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ABOUT COVER

Peer reviewer of *World Journal of Orthopedics*, Dr. Milan Kravarski is an Orthopedic and Trauma Surgeon and Practicing Consultant in the Canton of Nidwalden-Hospital (Stans, Switzerland). Having received his medical diploma from Medical Faculty of University of Belgrade (Serbia) in 2003, he passed the recognition exams of medical diploma for EU at the University of Ljubljana (Slovenia) in 2011. He received his medical diploma from the University of Bern (Switzerland) in 2013. Dr. Kravarski undertook his postgraduate training at the University Hospital of Bern as well as in several other canton, regional and city hospitals throughout Switzerland. His professional interests involve pathology and traumatology of the foot and ankle, and hip joint. Treatment of the diabetic foot as well as ultrasonography and traumatology of the musculoskeletal system complete his professional portrait. (L-Editor: Filipodia)

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ORIGINAL ARTICLE

Basic Study

Association of vitamin D and knee osteoarthritis in younger individuals

Sujit Kumar Tripathy, Amrit Gantaguru, Saurav Narayan Nanda, Sandeep Velagada, Anand Srinivasan, Manaswini Mangaraj

ORCID number: Sujit Kumar Tripathy 0000-0003-0179-9910; Amrit Gantaguru 0000-0003-2413-9851; Saurav Narayan Nanda 0000-0002-5706-377X; Sandeep Velagada 0000-0003-2441-3910; Anand Srinivasan 0000-0002-0663-0922; Manaswini Mangaraj 0000-0003-0179-9912.

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Sujit Kumar Tripathy, Amrit Gantaguru, Saurav Narayan Nanda, Sandeep Velagada, Department of Orthopaedics, All India Institute of Medical Sciences, Bhubaneswar, Bhubaneswar 751019, Odisha, India

Anand Srinivasan, Department of Pharmacology, AIIMS Bhubaneswar, Bhubaneswar 751019, Odisha, India

Manaswini Mangaraj, Department of Biochemistry, AIIMS Bhubaneswar, Bhubaneswar 751019, Odisha, India

Corresponding author: Sujit Kumar Tripathy, DNB, MBBS, MD, Associate Professor, Department of Orthopedics, All India Institute of Medical Sciences, Bhubaneswar, Sijua, Patrapada, Bhubaneswar 751019, Odisha, India. sujitortho@yahoo.co.in

Abstract

BACKGROUND

The incidence of primary osteoarthritis knee is gradually increasing among young individuals. The increasing prevalence of obesity, sedentary lifestyle, sporting activity, and vitamin D deficiency (VDD) has been hypothesized for this shifting disease trend. This study was designed to look for the association of serum vitamin D among these young arthritic patients.

AIM

To look for the association of serum vitamin D in younger knee osteoarthritis (KOA) patients.

METHODS

In a 2-year observational study, 146 non-obese KOA patients of 35-60 years were evaluated clinically (Knee injury and Osteoarthritis Outcome Score, KOOS) and radiologically (Kellegren-Lawrence stage, KL). The serum 25(OH)D level of these patients and 146 normal healthy individuals of same age group were estimated.

RESULTS

Both the groups were comparable in terms of age and sex. The average serum 25(OH)D level in healthy individuals and KOA patients was 45.83 ng/mL and 34.58 ng/mL, respectively ($P < 0.001$). Inadequate serum 25(OH)D level (< 30 ng/mL) was found in 46.57% of KOA patients and 24% of normal healthy

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participants indicating a significant positive association (odds ratio 2.77, 95%CI: 1.67-4.54, $P < 0.001$). The 25(OH)D level in KL grade I, II, III and IV was 43.40, 30.59, 31.56 and 33.93 ng/mL respectively (no difference, $P = 0.47$). Similarly, the KOOS score in sufficient, insufficient and deficient groups were 65.31, 60.36 and 65.31, respectively (no difference, $P = 0.051$).

CONCLUSION
The serum 25(OH)D level is significantly low in younger KOA patients. However, the clinical and radiological severities have no association with serum vitamin D level.

