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Association between vitamin D deficiency, inflammatory markers, and knee osteoarthritis: a retrospective study

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Abstract

Background Knee osteoarthritis (OA) is a prevalent condition influenced by various biochemical, anatomical, and lifestyle factors. Vitamin D deficiency has been implicated in OA, but its role in disease severity and associated symptoms remains unclear. We aimed to investigate the prevalence of vitamin D deficiency in knee OA patients and its relationship with inflammatory markers and clinical symptoms.

Methods This retrospective study analyzed 986 patients with knee OA over a 3.5-year period. Vitamin D levels, ESR, and platelet counts were assessed, along with demographic and clinical data. Statistical analyses were conducted to explore associations.

Result This study involved 986 patients with knee OA, majority of them (85%) were female with mean age 52.95 ± 12.44 years. More than half of patients 59.7% had unilateral knee OA and 40.3% had bilateral knee OA. The mean value of Vitamin D3 was 25.35 ± 14.125. Vitamin D deficiency was observed in 70.9% of patients, with moderate deficiency being most prevalent (36.94%). No significant association was found between vitamin D levels and inflammatory markers. However, a strong association was observed between vitamin D deficiency and symptoms like polyarthralgia ($p < .05$)., Bilateral OA was associated with higher vitamin D deficiency levels compared to unilateral OA ($P < .001$).

Conclusion OA more prevalence among female .As well as, vitamin D deficiency is highly prevalent in knee OA patients and its severity associated with Bilateral OA and polyarthralgia but not with inflammatory markers. Future research should focus on the long-term impact of vitamin D supplementation and the molecular mechanisms underlying these disparities.

Keywords Knee osteoarthritis, Vitamin D, Prevalence, Inflammatory markers, Yemen

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Introduction

Osteoarthritis (OA) is one of the most prevalent degenerative joint diseases worldwide, leading to chronic pain, stiffness, and significant disability in millions of individuals [1]. It primarily affects weight-bearing joints like the knees, hips, and spine, with knee OA being particularly common and debilitating. The Global Burden of Disease study in 2024 estimated that knee OA alone affects over 250 million people globally, underscoring the extensive public health impact of this condition [2]. Studies continue to illustrate the high prevalence of OA worldwide, with a greater burden among older individuals, women, some racial and ethnic groups, and individuals with lower socioeconomic status [3]. By 2030, the economic burden of OA is expected to double, highlighting the need for effective management strategies [2]. Vitamin D deficiency, defined as serum 25-hydroxyvitamin D levels below 25 nmol/L, is prevalent globally, particularly in regions like the Middle East, China, Mongolia, and India. High-risk groups include young children (especially low birth weight), adolescents, pregnant and lactating women, older adults, and non-Western immigrants. Adequate vitamin D levels (serum 25-hydroxyvitamin D > 50 nmol/L) are achieved by less than 50% of the global population, especially in winter. Prevention strategies include moderate sunlight exposure, eating fish, food fortification with vitamin D, and supplementation [4, 5]. However, research in this region is limited, underscoring the need for more comprehensive studies to clarify the role of vitamin D in OA incidence and severity [6].

While the exact pathogenesis of OA is multifactorial, involving genetic, environmental, and lifestyle factors, recent attention has focused on the potential role of vitamin D [7]. Widely recognized for its essential function in calcium and phosphorus regulation and bone health, vitamin D may also influence joint health due to its anti-inflammatory properties and potential effects on cartilage integrity [8]. Additionally, vitamin D receptors (VDRs) are found in various tissues beyond bone, including immune cells, suggesting that vitamin D may exert systemic effects that could impact OA progression [9]. Vitamin D may play a role in cartilage health, regulates calcium and phosphorus, which are crucial for healthy bones and cartilage. It also has anti-inflammatory properties that could help protect the joints from damage. Moreover, as vitamin D receptors have been found in various tissues such as the prostate, brain, breast, pancreas, colon, and immune cells; vitamin D also has non-skeletal effects. It can impact immune function and regulate cell proliferation and differentiation in different cell types including lymphocytes, endothelial cells, osteoblasts, and keratinocytes [10].

