

## Vitamin D Deficiency in knee Osteoarthritis and Its Relationship with Obesity in Saudi Arabia

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**Abstract: Background:** Vitamin D deficiency is a common problem worldwide and a high prevalence has been found in Saudi Arabia. Vitamin D influences cartilage and bone metabolism and its deficiency may influence the knee joint cartilage and lead to development and progression of knee osteoarthritis (KOA). Conflicting results have been reported about the association between vitamin D deficiency and knee osteoarthritis, while the association between low vitamin D and high body mass index (BMI) was reported in the published literature. Vitamin D deficiency may be one of the factors that account for increased pain in knee osteoarthritis. **Objective:** The study aimed to determine serum 25 – hydroxyl vitamin D (25-OHD) levels in patients with symptomatic KOA compared with controls and to evaluate the association of serum 25-OHD levels with obesity and KOA. **Methods:** A total of 100 patients with symptomatic knee OA and 100 controls were studied. All patients met the American College of Rheumatology (ACR) criteria for diagnosis of knee OA. The clinical status of patients with knee OA was evaluated. Knee pain was elicited using the VAS and WOMAC pain subscale, and the physical function evaluation consisted of the timed chair stand and 10-meter walking tests. BMI was assessed for all patients. Serum 25-OHD was measured for OA and controls; concentrations <20 ng/ml were considered as deficient levels. The radiological features of knee OA were graded on a five-point scale (0–4) for Kellgren and Lawrence (K/L) classification. **Results:** The study included 100 patients with symptomatic knee OA (mean age  $52.47 \pm 10.427$ ), 70 women (70 %) and 30 men (30%). It included 100 controls (mean age  $49.67 \pm 9.18$ ), 53 women (53 %) and 46 men (64 %). 68%, 55% of patients and controls, respectively were Saudi. Serum 25-OHD deficiency was observed in 66% of patients compared with 58 % in controls ( $P=0.244$ ), with mean serum 25-OHD level ( $18.10 \pm 10.99$  ng/ml) lower than controls ( $19.88 \pm 10.34$  ng/ml) ( $P=0.342$ ), with no significant difference between the two groups. Among KOA patients, 72.1% had BMI  $\geq 30$  (obese) (mean  $33.782 \pm 6.107$ ). A high BMI ( $\geq 30$ ) was observed in 77.3% of patients with low 25-OHD level versus 62.5% in patients with normal 25-OHD level with statistically significant difference ( $P=0.043$ ). Most of the patients (75.9%) had radiological evidence of KOA K/L grade 1-2, while only 24.1% had a K/L grade  $\geq 3$ . Vitamin D deficiency was significantly correlated with high BMI (obesity). High BMI (obesity) was significantly correlated with aging, greater knee pain (high VAS and WOMAC) and a slow walking speed. BMI also significantly associated with radiological severity of KOA. **Conclusion:** These findings indicate a significant association between vitamin D deficiency and high BMI, which in turn is associated with greater knee pain, poor physical function, and severe radiological evidence of KOA. **Recommendation:** These findings reveal the importance of measuring and monitoring vitamin D levels in patients with symptomatic knee osteoarthritis, particularly the obese patients.

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### 1. Introduction

Vitamin D deficiency, defined mostly as serum 25-hydroxyvitamin D (25-OH D) levels of <20 ng/ml, is a common problem worldwide [1, 2] and very prevalent in some communities, with a rate ranging from 50% to 80% [3-5]. In Saudi Arabia, specifically in urban areas such as the capital Riyadh, vitamin D deficiency is overwhelmingly high [6-16], despite of plentiful sunlight and vitamin D fortified food products as reported in one study, 65% participant had adequate exposure to sunlight and >90% reported adequate intake of dairy products [17].

Vitamin D deficiency is associated with many pathological conditions including osteoarthritis (OA), while sufficient levels of serum vitamin D decrease the risk of many chronic diseases [18,19].

Osteoarthritis (OA) is the most common chronic arthritis characterized by gradual cartilage loss and affects also the other joint structures; subchondral bone and periarticular muscles causing structural changes and eventually functional failure of synovial joints [20, 21]. Vitamin D has many biological functions in these structures by acting on vitamin D

receptors [22, 23], and may have beneficial effects on these joint structures in OA [24].

