females	34 (82.9)	34 (82.9)	1	34 (82.9)	31 (77.5)	0.5
Smokers	4 (9.8)	7 (17.1)	0.3	16 (39)	16 (40)	0.9
BMIs	30.23 ± 4.7	28.3 ± 5.5	0.06	28.5 ± 3.9	27.1 ± 4.8	0.07
s. Cr. (mg/dl)	0.8 ± 0.3 (0.4–1.2)	0.9 ± 0.2 (0.4–1.2)	0.09	0.8 ± 0.2 (0.4–1)	0.8 ± 0.1 (0.6–1)	0.6
ALT (IU/L)	21.7 ± 5.6 (13.3–39.5)	21.2 ± 6 (10.1–34.3)	0.7	24.2 ± 8.7 (8– 46)	25.9 ± 4.3 (19–34)	0.4
Ca^{++} (mmol/L)	1.2 ± 0.1 (1.1–1.4)	1.2 ± 0.1 (1–1.8)	0.4	1.1 ± 0.1 (1.1 – 1.3)	1.1 ± 0.3 (1.1–1.2)	0.9
P (mg/dl)	3.7 ± 0.6 (2.4– 6.2)	3.9 ± 0.8 (1.5–6.3)	0.04	3.5 ± 0.5 (2.4–4.6)	3.1 ± 0.5 (2.1– 4)	<0.001
ALP (U/L)	104.9 ± 23.7 (55–173)	100.4 ± 20.8 (55–135)	0.5	102.1 ± 22.6 (56–171)	99.7 ± 10.8 (81–136)	0.9
PTH (pg/ml)	55.4 ± 35.3 (19.5–178.9)	39 ± 17.6 (6.3–91.4)	0.03	44.9 ± 26.7 (3.1–106)	44.2 ± 18 (13.6–75.4)	0.8
s 25(OH)D (ng/ml)	13.3 (5.3–39.6)	27.7 (12.8–51.4)	<0.001	9.5 (3.8–49)	20.9 (8–45.5)	<0.001

Results are presented as mean ± SD or median (range) and n(%). KOA: knee osteoarthritis, BMIs: body mass index, Cr .: creatinine, ALT: alanine transaminase, Ca^{++}: ionized calcium, P: phosphorous, ALP: alkaline phosphatase, PTH: parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D. Bold values are significant at p < 0.05.

Table 2
Demographics, serum 25(OH)D levels, physical function scores, radiographic grading of Egyptian and Yemeni knee osteoarthritis (KOA) patients.

Parameter		KOA patients (n = 41 each)		p
		Egyptians	Yemeni	
Age (years)		53.4 ± 7.1	56.2 ± 7.5	0.05
Females		34 (82.9)	34 (82.9)	1
Smokers		4 (9.8)	16 (39)	0.002
BMI		30.2 ± 4.7	28.5 ± 3.9	0.1
Niqab (females)		4 (11.4)	32 (94)	<0.001
s25(OH)D (ng/ml)		13.3 (5.3–39.6)	9.5 (3.8–49)	0.008
6MWT (meters)		359.2 ± 62.4 (228.5–454)	326.8 ± 105.4 (108–552)	0.1
CST (repetitions)		9.4 ± 2.9 (5–15)	8.8 ± 2.8 (4–15)	0.4
WOMAC		48.7 ± 12.9 (23–74)	43.9 ± 13.6 (18–70)	0.09
KL grade	I	0 (0)	1 (2.4)	0.2
	II	6 (14.6)	13 (31.7)	
	III	22 (53.7)	17 (41.5)	
	IV	13 (31.7)	10 (24.4)	

Results are presented as mean ± SD or median (range) and n(%). KOA: knee osteoarthritis, BMIs: body mass index, 6MWT: 6 min walk test, CST: Chair stand test, WOMAC: Western Ontario and McMaster Universities Osteoarthritis. KL: Kellgren-Lawrence. Bold values are significant at p < 0.05.

