Relationship between serum 25-hydroxy vitamin D levels, knee pain, radiological osteoarthritis, and the Western Ontario and McMaster Universities Osteoarthritis Index in patients with primary osteoarthritis

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Objective
This study aims to detect the relationship between serum 25-hydroxy vitamin D (25-OHD) levels in patients with primary osteoarthritis (OA) of the knees and with other disease parameters of OA, mainly radiological findings, functional assessment using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and pain [numerical rating scale (NRS)].

Patients and methods
We studied 140 consecutive patients with primary knee OA, 110 female patients and 30 male patients. They were clinically, radiologically, and also functionally evaluated regarding OA; pain was also assessed using NRS, and serum 25-OHD, serum parathormone, serum calcium, phosphorus, and alkaline phosphatase were measured.

Results
In our patient sample, we found that 90 (64.3%) patients had lower 25-OHD levels. The mean serum 25-OHD was 35.77 ± 14.6 (range 10.62–71.82) ng/ml; 25-OHD was negatively significantly correlated with patients' age ($P = 0.013$, $r = -0.236$), radiological degree of OA ($P = 0.036$, $r = -0.20$), WOMAC ($P < 0.0001$, $r = -0.337$), and NRS for pain ($P < 0.0001$, $r = -0.580$). When comparing between patients with hypovitaminosis, 25-OHD less than 40 ng/ml, and patients with desirable 25-OHD levels, we found that radiographic grading of OA was significantly higher in the hypovitaminosis group ($t = 2.024$, $P = 0.045$); WOMAC was also significantly higher in the hypovitaminosis group ($t = 3.226$, $P = 0.002$) and NRS was also higher in the hypovitaminosis group ($t = 4.468$, $P < 0.0001$).

Conclusion
25-OHD deficiency is prevalent in our patients suffering from OA; in addition, 25-OHD may play a role in patients suffering from OA.

Introduction

Osteoarthritis (OA) is a progressive and disabling joint disease. It is one of the most common widespread musculoskeletal disorders that affects middle-aged and older people all over the world [1,2]. In the National Health Interview Study, OA and related disorders were the third leading chronic condition causing work limitation (1.6 million people or 8.3% of main conditions of impairment), just after heart disease (10.9%) and back disorder (21.1%) [3].

OA can occur in every synovial joint, but the most common sites are hip, knee, hand, foot, and spine [4]. It is reflected on the patient in the form of painful joint and/or limitation of joint function. In a synovial joint, several structures can cause these clinical symptoms. Bone, cartilage, synovial fluid, ligaments, and also the muscles around the joint are affected and cause the changes with OA that affect the joint function [5].

Knee OA is likely to become the fourth most important global cause of disability in women and eighth most important in men [6]. Although the pathogenesis of this condition is not completely understood yet, several environmental factors have been associated with OA, including obesity [7,8], previous injury [9], and occupational and other metabolic factors [10,11]. In addition, a study demonstrated a clear genetic influence on radiologic knee OA in women, with up to 65% of the variance being explained by genetic factors [12].

Many studies discussed some different roles for 25-hydroxy vitamin D (25-OHD) and its relationship to pain [13], cartilage metabolism [14], in-vitro synthesis of proteoglycan by mature articular cartilage [15], and

metalloproteinase production and modulating the degradative capacity of the tissue macrophage [16], and great debate aroused about the role of 25-OHD as a contributing factor to OA [17–23].

Patients and methods
Study populations
This was a cross-sectional study that included 140 consecutive patients with primary knee OA who were recruited from the Rheumatology and Rehabilitation Outpatient Clinic of Minia University Hospital in Egypt during a period of 6 months from April to September 2011. Minia is located at 28°N latitude and 31°E longitude, with abundant sunshine throughout the year. Diagnosis of knee OA was made by using the American College of Rheumatology diagnostic criteria for classification of knee OA [24]. We excluded from the study patients with a history of inflammatory arthritis or any rheumatic disease rather than OA, patients with celiac disease, malabsorption syndrome, abnormal hepatic or renal function tests, and patients taking medications known to affect 25-OHD level (anticonvulsants, antituberculous drugs, 25-OHD, or analogs). In addition, patients who used glucosamine, chondroitin, doxycycline, or intra-articular injections within 3 months of the study were excluded. Informed consent was obtained from all patients, and hospital ethical committee approval was granted before the study. All patients were evaluated clinically, radiologically as well as for functional assessment.

Clinical evaluation
Thorough history taking including history of falls and the daily hours of sun exposure, and clinical examination of the knee pain were performed. This included site, duration, severity of pain using the visual analogue scale and patient global assessment of pain, the presence of swelling, nocturnal pain, pain at rest or activity (stairs, kneeling, and squatting), stiffness/gelling phenomena, deformities, bony enlargement, joint crepitus, tenderness, and range of motions.