Subchondral bone changes in OA play an essential role in the onset and progression of cartilage lesions, where there is increase in bone resorption markers and decrease in bone formation markers compared with a control group [25, 26]. Bone metabolism and turnover are increased in progressive OA. Vitamin D deficiency increased osteoclastic activity and bone turnover [27], as well may lead to increased inflammation [28,29]. While raising serum 25-OHD to sufficient levels with vitamin D supplementation will decrease the rate of bone turnover, suppress the Parathyroid hormone (PTH) level, increase bony mass density (BMD) and even decrease fracture risk in the elderly population [30,31]. Thus Vitamin D deficiency may play an important role in the etiology of OA [32].

Vitamin D deficiency co-exists frequently with OA in older people (33) and its status influences the incidence and progression of knee OA (34). The prevalence of OA in serum 25-OHD deficient men was two times greater than those with sufficient levels [35]. Some studies have concluded that low levels of vitamin D in the serum are associated with worsening radiographic hip and knee osteoarthritis (OA), while other studies' results have not proved so. Vitamin D deficiency patients had higher risk of KOA progression [40, 41].

Obesity, defined by the World Health Organization as a body mass index (BMI) of 30 kg/m<sup>2</sup> or more, is pandemic, affecting at least five million Australians and substantial numbers in most developed nations [42]. If overweight (BMI 25–29.9) is included, then approximately 14 million Australians, and 70% of Americans aged over 60, are obese or overweight [43].

In Saudi Arabia (KSA), based on the National Nutrition Survey of 2007, the prevalence of obesity was 23.6% in women and 14% in men. The prevalence of overweight in the community was determined to be 30.7% for men as compared to 28.4% for the women [44].

There is a consistent association in the published literature between increasing BMI and lower serum 25-OHD concentrations [45-48], the authors found that obesity associated with lower serum 25-OHD concentrations, high PTH concentrations and low 1,25D concentrations. Moreover, body fat content has been reported to inversely related to serum 25-OHD concentration, and this associations is stronger than those between 25-OHD and BMI and body weight [49]. It has been suggested in one study that higher BMI leads to lower 25-OHD, with the effects of lower 25-OHD on BMI likely to be less [50].

The association between reduced 25-OHD concentrations and obesity is well established.. Several mechanisms for Lower 25-OHD concentrations in obese Individuals have been reported by Simon Vanlint, 2013 [51]: 1. *lower dietary intake*, 2. *reduced cutaneous synthesis due to altered behaviour and reduced synthetic capacity*, 3. *reduced intestinal absorption*, 4. *altered metabolism due to reduced activation and/or increased catabolism and sequestration of 25D in adipose tissue*, 5. *A much simpler explanation is that a volumetric dilutional model accounted for essentially all the variability in serum 25D concentrations attributable to obesity.*

## 2. Subjects and Methods

### Study population

The population of this cross-sectional study consisted of 100 patients with symptomatic knee OA and age-matched 100 controls. All patients and controls should be Saudi or non Saudi stayed in Saudi Arabia for at least 5 years.

Patients were selected consecutively among individuals who presented with knee pain to a Rheumatology Outpatient Clinic of Salman bin Abdulaziz University Hospital, Al Kharj, Saudi Arabia. Diagnosis of knee OA was confirmed by the American College of Rheumatology (ACR) diagnostic criteria for classification of knee OA [52].

Exclusion criteria were presence of rheumatic diseases other than OA as, inflammatory arthritis and connective tissue disease, hyperuricemia, use of vitamin D supplements, chronic steroid use, intra-articular injections (steroids or haluronic acid) in the last three month.

Subjects of the control group were selected among those who presented to the Outpatient Clinics over the same period for non-musculoskeletal symptoms such as recent respiratory or gastrointestinal symptoms or among subjects without any clinical symptoms who presented for check-up laboratory tests. The control group had no clinical features of knee OA based on history and clinical examination.

### Clinical Examination

Demographic information and history were obtained for KOA patients as well clinical examination were done for all patients.