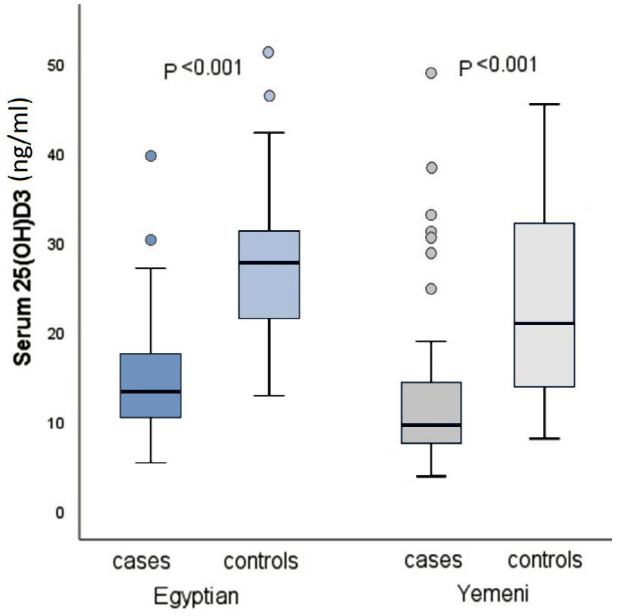

Fig. 1. Serum vitamin D level in primary knee osteoarthritis (KOA) Egyptian and Yemeni patients and their corresponding control.

Serum 25(OH) D level significantly negatively correlated with KL radiographic grading of Egyptian (r = −0.3, p = 0.03) and Yemeni (r = −0.4, p = 0.02) patients. In Yemeni patients, 25(OH)D significantly correlated with WOMAC (r = −0.3, p = 0.03), and 6MWT (r = 0.3, p = 0.03) (Table 4). The relationship of vitamin D level with physical function and radiographic grading in Egyptian and Yemeni KOA patients was further analysed using a multivariate linear regression and revealed no significant association to WOMAC, 6MWT or CST after adjustment for age, gender, BMIs and KL grading scale. In Yemeni patients, age (p < 0.001) was a significant independent predictor of physical performance (6MWT: p < 0.001 and CST: p = 0.002); furthermore gender was a significant predictor of 6MWT (p = 0.003). There was a significant relation of age and vitamin D level with KL grading in Egyptian (p = 0.01 each) and Yemeni patients (p = 0.004 and p = 0.005 respectively). The multivariate regression to detect independent predictors of primary KOA revealing that aside of age, gender and BMIs, serum 25(OH)D level was the only significant predictor in Egyptian (OR = 0.8, p < 0.0001) and Yemeni (OR = 0.9, p = 0.001) patients.

4. Discussion

In the present study, primary KOA patients exhibited significantly lower levels of serum 25(OH) D compared to controls, which is in accordance with Al-Jarallah et al. [17], Cakar et al. [18], and Baskan et al. [19] who reported that there is a high prevalence rate of vitamin D deficiency in primary KOA patients. Furthermore, Bassiouni et al. [20] and Veronese et al. [21] reported a significant decrease in 25(OH) D serum levels in KOA patients and noted that medial meniscal deterioration was observed in patients with low vitamin D levels.

The present results demonstrated that among various confounders implicated in the development of primary KOA, serum 25(OH) D level was the only significant predictor of primary KOA. The relationship between vitamin D deficiency and the development of primary KOA could be attributed to the fact that on one hand changes in subchondral bone plays an essential role in the onset and progression of cartilage lesions, and on the other hand normal bone and cartilage metabolism depends on the presence of normal vitamin D level, thus, low serum 25(OH) D level has adverse effects on bone and cartilage metabolism including osteoblastic activity, calcium metabolism, matrix ossification, bone density, and cartilage turnover [22].

Table 3
Comparison between mild and severe KL grading scale in Egyptian and Yemeni knee osteoarthritis (KOA) patients.

Parameter	KL grading in KOA patients (n = 41 each)					
	Egyptians			Yemeni		
	Mild (n = 6)	Severe (n = 35)	p	Mild (n = 13)	Severe (n = 28)	p
Age (years)	52.7 ± 5.3 (47–61)	53.6 ± 7.4 (45–75)	1	53.3 ± 7.7 (45–70)	57.7 ± 7.1 (48–75)	0.08
BMIs	29.4 ± 5.1 (23.3–35.5)	30.4 ± 4.71 (21–38.6)	0.6	29.1 ± 4.1 (22.6–37.8)	28.2 ± 3.9 (20–35.6)	0.6
s 25(OH)D (ng/ml)	22.3 ± 11.1 (9.1–39.6)	13.5 ± 4.4 (5.3–27.1)	0.05	18.5 ± 10.9 (6.1–38.4)	11.2 ± 8.9 (3.8–49)	0.02

Results are presented as mean ± SD (range). KL: Kellgren-Lawrence, KOA: knee osteoarthritis, BMIs: body mass index. Bold values are significant at p < 0.05.