Key Words: Degenerative disease; Early-onset arthritis; Cholecalciferol; Sunlight; Knee joint; Arthroplasty; Knee replacement

Core Tip: The association of vitamin D deficiency in young knee osteoarthritis (KOA) patients were studied. Serum 25(OH)D level of young KOA patients and healthy individuals were estimated along with clinical and radiological severity assessment of KOA patients. Serum vitamin D level in healthy individuals and KOA patients were found to be 45.83 and 34.58 ng/mL, respectively; 46.57% of KOA patients had inadequate vitamin D compared to 24% healthy participants (odds ratio 2.77, $P < 0.001$). The clinical and radiological severities had no association with vitamin D. Although disease severity cannot be predicted from vitamin D level, it is significantly low in younger KOA patients.

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INTRODUCTION

Knee osteoarthritis (KOA) is a common musculoskeletal problem worldwide affecting 3.8% of the world's population[1,2]. The prevalence of KOA is similar across the globe; however, it is expected to increase dramatically in low and middle-income nations[3]. KOA generally progresses with age, and is usually seen after 50 years; however recently, it has been increasingly noticed in younger individuals. KOA and its associated symptoms such as pain, swelling, and stiffness impair the health-related quality of life (HRQOL), thereby causing a substantial direct and indirect economic burden[3]. The increasing prevalence of obesity, sedentary lifestyle, sporting activity, and vitamin D deficiency (VDD) is attributable to this shifting disease trend[3,4].

Many observational and longitudinal studies across the world reported a higher prevalence of KOA and increased risk of disease progression in vitamin D deficient patients[5-13]. However, few studies contradicted this association[14-20]. A recent review by Vaishya *et al*[20] reported that there was moderate evidence of a positive association between VDD and progression of radiographic OA (ROA). They reported limited evidence for a positive correlation between VDD and cartilage volume loss. There was also limited evidence of cartilage regeneration and relief of knee pain with vitamin D supplementation[20]. Most research on the progression of KOA in vitamin D deficient patients are based on older individuals[20-22], and no study has evaluated the association of vitamin D deficiency in younger KOA patients. Heidari *et al*[14] observed significant vitamin D deficiency among young KOA patients who were below 60 years of age, but they could not notice this association in elderly patients. With the rising incidence of younger adults suffering from KOA, this study was designed to determine if there was an association between VDD and KOA in younger individuals. The effect of the severity of the deficiency was correlated with the clinical and radiological severity of the disease.

MATERIALS AND METHODS

In a case-control study (study duration 2 years, August 2016 to August 2018), all patients between 35 and 60 years of age, who presented with knee pain and were diagnosed with primary OA knee, were evaluated for vitamin D deficiency. Similarly, healthy individuals in the same age group were also evaluated for serum vitamin D level for comparison. Primary OA knee in young patients was diagnosed clinically (using American College of Rheumatology criteria) and radiologically using X-ray and magnetic resonance imaging (in doubtful cases). For inclusion in this study, the patients must have a body mass index (BMI) of < 30 kg/m^2. The patients with inflammatory arthritis, chronic diseases, previous surgery or trauma to the knee joint, systemic debilitating diseases or limitation of physical activities, and on vitamin D supplementation were excluded. Approval of the institutional ethics committee was obtained prior to patient recruitment (project code T/IM-F/Ortho/15/16).

The KOA patients were evaluated clinically (swelling, tenderness and range of motion, Knee injury and Osteoarthritis Outcome Score [KOOS]) by an orthopedic surgeon[23]. The anteroposterior and lateral radiographs of the knee joints were taken, and disease severity was categorized by Kellegren-Lawrence stage. The blood parameters such as intact parathyroid hormone (iPTH) (reference 12-88 pg/mL), alkaline phosphatase (ALP) (9-116 IU/L), and 25(OH)D (30-100 ng/mL) levels in the patient and the control groups (healthy individuals within the same age group and BMI) were analyzed using standard methods. In addition, erythrocyte sedimentation rate (ESR, 0-20 mm/h), C-reactive protein (< 5 mg/L), total serum calcium, ionized calcium, urea, creatinine, phosphorous, total protein, and albumin levels were measured with the standard autoanalyzer. Serum vitamin D level of > 30 ng/mL was considered sufficient, 20-30 ng/mL insufficient, and < 20 ng/mL deficient. The demographic profiles, clinical and radiological findings and serum vitamin D level were entered into a predesigned proforma.

Statistical analysis was done using SPSS 20 version software. Descriptive statistics were used to determine the mean, median, and standard deviation. The patients were grouped based on age, sex, religion, nativity (rural/semi-urban/urban), and socioeconomic status. The association of vitamin D deficiency and knee OA was evaluated using the chi-square test with calculation of odds ratio (OR) and 95% confidence interval (95%CI). The independent effect of serum vitamin D deficiency was determined after adjustment for age, sex, and socioeconomic status using logistic regression analysis. The radiographic and functional severity of OA was correlated with vitamin D level (normal, insufficiency and deficiency) in these patients.