The relationship between vitamin D and knee OA is supported by evidence linking vitamin D deficiency with higher inflammatory markers, oxidative stress, and cartilage degradation [11]. Vitamin D supplementation has shown modest symptomatic benefits, particularly in pain and stiffness reduction, but there is limited evidence supporting its use for structural improvement in OA. Population-specific factors, such as regional prevalence rates, lifestyle, and dietary practices, further complicate the interpretation of vitamin D's role in OA. As such, vitamin D may be most beneficial as an adjunct therapy in a multi-faceted approach, especially for populations at risk of deficiency and high OA incidence.

Despite its theoretical benefits, the relationship between vitamin D deficiency and OA remains inconclusive. Some studies have reported a higher prevalence of vitamin D deficiency among OA patients, especially those with knee OA, as well as associations between low vitamin D levels and increased pain and functional impairment [12]. However, findings on vitamin D supplementation as a treatment for OA are inconsistent, with certain studies observing symptomatic improvements while others report minimal or no effect [10]. Factors that have been associated with an increased risk of knee osteoarthritis include older age, female sex, overweight or obesity, knee injury, occupational factors (e.g., knee bending, heavy lifting, and squatting), and varus or valgus alignment. Risk is not increased with recreational physical activity [13].

In this retrospective study, we focused on analyzing specific laboratory markers, including vitamin D levels, ESR, and platelet count, to evaluate their relationship with knee osteoarthritis. Additionally, we collected extensive patient data to prepare for a subsequent study, which will compare the outcomes of intra-articular injections among four groups to provide a comprehensive understanding of treatment efficacy and their potential effects on the selected laboratory markers.

There is a significant shortage of studies and statistical data regarding the relationship between osteoarthritis (OA) and vitamin D in Yemen, making it challenging to draw definitive conclusions from existing research. Additionally, the optimal dose of vitamin D for OA management is still unknown. In clinical practice, there is an increase in the number of osteoarthritis cases associated with vitamin D deficiency, which we encounter daily in hospitals and outpatient departments. Therefore, it is essential to conduct further research to fully understand the effects of vitamin D and its potential benefits for preventing or managing OA, as well as to develop knowledge and raise awareness about knee osteoarthritis.

Methodology

This was a retrospective study conducted over 3.5 years (May 2021–September 2024) at private outpatient clinics in Sana'a, Yemen. We assessed 2,500 patients with knee

pain, out of which 986 met the inclusion criteria for knee OA diagnosis. Diagnosis was based on clinical evaluation, radiographic evidence, and laboratory markers, including CBC, ESR, platelet counts, and vitamin D levels.

Sample size included adults aged 30 years and older, diagnosed with OA based on American College of Rheumatology criteria. Patients with incomplete data, chronic inflammatory diseases, or previous knee surgeries were excluded. Statistical analyses were performed using SPSS 26, employing, T-test, ANOVA test and chi square test to identify associations between vitamin D and inflammatory markers.

Blood samples were collected in the afternoon (between 3:00 PM and 7:00 PM). Three ml blood sample was collected on tubes with clot activator and gel to get serum for Vitamin D measurement, two ml of blood was collected on K3EDTA tubes for measurement of platelets, and 1.6 ml of blood was collected on sodium citrate tubes for measurement of ESR. The time between sample collection and analysis did not exceed 1 h. We used the in vitro chemiluminescence immunoassay for the quantitative determination of 25-OH Vitamin D in samples using the MAGLUMI 800 fully-auto chemiluminescence immunoassay analyzer. Inflammatory markers(ESR, platelets count) were measured using ESR Fast Detector that match 1.6 ml, 9 × 120 mm ESR tubes, and Hemaray 83 (5-part hematology analyzer) respectively.

We classified into subgroups based on their vitamin D status, age, and inflammatory markers. Giustina A, adler et, al (2019) which reported the 25-hydroxyvitamin D concentrations between 20 and 50 ng/mL (50 to 125 nM) appear to be safe and sufficient for skeletal health in the healthy general population [14, 15]. A vitamin D status can be considered adequate (serum 25-hydroxyvitamin D > 50 nmol/L) (Van Schoor, 2024) [4].

Results

Nine hundred and eighty- six (986 patients) who met the criteria for our study and were confirmed to have knee osteoarthritis. In this retrospective study, we focused on analyzing specific laboratory markers, including vitamin D levels, ESR, and platelet count, to evaluate their relationship with knee osteoarthritis. The majority of patients 85% were female gender, while only about 14.6% of them were male gender. The minimum age was 30 years, the maximum age was 100 years, the median age 50 years and 52.95 ± 12.44 years. More than half of patients 59.7% had unilateral knee OA and 40.3% had bilateral knee OA. The mean value of Vitamin D3 was 25.35 ± 14.125, the mean value of ESR was 24.56 ± 16.55 and the mean value of platelets was 271.59 ± 66.48. one fifth (20%) of patients had insufficient vitamin D3, 29% had mild deficiency, one-third (33%) had moderate deficiency and 3.7% had sever deficiency, while only 4.2% of them had normal values of vitamin D3. See Table 1 for more details.