Table 4
Correlations of serum 25(OH)D level in Egyptian and Yemeni knee osteoarthritis (KOA) patients.

Parameters p (r)	25(OH)D in KOA patients (n = 41 each)			
	Egyptians		Yemeni	
Age	−0.2	(0.3)	−0.02	(0.9)
BMIs	−0.2	(0.3)	−0.1	(0.3)
PTH	−0.1	(0.4)	−0.2	(0.2)
6MWT	0.2	(0.2)	0.3	(0.03)
CST	0.2	(0.1)	0.2	(0.1)
WOMAC	−0.09	(0.5)	−0.3	(0.03)
KL grading	−0.3	(0.03)	−0.4	(0.02)

25(OH) D:25-hydroxyvitamin D, KOA: knee osteoarthritis, BMIs: body mass indices, PTH: parathyroid hormone, 6MWT: 6 min walk test, CST: Chair stand test, WOMAC: Western Ontario and McMaster Universities Osteoarthritis. KL: Kellgren-Lawrence. Bold values are significant at $p < 0.05$.

Low vitamin D levels have been found to increase osteoblastic activity and bone turnover of sub-articular bone by raising PTH levels, resulting in thickening of the subchondral bone, with subsequent osteophyte formation and cartilage damage [23]. Moreover, a pathophysiological role for vitamin D in KOA is sustained by the presence of VDRs on articular chondrocytes. Vitamin D, acting via VDRs, stimulates mature chondrocytes to synthesize proteoglycan matrix proteins which are necessary for maintaining cartilage health, and decrease MMP activity which in turn degrades cartilage. Therefore, vitamin D deficiency diminishes the synthesis of proteoglycan matrix proteins and increases MMP activity leading to cartilage degradation, which is the hallmark in KOA [24]. Additionally, VDRs signal caspase 9 production which an initiator caspase is leading to caspase 3 activation which is an effector caspase thus increasing nitric oxide production, which activates the caspase induced chondrocyte apoptosis [25].

Despite abundant sunshine in Egypt and Yemen, there was a significant evident hypovitaminosis D in Yemeni KOA patients compared to Egyptian patients which could be attributed to several factors including the clothing style where females wearing niqab comprised 11.4% of Egyptian KOA patients, while they comprised 94% of Yemeni patients. Niqab wearing which covers a large portion of the skin, when worn on a consistent and regular basis, limits the exposure to sunlight, thus decreasing the level of vitamin D in the body [26]. Moreover, there was significant increase in smokers' number in Yemeni patients, where smoking adversely affect vitamin D metabolism by impairing the 1α-hydroxylation of 25(OH) D to form 1, 25-OH_2D [27]. Also, environmental factors have a fundamental role in determining vitamin D status. This study setting took place at an altitude of about 2253 m (7392 ft) in Sana'a which is located very high in the mountains, whereas the altitude of Cairo is only about 23 m (75 ft). It is believed that there is a significant inverse association between altitude and serum vitamin D levels where insufficient intensity of sunlight at higheraltitudecausesvitamin D deficiency [28].

In the current study, a significant inverse relationship between serum levels of 25(OH) D and radiographic grading of primary KOA was found, furthermore, serum 25(OH) D levels were significantly lower in KOA patients with severe KL grading compared to those with mild KL grading, which is in agreement with Guleret al. [29], Lotfi et al. [30] and Malas et al. [22], who found that vitamin D deficiency is linked to radiological severity of KOA. Indeed, Zheng et al. [31] stated in a prospective study that patients with sufficient serum 25(OH) D levels showed significantly less loss of tibial cartilage volume.