The sample size was determined with a confidence level of 95% and power of 80% to detect 15% difference in the proportion of vitamin D deficiency between KOA patients and controls at a significance level of 0.05%. Considering a 30% VDD in the general population of this study, 146 subjects were needed for each group.

RESULTS

The average age of normal healthy individuals and OA knee patients was 49.42 years and 51 years, respectively (P = 0.07). The numbers of male and female patients in the KOA group were 60 and 86 respectively, and it was not significantly different from the healthy individual group (male 68, female 78). The serum calcium (mean 9.4 mg/dL, range 8.5-10.3 mg/dL), iPTH, and albumin levels were within normal limits in all patients and healthy individuals. The average serum vitamin D level in normal healthy individuals was 45.83ng/mL. However, the average serum vitamin D level in OA knee patients was significantly low (34.58 ng/mL, P < 0.001); this indicated a relative vitamin D deficiency in KOA patients (Table 1).

There was no difference in the number of vitamin D deficient patients in both groups (P > 0.05). However, 68 patients (46.57%) in the KOA group and 35 participants (23.97%) in the healthy group had inadequate serum vitamin D (serum vitamin D level of < 30 ng/mL, includes both vitamin D deficient and insufficient individuals). There was a statistically significant positive association between inadequate vitamin D level and KOA (odds ratio 2.77, 95%CI: 1.67-4.54, P < 0.001, chi-square test, Table 2). The odds of developing KOA in inadequate vitamin D patients were 2.77 times higher than healthy individuals. By using logistic regression analysis for age, sex and socioeconomic status, the odds ratio was found to be 2.84 (CI: 1.63-4.90, P < 0.001).

The vitamin D level in Kellegren-Lawrence grade I, II, III and IV were 43.40, 30.59, 31.56 and 33.93 ng/mL respectively; there was no significant difference in vitamin D

Table 1 Comparison of various parameters between control (*n*1 = 146) and osteoarthritis (*n*2 = 146) patients with details of their vitamin D status as per radiographic disease severity and residency

Sl. No	Parameter	Control	Cases	*P* value
1	Age	49.42 (5.57)	51.00(6.67)	0.07
2	Sex			
	Male	68	60	0.41
	Female	78	86	
3	Vitamin D	45.83 (21.30)	34.58 (21.76)	< 0.001
Sl. No	**Parameter**	**Number**	**Vitamin D level**	***P* value**
1	Disease severity based on X-ray			
	I	35	43.40 (25.30)	0.47
	II	44	30.59 (16.23)	
	III	38	31.56 (17.78)	
	IV	29	33.93 (26.79)	
2	Residence			
	Village	102	35.40 (19.87)	0.42
	Semi-urban	13	31.61 (28.72)	
	Urban	31	34.24 (26.21)	

Table 2 Odds ratio for vitamin D deficiency in knee osteoarthritis patients

Vitamin D status	Cases (OA patients)	Control	Odds ratio (95%CI)	*P* value (Chi-square test)
Below normal (deficient and insufficient)	68	35	2.77 (1.67-4.54)	< 0.001
Adequate (sufficient)	78	111		

OA: Osteoarthritis.

level as per disease severity (radiological) in OA knee patients (P = 0.47). Also, there was no difference in vitamin D level between patients of urban dwellers (34.24 ng/mL) and village dwellers (35.40 ng/mL, Table 1). Subgroup analysis of vitamin D level with disease severity on x-ray did not show any significant difference (Table 3). The clinical severity of the KOA patients had a positive association with the radiological severity (Kellegren-Lawrence grade, Table 3). The patients with early OA had KOOS score of 80.05, whereas the patients with advanced OA had significantly (P < 0.001) low KOOS score (50.70). The KOOS score was not significantly different in the OA patients when they were subcategorized as sufficient, insufficient and deficient as per their vitamin D level (Table 3). The clinical and radiological severity of OA knee did not correlate with the vitamin D level.

DISCUSSION

This study showed a significantly low vitamin D level in younger OA knee patients compared to healthy individuals. There were 47% OA knee patients with inadequate vitamin D, but only 24% of healthy individuals had inadequate vitamin D level. The odds of development of KOA were 2.77 times more in younger individuals with inadequate vitamin D compared to healthy individuals. We did not observe any association of severity of vitamin D deficiency with the clinical severity and radiological severity of KOA.