The clinical status of knee OA patients was evaluated by knee pain and physical function evaluation [53]. Knee pain was evaluated using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC pain subscale) [54] and Visual Analog Pain scales (VAS) [55]. The physical function evaluation comprised 30 second (timed) chair stand test [56] and 10-meter walking tests [57].

### Assays

Serum 25-hydroxy Vitamin D level was assessed for both patients and control. Measures of alkaline phosphatase, serum parathyroid hormone (PTH), calcium, phosphate and uric acid were performed for all patients.

The serum calcium, phosphate and alkaline phosphatase and uric acid were estimated colorimetry according to the instructions of the Cobas Integra 400 Plus Roche. The serum 25-hydroxy Vitamin D and parathyroid hormone were estimated by electrochemiluminescence immunoassay technique according to the instructions of Cobas e 411 Roche. Serum 25-hydroxy Vitamin D concentrations <20 ng/ml were considered as deficient levels.

### Radiographs

Radiographs of the knees were obtained for all KOA patients with a weight-bearing anteroposterior view in full extension, lateral and skyline view. All radiographs were assessed by radiologist who was blind to the clinical findings. The radiological features of knee OA were graded on a five-point scale (0–4) for Kellgren and Lawrence (K/L) classification [58].

### Statistical analysis

Data was analyzed using SPSS. Mann-Whitney test and Student independent T test was used to compare means. Chi-square test were used to compare frequencies. Significant was set at  $p < 0.05$ . The relationship between vitamin D deficiency and knee OA measures was assessed by Pearson's correlation coefficient (r).

### 3. Results

The study included 100 patients with symptomatic knee OA (70 women and 30 men) with mean age  $52.47 \pm 10.427$ , and 100 controls (53 women and 46 men) with mean age  $49.56 \pm 9.429$ . Saudi patients represent 66% of OA patients and 55% of the control, respectively. Serum 25-OHD deficiency was observed in 68% of the patients versus 58% of the controls ( $P = 0.244$ ). In the entire population of OA, the mean serum 25-OHD level was lower than controls but the difference was not statistically significant ( $18.10 \pm 10.99$  ng/ml vs.  $19.88 \pm 10.34$  ng/ml,  $P = 0.342$ ). There was an association between serum 25-OHD deficiency and knee OA which was not statistically significant ( $P = 0.244$ ) (Table 1).

**Table-1. Comparison between KOA patients and control cases**

	Control group (n = 100)	KOA Cases (n = 100)	P-value
<b>Nationality</b>			
Saudi	55 (55 %)	68 (68 %)	0.059 *
Non-Saudi	45 (45%)	32 (32 %)	
<b>Vit. D</b>			
Mean $\pm$ SD	$19.88 \pm 10.34$	$19.10 \pm 10.99$	0.342 **
Median (minimum – maximum)	17.7 (4 – 60)	15.75 (4 – 57)	
< 20	58 (58 %)	66 (66 %)	0.244 *
$\geq$ 20	42 (42 %)	34 (34 %)	

\*By Chi-square test. \*\* By Mann-Whitney test.

Among KOA patients 72.1% had BMI  $\geq 30$  (obese) (mean  $33.782 \pm 6.107$ ). A high BMI ( $\geq 30$ ) was observed in 80.6% of patients with low 25-OHD level (mean  $34.448 \pm 5.902$ ) versus 55.0% in patients with normal 25-OHD level (mean  $32.563 \pm 6.411$ ) with statistically significant difference ( $P = 0.043$ ). Most of our patients (74%) had radiological evidence of KOA K/L grade 1-2, while only 26% had a K/L grade  $> 3$ .

Clinical evaluation of all KOA patients' pain and the physical function showed a mean WOMAC

pain subscale and %  $46.72 \pm 20.792$ ,  **$48.989 \pm 22.114$** , respectively, mean VAS pain score  $6.04 \pm 1.899$ , mean timed chair stand test  $8.49 \pm 2.800$ , mean 10-meter walking test velocity, selected and fast  $0.77206 \pm 0.197$ ,  $1.0166 \pm 0.264$ , respectively (Table 2). The difference in these parameters on comparing KOA patients with low serum 25-OHD levels (<20 ng/ml) and those with normal serum 25-OHD levels (>20 ng/ml) did not reach the significant level (Table 2).