Table 1 Sociodemographic characteristics of the patients

Variables		Frequency	Percentage
Sex	Male	144	14.6
	Female	842	85.4
	Total	986	100.0
Age Mean ± SD = 52.95 ± 12.44	30–40 years	198	20.1
	41–50 years	310	31.4
	51–60 years	249	25.3
	> 60 years	229	23.2
	Total	986	100.0
Site of Knee OA	Bilateral knee OA.	589	59.7
	Unilateral knee OA	397	40.3
	Total	986	100.0
Vitamin D3 Level Mean ± SD = 25.35 ± 14.12	Normal > 50 (nmol/L)	41	4.2
	Insufficient 30–50 (nmol/L)	201	20.4
	Mild deficiency 30 – 20 (nmol/L)	287	29.1
	Moderate deficiency 20 – 10(nmol/L)	331	33.6
	Sever deficiency < 10 (nmol/L)	36	3.7
	Total	896	90.9
Platelets		Mean ± SD = 52.95 ± 66.48	
Erythrocyte Sedimentation Rate (ESR)		Mean ± SD = 24.56 ± 16.55	

SD: **Standard deviation**

Table 2 Demonstrates distribution of cases regarding associated complications

Associated Symptoms/Diseases	Frequency	Percentage
LUMBAGO	356	36.1%
Neck spasm	197	20.0%
Polyarthralgia	66	6.8%
Planter fasciitis	37	3.8%
Lumber spondylitis	27	2.7%
Lumbar and Sacrum herniation	61	6.2%
Cervical herniation	12	1.2
Lumbar disc herniation	17	1.7%
Lumbosacral spondylolisthesis	15	1.5%
Cervical spondylitis	12	1.2%
Hip OA	8	0,8%
Carpal tunnel syndrome	2	0.2%
Others	13	1.3%

Associated symptoms/diseases

Table 2 shows that the highest associated Symptoms/Diseases was LUMBAGO by 36% of patients, followed by neck spasm by 20%, then polyarthlagia by 6.8%, planter facilities by3.8% lumbar and sacrum herniation by 6.2% and lumber spondylitis by 2.7%, while other Symptoms/Diseases were less frequenting.

Association between side of knee OA and vitamin D3 measurements

Table 3 shows that there was a strong statistically association between side of knee OA and vitamin D3 measurements of p. value of < 0.001 by one-way ANOVA test. there was no significant statistically association between side of knee OA and ESR measurements by one-way-ANOVA test. Lastly no significant statistically association between side of knee OA and platelets measurements by one-way- ANOVA test.

Association B/n vitamin D3 severity measurements & other variables

Table 4 shows that there was no significant association between Vitamin D3 levels and age or gender. A strong association was found between the side of knee OA and Vitamin D3 levels ($p < .001$), with bilateral OA associated with higher vitamin D3 levels deficiency. As well as severity of Vitamin D3 deficiency was associated with polyarthralgia ($p = .029$).

Discussion

Over a three-and-a-half-year period (May 2021–September 2024), 2,500 patients with knee pain were assessed for knee osteoarthritis (OA) through detailed medical history, clinical examination, laboratory investigations and assessment through X-ray imaging. Of these, 986 patients met the inclusion criteria for this retrospective study. When data collecting and analyzing we were focused on specific laboratory markers, including vitamin D levels, ESR, and platelet count, to evaluate their relationship with knee osteoarthritis. The findings reveal a high prevalence of vitamin D deficiency among patients with knee OA, which aligns with previous research but also highlights unique demographic and clinical correlations.

Our study found that 70.9% of patients with knee OA had some level of vitamin D deficiency, with moderate deficiency (10–20 nmol/L) being the most common. This resuts align with many studies like Tekeli et al. (2024) reported a 49.2% prevalence of vitamin D deficiency among knee OA patients [16]. Similarly, the research by Elbashir et al.(2023) reported vitamin D deficiency in 58% of patients with knee OA [1]. Additionally, Zhang et al. (2014) suggested that individuals with lower vitamin D levels faced more than double the risk of knee OA progression [17].