Moreover, Ding et al. [32] documented that vitamin D insufficiency was associated with increased moderate to severe joint space narrowing in older adults. Similarly, Zhang et al. [9] conveyed that the risk of progression of radiographic KOA is significantly increased in vitamin D deficient patients. Recently, a moderate evidence of a positive correlation between vitamin D deficiency and progression of radiographic KOA was shown in a systematic review of 86 studies [10]. In addition, Arden et al. [33] found that daily supplementation of vitamin D for 3 years was associated with stability in the rate of knee joint space narrowing and worsening in the placebo group.

Current results are coinciding with the postulation that vitamin D deficiency is related to a significant cartilage loss and degradation which is explained by several mechanisms; firstly the Dickkopf-1 (DKK-1) protein factor expression in OA osteoblasts is significantly increased with vitamin D deficiency. Increased expression of DKK1 correlates with inflammatory cytokine levels e.g. interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) expressions, also correlates with proapoptosis regulators (e.g. caspase-3 expressions) in OA cartilage tissues, consequently increased expression of DKK1 contributes to cartilage deterioration, chondrocyte apoptosis and is a potent factor in OA pathogenesis. Hence vitamin D supplementation with subsequent attenuation to DKK1 may reduce cartilage deterioration in OA [34].

Secondly, vitamin D is considered as an immunoregulator. VDRs upon binding to 1, 25$(OH)_2$ D interacts with other nuclear hormone receptors, in particular the family of retinoid X receptors. This complex then binds to special DNA sequences called vitamin D response elements (VDREs). Activation of the VDREs in the promoter region of cytokine genes blocks transcription of nuclear transcription factors such as nuclear factor of activated T cells (NF-AT) and NF-κB. This interference blocks the cellular response to TNF-α and IL-1 and allows for the up regulation of Interleukin-10 (IL-10) which is an anti-inflammatory cytokine [35]. Thus vitamin D deficiency up regulates TNF-α and IL-1. IL-1is capable of inducing the expression of MMPs, aggrecanases, which allows for the degradation of collagens and cartilage degeneration [36].

Regarding physical function; there was no relationship between vitamin D level and physical function in Egyptian KOA patients, and in Yemeni KOA patients, multivariate linear regression analysis revealed that age and gender were the only significant predictors of physical performance, which is in accordance with Al-Jarallah et al. [17], Baskan et al. [19], and Jin et al. [37] who concluded that functional disability is not affected by vitamin D deficiency. Indeed, Hussain et al. [10] conducted a systematic literature review, concluding that all included randomized control trials showed no significant difference in physical performance on WOMAC scale in KOA patients upon vitamin D supplementation.

In contrast, Dang et al. [38], and Nascimento et al. [39] reported a linkage between vitamin D deficiency and poor physical performance, however these studies merely enrolled elderly adults with mean age $\geq$ 65 years, hence, it could not be conclusive whether this linkage was related to the ageing process itself or due to decrease in serum 25(OH) D levels, especially that in elderly there are numerous intermingling factors influencing physical function, among which is decrease in muscle strength, medical comorbidities, relative immobility, and malnutrition [40].

In summary, serum 25(OH) D level was significantly decreased in KOA patients and it was the only significant independent predictor of primary KOA, thus suggesting its central role. Yemeni KOA patients exhibited significantly lower levels of vitamin D compared to Egyptian patients, suggesting the impact of clothing style, smoking and environmental factors on serum vitamin D status. Serum 25(OH) D was significantly negatively related to radiographic severity with a significant decrease in its level among patients with severe KL grading, yet there was no relation between serum 25 (OH) D level and physical function scores. The relevant aspect of this study is that early detection and treatment of vitamin D deficiency may provide an opportunity for retarding the ongoing degenerative process of KOA, also this study highlights the fact that screening for hypovitaminosis D is fundamental even in sunny areas, where it is influenced by multifactorial elements among different ethnicities including different customs, cultures and environmental factors.

Among the study limitations are small sample size and the case control study design. Results need to be confirmed on a larger cohort of patients and a rather longitudinal follow up study could allow better assessment of the relation to radiographic progression.

In conclusion, there is an association between vitamin D deficiency and primary KOA; vitamin D deficiency was related to radiographic severity but not to physical function of primary KOA patients. Further research is recommended to clarify the role of vitamin D deficiency as a contributing risk factor of primary KOA and its impact on radiological severity, also screening for hypovitaminosis D as a part of the national health strategy is warranted.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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