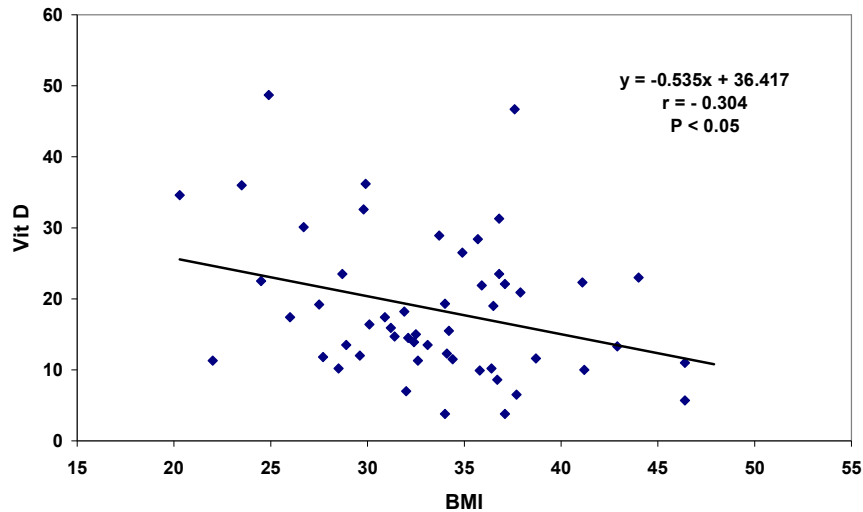
**Table 2** Clinical variables and vitamin D level in KOA patients

	Minimum	Maximum	Mean	Std. Deviation
AGE	36	82	52.47	10.427
BMI	20.3	47.9	33.782	6.1070
WOMAC_Score	4	89	46.72	20.792
WOMAC_%	4.17	96.00	48.9891	22.11415
VAS	1	10	6.04	1.899
Timed Chair	4	17	8.49	2.800
Walk Test Selected	.258	1.279	.77206	.197517
Walk Test Fast	.359	1.704	1.01660	.264847
Vit. D	3.8	57.0	19.103	10.9911

**Table 3** Comparison of KOA patients with low and normal vitamin D level

	Vit. D	Mean	Std. Deviation	Std. Error Mean	P-value
AGE	< 20	52.50	11.048	1.360	0.968
	> 20	52.41	9.258	1.588	
BMI	< 20	34.448	5.9028	.8899	0.226
	> 20	32.563	6.4112	1.3087	
WOMAC_Score	< 20	44.91	20.086	3.063	0.349
	> 20	49.84	22.016	4.403	
WOMAC%	< 20	47.1906	21.72489	3.31301	0.383
	> 20	52.0827	22.88036	4.57607	
VAS	< 20	5.98	1.865	.278	0.808
	> 20	6.16	1.993	.399	
Timed Chair	< 20	8.34	2.811	.424	0.554
	> 20	8.76	2.818	.564	
Walk Test Selected	< 20	.77123	.217611	.032806	0.964
	> 20	.77351	.160281	.032056	
Walk Test Fast	< 20	1.04400	.272062	.043017	0.289
	> 20	.97094	.251287	.051294	

Study the correlation of vitamin D deficiency with different clinical variables and radiological grading showed that vitamin D deficiency was significantly negatively correlated with BMI (obesity) as shown in this figure.

**Relationship between Vit D and BMI (Body Mass Index)**

High BMI (obesity) was significantly correlated with aging; X-ray severity of OA; greater knee pain (high VAS and WOMAC score) and slow walking speed. Knee pain measures, VAS, WOMAC subscale were significantly correlated with each other and with physical function parameters, timed chair stand test and 10-meter walking tests. X-ray severity of OA significantly correlated with aging, knee pain measures and physical function parameters. Both X-ray severity and aging significantly correlated with greater knee pain, high VAS and WOMAC, slow walking speed and low timed chair stand.