Sakr et al. (2021) found that Yemeni patients had significantly lower levels of 25(OH)D compared to Egyptian patients. They suggested that this discrepancy may be linked to lifestyle factors, such as increased niqab wearing and higher smoking rates. However, this study presents a different argument, as all Yemeni females wear the niqab, which means the results did not account for the varying amounts of sun exposure among Yemeni women, particularly in specific areas of their homes, such as near windows or in yards. Additionally, the study did not differentiate between rural and urban residences [18]. Several studies in many countries which that the clothing style where females don't wear niqab have knee osteoarthritis. However, many studies aligns with current study [10, 19, 20, 21, 16, 22, 18].

Women accounted for 85% of our cases, with the most affected age group being 41–50 years. Hormonal changes post-menopause, as noted by Segal et al. (2024), significantly contribute to the prevalence and severity of osteoarthritis (OA). Hernandez et al. (2024) highlighted anatomical and hormonal factors, such as gait, joint alignment, and cartilage volume, as contributing to sex differences in OA prevalence and symptom severity [22]. Women with symptomatic knee OA may exhibit enhanced central sensitivity compared to men, although the underlying mechanism remains unknown [23]. MRI findings from studies, such as those conducted by Hyuksoo, et al., indicate that differences in cartilage volume between sexes may begin in adolescence, impacting OA risk later [24]. However, study by Zhou et al., that reported the vitamin D's role in OA is limited compared to other risk factors for OA are confirmed, including sleep deprivation, advanced age, female and high body mass index (BMI).

In current study, we found that there were no significant relations between the prevalence of knee

Table 3 Association between side of knee OA with vitamin D3 measurements, ESR and platelets counts measurements

Side	*N*	Mean	SD	Minimum	Maximum	*P*. value
Association between side of knee OA and vitamin D3 measurements						
Unilateral	**589**	**23.63**	**12.850**	**5**	**150**	**< 0.001***
Bilateral	**397**	**28.34**	**15.639**	**5**	**150**	
Association between side of knee OA and ESR measurements						
Unilateral	**536**	**24.57**	**16.697**	**4**	**100**	0.989
Bilateral	**353**	**24.55**	**16.352**	**3**	**98**	
Association between side of knee OA and platelets counts measurements						
Unilateral	**552**	**272.44**	**67.035**	**82**	**596**	0.635
Bilateral	**366**	**270.30**	**65.698**	**93**	**489**	

*: Ssignificant, SD: Standard deviation

Table 4 Association B/n vitamin D3 severity measurements and other variables

Variables	Vitamin D3 deficiency measurements						*P*. value
	Normal	Subnormal	Mild	Moderate		Sever	
	Row *N*%	Row *N*%	Row *N*%	Row *N*%		Row *N*%	
Gender	Male	3.2%	24.0%	36.8%	34.4%	1.6%	0.385
	Female	4.8%	22.2%	31.3%	37.4%	4.4%	
Age categories	30–40 y	3.9%	24.0%	34.6%	31.3%	6.1%	0.293
	41–50y	4.3%	20.1%	30.2%	40.3%	5.0%	
	51–60 y	4.4%	19.7%	35.1%	38.2%	2.6%	
	> 60 y	5.7%	27.0%	28.9%	36.0%	2.4%	
Side of knee OA	Unilateral	2.5%	17.9%	34.3%	39.6%	5.7%	**< 0.001***
	Bilateral	7.5%	28.8%	28.8%	33.2%	1.6%	
LUMBAGO	Yes	5.8%	21.0%	30.4%	37.7%	5.2%	0.493
	No	3.4%	25.4%	30.5%	36.9%	3.8%	
Neck Spasm	Yes	2.2%	20.0%	30.0%	41.1%	6.7%	0.092
	No	6.0%	24.2%	30.5%	35.7%	3.6%	
Polyarthralgia	Yes	8.2%	31.1%	21.3%	29.5%	9.8%	**0.029***
	No	4.4%	21.8%	31.5%	38.3%	4.0%	
Plantar Fasciitis	Yes	5.9%	35.3%	20.6%	35.3%	2.9%	0.411
	No	4.7%	22.0%	31.1%	37.5%	4.7%	
Lumbar spondylosis	Yes	3.8%	19.2%	42.3%	30.8%	3.8%	0.770
	No	4.8%	23.0%	29.9%	37.7%	4.6%	
Lumbar and sacrum disc herniation	Yes	1.9%	30.8%	34.6%	32.7%	0.0%	0.210
	No	5.1%	22.0%	30.0%	37.8%	5.1%	
Cervical disc herniation	Yes	0.0%	40.0%	40.0%	10.0%	10.0%	0.310
	No	4.9%	22.5%	30.3%	37.8%	4.5%	
Lumbar disc herniation	Yes	6.3%	25.0%	31.3%	37.5%	0.0%	0.853
	No	4.7%	22.8%	30.4%	37.3%	4.7%	
Lumbosacral Spondylolesthesis	Yes	0.0%	23.1%	23.1%	53.8%	0.0%	0.103
	No	4.9%	22.8%	30.6%	37.0%	4.7%	
cervical spondylosis	Yes	0.0%	8.3%	16.7%	75.0%	0.0%	0.103
	No	4.9%	23.1%	30.7%	36.5%	4.7%	
HIP O A	Yes	12.5%	25.0%	50.0%	12.5%	0.0%	0.439
	No	4.7%	22.8%	30.2%	37.7%	4.7%	
Carpal Tunnel Syndrome	Yes	0.0%	0.0%	100.0%	0.0%	0.0%	0.332
	No	4.8%	22.9%	30.2%	37.5%	4.6%	
****Others**	Yes	10.0%	20.0%	50.0%	20.0%	0.0%	0.527
	No	4.7%	22.9%	30.1%	37.7%	4.7%	