The exact role of vitamin D in bone metabolism and on chondrocytes has been previously studied[20,22]. Suboptimal levels of vitamin D have adverse effects on calcium metabolism, osteoblastic activity, matrix ossification, and bone mineral density. A direct effect of vitamin D metabolites on articular chondrocytes, subchondral bone

Table 3 The vitamin D status and the disease severity among the knee osteoarthritis patients

Vitamin D status	Disease severity on X-ray				*P* value
	I	II	III	IV	
Sufficient	27	22	17	12	0.07
Insufficient	4	9	11	9	
Deficient	4	13	10	8	
Parameter		KOOS Score			*P* value
Severity based on X-ray findings					
Early (KL grade I, II)		80.05 (9.30)			< 0.001
Advanced (KL grade III, IV)		50.70 (14.71)			
Severity based on vitamin D level					
Sufficient		65.31 (18.58)			0.051
Insufficient		60.36 (19.61)			
Deficient		65.31 (18.58)			

KOOS: Knee Injury and Osteoarthritis Outcome Score; KL: Kellegren-Lawrence stage.

quality, and early degenerative changes could, therefore, increase the susceptibility to OA[20-22]. A significant association between low vitamin D intake and KOA has been reported in diverse populations' worldwide[5-13,20-22].

In Framingham study, McAlidnon *et al*[10] (1996) observed threefold increased risk of KOA progression in participants in the middle and lower tertiles for both vitamin D intake and serum levels. A follow-up to this study a decade later (2007) revealed that vitamin D status was unrelated to the risk of joint space or cartilage loss in knee OA[16]. However, Bischoff-Ferrari *et al*[7] observed a significant positive association between serum 25(OH)D and BMD in individuals with primary knee OA, independent of sex, age, BMI, knee pain, physical activity, and disease severity. As there was a high prevalence of low serum 25(OH)D in KOA patients, and there was a positive association between 25(OH)D and BMD, vitamin D supplementation might enhance BMD in these patients. A similar observation was reported in the "Rotterdam Study" where low dietary vitamin D intake was associated with increased risk of knee OA progression over a mean follow-up time of 6.5 years[12]. There were reports showing a positive association between VDD and knee cartilage loss supported by joint space narrowing and distal femoral cartilage thinning[20,22,24].

Heidari and associates evaluated the status of vitamin D in patients suffering from OA knee (n = 148) compared to an age-matched control group (n = 150)[14]. The mean serum 25-(OH)D in OA patients was not significantly lower than controls (P = 0.28) but on subgroup analysis the mean 25-(OH)D in OA patients aged < 60 years was significantly lower than controls (23.8 ± 18.8 ng/mL *vs* 34.5 ± 29.6 ng/mL, P = 0.01). After adjustment of age and sex in this age group (< 60 years), the authors found a significant association of vitamin D level with OA knee. They found a greater association of OA knee in patients aged < 55 years (OR = 2.63, 95%CI: 1.16-5.95, P = 0.01); whereas the association between OA and serum 25-(OH)D deficiency in patients aged ≥ 60 years did not reach to a significant level[14]. Konstari *et al*[19] from Finland found no significant association between serum 25(OH)D level and the risk of development of knee or hip OA. Al-Jarallah *et al*[15] from Kuwait reported that most of their patients had vitamin D deficiency, but the level of 25(OH)D was not related to the severity of the knee X-ray grading or to the functional assessment in patients with primary knee OA.

There are many studies related to dietary supplementation of vitamin D in KOA. In longitudinal studies, Sanghi *et al*[11] found a small but statistically significant clinical benefit of vitamin D treatment in patients with knee OA at 12-months follow up. In VIDEO study, Arden *et al*[17] did not observe improvement in pain, function, stiffness or joint space narrowing after 3 years of vitamin D supplementation. In a systematic review of randomized controlled trials, Hussain *et al*[21] did not observe any improvement in Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain or function except the study by Sanghi *et al*. They did not observe improvement

in WOMAC stiffness and joint cartilage thickness in any of the studies[22]. Two of three studies documented an improvement in pain using visual analog scale score. Overall there is insufficient evidence to support the benefit of vitamin D supplementation in KOA[20,21].