#### 4. Discussion

Systematic review of the evidence for association between serum 25-hydroxyvitamin D (25-(OH)D) and OA has been investigated by **Yuelong *et al.*, 2013**. This review revealed that there was moderate evidence for the association of low levels of 25-(OH)D with increased progression of radiographic OA as assessed by the Kellgren and Lawrence (KL) score. While strong evidence for an association between 25-(OH)D and cartilage loss was apparent when joint space narrowing and changes in cartilage volume were considered collectively as cartilage loss. The authors of the review concluded that 25-(OH)D appears to be implicated in structural changes of knee OA rather than symptoms [59]. But the results of other research suggested that low vitamin D levels may cause greater knee pain and difficulty walking [60].

The current study evaluated serum 25-hydroxy Vitamin D level for KOA patients and controls and possible relationship between serum 25-hydroxy Vitamin D level and KOA

The findings of the present study indicated a high prevalence rate of serum 25-OHD deficiency (68% of KOA patients versus 58% of controls), but no significant association has been found between serum 25-OHD deficiency and knee OA (KOA). These results are consistent with the study done by Felson *et al.* [61] and Salman [62].

However, other studies suggested that low serum levels of vitamin D appear to be associated with an increased risk of progression of KOA [61, 63-66].

Behzad Heidari's, study [67] has demonstrated a high prevalence rate of serum 25-OHD deficiency and a significant association with KOA in a younger age (less than 60 years). This age group is consistent with initiation of early OA symptoms corresponding with the development of knee cartilage damage.

Patients with knee OA are expected to have higher body mass index (BMI). Obese patients may have low serum 25-OHD levels due to decreased passage of vitamin D from skin to the general circulation.

In the present study, higher BMI values greater than 30 kg/m<sup>2</sup> (obese) were observed in 72.1% of all KOA patients with mean 33.782±6.107 and in 80.6% of patients with low 25-OHD level (mean 34.448 ±5.902) versus 55.0% in patients with normal 25-OHD level (mean 32.563±6.411). These results are consistent with Sami's study who reported that vitamin D deficiency was more severe among obese and overweight females than normal weight females [62] However, in a previous study of patients with knee OA with mean age of 60±11 years, the mean BMI was 27.8±8.1 kg/m<sup>2</sup> [68].

High BMI values greater than 30 kg/m<sup>2</sup> were shown to be associated with low vitamin D level. The results of this study are consistent with previous reports [61, 69]. High BMI (obesity) was significantly correlated with aging; X-ray severity of OA; greater knee pain (high VAS and WOMAC score) and slow walking speed.

The clinical status of patients with knee OA is primarily predicated by their level of pain and their muscle function. Recent studies have shown that vitamin D influences both musculoskeletal health and neuromuscular function. Vitamin D deficiency is common among elders and those with comorbidities. This suggests that vitamin D may especially influence the clinical status of patients with knee OA. The present study examined whether serum 25-hydroxyvitamin D (25(OH)D) level was associated with pain and physical function in patients with symptomatic knee OA.

In a study among patients with knee OA, a low 25(OH)D level was associated with greater knee pain and slower walking speed [60]. Moreover, another recent study revealed that black Americans display lower levels of vitamin D and greater pain sensitivity compared to white Americans. Findings indicate that vitamin D deficiency may be one of many factors that account for increased pain in older black Americans with knee OA [71].

**Baker *et al.* reported that patients with knee osteoarthritis (OA) and vitamin-D deficiency have more pain and disability than those with normal levels [72]**

In the present study, we could not find direct correlation between a low 25(OH)D level and level of pain and physical (muscle) function, But Vitamin D deficiency was significantly negatively correlated with obesity which in turn correlated with greater knee pain (high VAS and WOMAC score) and slow walking speed.

#### Conclusion

Vitamin D deficiency is significantly correlated with high BMI, which in turn is correlated

with greater knee pain, poor physical function, and severe radiological evidence of KOA.

### Recommendation

- The present findings reveal the importance of measuring and monitoring vitamin D levels among patients with symptomatic knee osteoarthritis, particularly the obese patients.
- The role of vitamin D supplementation in prevention of progression of OA and for treatment requires further studies.

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