**Others List

– lumbago &osteoporosis

– protrusio acetabula and lumbago

– Acute DVT

– Osteoporosis

– coccydynia and lumbago

– Rotator cuff arthropathy

– SubTalar ankle OA

– spina bifida

– Shoulder tendonitis

***: Significant**

osteoarthritis (OA) and age. However, older female had higher OA. The observed differences may be attributed to sex differences in cartilage thickness and volume, as noted by Paula et al. (2024) [22]. Cui et al. reported a global knee OA prevalence of 16% among individuals aged 15 + years, which increased to 22.9% among those aged 40 years and older [25]. Additionally, Jones et al. measured knee cartilage thickness in children aged 9 to 18 years and found that boys had 16–31% more cartilage volume compared to girls, with the most significant

differences observed at the medial tibial site, even after adjusting for age, body mass index, bone area, and physical activity.

The minimum age in our study was 30 years, the maximum age was 100 years, with mean age 52.95 ± 12.44 years. Tripathy et, al,.(2020). demonstrated significantly lower vitamin D levels in younger patients with osteoarthritis (OA) of the knee compared to healthy individuals [26]. The study by Heidari et al. (2011) indicated a significant association between serum 25-hydroxyvitamin D (25-OHD) deficiency and knee OA in patients aged < 60 less than and years. It suggests serum 25-OHD measurement in any patient with symptoms suggestive of knee OA particularly at the initial stage of disease [20]. Study from India reported an overall prevalence of knee OA of 28.7%, with factors such as female gender, obesity, age, and sedentary work being associated with a higher prevalence [27]. Bakılan et al., (2022), showed that the mean age of one hundred and thirty-six (136) patients had knee OA was 60.85 ± 10.02. In 2011 Thailand study by Kim et al. they found 35.4% high prevalence of knee OA in elderly population, especially in females and those with a higher BMI [21].

The inferential analysis revealed no significant association between ESR and platelets count in relation to knee OA, These results are consistent with the findings of Bakılan and Ortanca (2022), who reported that ESR, reactive protein (CRP), and platelet-to-lymphocyte ratios are not reliable markers for low-grade inflammation in knee OA [28]. Conversely, Amirkhizi et al. identified vitamin D deficiency as a potential contributor to elevated inflammatory markers, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), suggesting possible methodological differences in the assessment of inflammatory markers [29].

Systematic reviews, including those conducted by Georgescu et al. (2024), confirm a connection between vitamin D levels and osteoarthritis (OA), but they emphasize the mixed findings across various studies. These reviews indicate that, while there is evidence linking vitamin D to improved inflammation control and symptom reduction, definitive conclusions regarding its role in structural preservation and functional outcomes in OA remain elusive [30].