The patients recruited in previous studies were mostly older adults where primary OA knee and vitamin D deficiency could exist as an isolated problem. Bischoff-Ferrari *et al*[7] advocated that the high prevalence of suboptimal vitamin D levels in persons with knee OA was not unexpected because the mean age was 74 years. Their previous study based on a United States national survey had revealed that only 33% of ambulatory white persons ≥ 60 years have normal 25(OH)D levels[25]; This emphasizeds the general need for vitamin D supplementation, especially in older persons, including those with KOA. However, there are no studies evaluating the vitamin D status in younger KOA patients. The study by Heidari *et al*[14] prompted us to look into the association VDD in younger KOA patients. Although we did not observe a statistically significant difference in proportions of patients with vitamin D deficiency (< 20 ng/mL) between KOA and control group, there was a significant difference in serum vitamin D level between these two groups. Also, there was a significant difference in the proportion of patients with inadequate vitamin D level (< 30 ng/mL). "What is optimal vitamin D level to prevent KOA in younger individuals?" is difficult to evaluate. But patients even below 30 ng/mL are at increased risk and hence ≥ 30 ng/mL may be the desired vitamin D level in this population. The association of inadequate serum vitamin D with KOA in younger age groups may be explained by greater bone health and higher activity of bone remodeling in these younger individuals than older persons. Healthy bone remodeling requires the availability of adequate vitamin D. Therefore, younger individuals are more dependent on vitamin D and expected to be more sensitive to serum 25-(OH)D deficiency[14].

There are a few limitations to our study. One limitation was the cross-sectional design of the study, which could not be used to establish a causal relationship between vitamin D levels and knee OA. We did not measure the BMD of these younger patients. The radiographic examination of the knees in healthy individuals was not clinically indicated; hence the inclusion of asymptomatic OA to the control group could not be ignored. Although propensity matching was done for the control group participants, a perfect matching of these individuals taking all variables into consideration could not be assured. Despite this limitations, the study had important information. Unlike many other studies, there was a control group in this study which were from the same age group and same community. For patients' recruitment, a stringent inclusion and exclusion criteria were adopted whereby the obese patients and elderly patients were excluded.

CONCLUSION

Serum vitamin D level is significantly low in the younger KOA patients compared to healthy young individuals. The odds of developing OA knee in inadequate vitamin D individuals (< 30 ng/mL) is 2.77 times more than healthy individuals. However, the clinical and radiological severities of the OA knee have no association with vitamin D level in these patients.

ARTICLE HIGHLIGHTS

Research background

The rise in the incidence of primary osteoarthritis knee among young individuals is alarming. The increasing prevalence of obesity, sedentary lifestyle, sporting activity and vitamin D deficiency (VDD) has been hypothesized for this shifting disease trend. However, there are limited studies evaluating the association of vitamin D deficiency among young osteoarthritic knee patients.

Research motivation

Vitamin D deficiency (VDD) has been associated with knee osteoarthritis in elderly individuals. The association of VDD among young arthritic individuals has never been studied.

Research objectives

The objectives of this study were to look for the association of serum vitamin D and knee osteoarthritis (KOA) in younger individuals between 35 and 60 years of age.

Research methods

In a 2-year observational study, 146 non-obese KOA patients of 35-60 years were evaluated clinically and radiologically. The serum 25(OH)D level of these patients and 146 normal healthy individuals of same age group were estimated.

Research results

There was a significantly low vitamin D level in younger OA knee patients compared to normal individuals. There were 47% OA knee patients who had inadequate serum vitamin D compared to 24% normal individuals. The odds of development of KOA were 2.77 times more in younger individuals with below-normal vitamin D compared to healthy individuals with normal vitamin D, but the clinical and radiological severities of OA knee had no association with serum vitamin-D level.

Research conclusions

The serum vitamin D level is significantly low in younger KOA patients. However, the clinical and radiological severities have no association with the vitamin D level.

Research perspectives

The association of inadequate serum vitamin D with KOA in younger individuals may be explained by greater bone health and higher activity of bone remodeling compared to elderly individuals. Therefore, younger individuals are more dependent on vitamin D and expected to be more sensitive to serum 25-(OH)D deficiency. Vitamin D supplementation might prevent the onset of the OA knee in these young individuals. However, the disease progression is probably dependent on other variables as the severity of OA knee is not correlated with the severity of vitamin D deficiency. Further research at the molecular and genetic level will probably clarify the association in a better way.

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