In terms of knee involvement, the majority of patients ($n = 589$) exhibited unilateral knee osteoarthritis (OA). In addition, our study revealed a significant relationship between severity of vitamin D deficiency and bilateral OA with a p-value of < 0.001. A study in Saudi Arabia by Elbasheer et al. (2023), reported that bilateral knee OA was predominant in 79% of cases.

The severity of vitamin D3 deficiency was associated with polyarthralgia. These results align with the study by Baral et al., which demonstrated that patients with polyarthralgia who had serum levels of 25-(OH)D below the optimal range experienced significant improvement in their symptoms following vitamin D supplementation [31].

Praveen N. (2020) identified a correlation between chronic low back pain and vitamin D deficiency in Indian populations, which is consistent with the high prevalence of lumbago observed in our study [32]. The elevated incidence of neck spasms and polyarthralgia also underscores the association with lower levels of vitamin D. These findings suggest that vitamin D may enhance muscle function, as concluded by several meta-analyses [33, 34, 35]. Furthermore, Giustina et al. (2019) reported on observational studies indicating that the association between lower levels of 25-hydroxyvitamin D and an increased risk of falls and fractures may be linked to muscle dysfunction [14].

A systematic review, including studies by Aloufi et al. (2024), confirms that many individuals with chronic pain have low levels of vitamin D; however, it remains unclear whether this deficiency is a causative factor for the pain. These reviews indicate that, in certain populations, lower vitamin D levels have been associated with more severe pain, potentially due to inflammation indicated by elevated inflammatory markers in specific cases. However, they results have been inconsistent, with some studies reporting no direct Correlation between vitamin D levels and persistent chronic pain [36].

Strengths and limitations of the study

This study analyzed data from 986 patients with confirmed knee osteoarthritis, offering robust statistical power and enhancing the reliability of the findings. By excluding incomplete or inconsistent data, the analysis was based on high-quality and reliable records. One of the strengths of this study is the targeted analysis of vitamin D deficiency, as patients were categorized into subgroups based on their vitamin D status, providing valuable insights into the potential role of vitamin D in osteoarthritis progression and its relationship with inflammation. However, there were some limitations that limits generalizability and introduces potential biases. Such as retrospective design, our efforts were made to mitigate this by excluding records with missing or incomplete data. Additionally, the absence of a healthy control group prevents direct comparisons to a baseline population without osteoarthritis. Furthermore, the study did not account for other factors such as intestinal malabsorption syndromes, digestive alterations, joint malalignment, high-impact sports, and high-risk work activities, particularly since the participants were aged 30 and above. Additionally, selecting only patients from a private outpatient clinic may introduce significant bias, as this population might not represent the broader community.

Conclusion

This study confirms the high prevalence of vitamin D deficiency among patients with knee osteoarthritis (OA), with moderate deficiency being the most common. While no significant associations were found between vitamin D levels and inflammatory markers (ESR and platelets), a relationship was observed between vitamin D deficiency and symptoms like polyarthralgia and bilateral OA. Gender and age differences in knee OA prevalence are evident, with women, particularly post-menopausal, being disproportionately affected. Regular screening for vitamin D deficiency in patients with knee osteoarthritis (OA) is crucial, particularly for women and older adults. To better understand the relationship between vitamin D and OA, longitudinal studies should be conducted to evaluate both the dosage and long-term effects of vitamin D supplementation on the structural progression of OA. Additionally, it is important to investigate the role of lifestyle factors, such as physical activity and joint load, in the development of knee OA across various age groups. Promoting awareness about the significance of sunlight exposure and dietary sources of vitamin D is essential, aiming to maintain vitamin D levels in the normal range above 50 nmol/L. Finally, developing community-based interventions can help reduce OA risk factors, including obesity and sedentary lifestyles.

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Author contributions
KS, MS, GAAM and MAS conceptualized the research. KS, MS, GAAM and MAS participated in data col-lection and writing the methods. KS, MS, GAAM and MAS analyzed and interpreted the data. KS, MS, GAAM and MAS drafted the original manuscript. All the authors critically reviewed the manuscript and approved it for publication. All authors contributed equally to this work. Authors' contributions.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study approved by IRB faculty of Medicine, Sana'a University. Written consent obtained from participants after informed them about the study's aim, and maintained confidentiality during data collection. Participants had the freedom to withdraw without coercion, and no individual information was shared with third parties. All protocols in this study were done according to the Declaration of Helsinki (1964).

Competing interests
The authors declare no competing interests.

Consent for publication
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