Radiographic assessment
Radiographs of the knee were taken at an anteroposterior position and weight bearing was assessed using the Kellgren–Lawrence grade [25]. All patients were also scored for joint space narrowing and osteophytes separately on a scale from 0 to 3 (0 = normal; 3 = severe) according to the Osteoarthritis Research Society International Atlas [26].

Functional assessment
All patients were assessed for function using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) that is used to assess patients with knee OA using 24 parameters. The score ranges from 'none' (value = 0) to 'extreme' (value = 4) and includes questions such as: 'walking', 'sitting', and 'standing'. From these 24 parameters, five are for pain and 19 are for stiffness and physical functions. The scores add up to 96 points and the final score is calculated based on the addition of the numbers divided by the amount of answers [27]. In addition, patients were asked to grade their knee pain on a scale from 0 to10 according to the numerical rating scale (NRS) [28].

Laboratory evaluation
Venous blood sampling was performed for serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-OHD. Serum calcium was determined by ion-selective electrodes, whereas serum phosphorus and ALP were determined by the colorimetric method. Measurement of serum level of intact parathormone (PTH) was performed by enzyme-linked immunosorbent assay (kit manufactured by Biosource, Camarillo, California, USA). Serum 25-OHD was measured using radioimmunoassay kits Dia Sorin (Stillwater, Minnesota, USA). 25-OHD was considered normal when serum level was above 40 ng/ml, whereas hypovitaminosis D was defined as serum 25-OHD between 20 and 40 ng/ml, levels between 10 and 20 ng/ml as 25-OHD insufficiency, and 25-OHD levels below 10 as deficient [29].

Statistical analysis
Statistical analysis was performed using SPSS version 17.0; (SPSS Inc., Chicago, Illinois, USA) for Windows; two-tailed tests were used throughout, and statistical significance was set at P value less than 0.05 levels. The following statistics were carried out: descriptive statistics of range, mean, and SD were calculated for interval and ordinary variables, and frequencies and percentages for categorical variables and correlations (bivariate correlations procedure computes Pearson's correlation coefficient with its significance levels).

Results
A total of 140 patients with a mean age of 52.42 ± 9.80 (range 40–77) years were included in the study, 110 (78.6%) were female patients, whereas 30 (21.4%) were male patients. The mean serum 25-OHD was 35.77 ± 14.6 (range 10.62–71.82) ng/ml as shown in Table 1. Serum 25-OHD deficiency was observed in 90 (64.3%) patients.

Seventy-seven (70%) of the female patients were found to suffer from low 25-OHD levels, whereas only 13 (43.3%) male patients suffered from low serum

25-OHD levels. The mean serum 25-OHD level in female patients was 51.50 ± 10.17, whereas mean 25-OHD serum level in male patients was 55.8 ± 7.47; this difference was statistically nonsignificant.

Serum 25-OHD was negatively significantly correlated with radiological degree of OA ($P = 0.036$, $r = -0.20$) (Fig. 1); it was negatively highly significantly correlated with WOMAC ($P < 0.0001$, $r = -0.337$) (Fig. 2). 25-OHD was negatively significantly correlated with patients' age ($P = 0.013$, $r = -0.236$) and was positively highly significantly correlated with daily hours of sun exposure ($P < 0.0001$, $r = 0.646$).

Daily hours of sun exposure of the patients was negatively significantly correlated with both radiographic grading for OA ($P = 0.006$, $r = -0.258$) and WOMAC ($P < 0.0001$, $r = -0.346$); in addition, it was negatively significantly correlated with the age of the patients ($P = 0.001$, $r = -0.303$) and PTH levels ($P < 0.0001$, $r = -0.557$).

NRS for pain was highly negatively significantly correlated with serum 25-OHD ($P < 0.0001$, $r = -0.580$) and daily hours of sun exposure ($P < 0.0001$, $r = -0.404$); it was positively significantly correlated with WOMAC ($P < 0.004$, $r = 0.268$), whereas it was not significantly correlated with radiological findings of OA (Kellgren–Lawrence grade) ($P = 0.224$, $r = 0.116$).

History of falls was positively highly significantly correlated with radiological findings of OA (Kellgren–Lawrence grade) ($P < 0.0001$, $r = 0.380$), WOMAC ($P < 0.0001$, $r = 0.366$), patients' age ($P < 0.0001$, $r = 0.520$), NRS for pain ($P = 0.023$, $r = 0.215$), and with serum PTH levels ($P = 0.005$, $r = 0.434$), whereas it was negatively highly significantly correlated with

25-OHD levels ($P < 0.0001$, $r = -0.409$) and sun exposure duration ($P = 0.001$, $r = -0.305$).

Disease duration was positively significantly correlated with WOMAC ($P < 0.0001$, $r = 0.380$), radiographic finding of OA ($P < 0.0001$, $r = 0.312$), and history of falls ($P = 0.002$, $r = 0.289$), whereas it was negatively significantly correlated with serum 25-OHD levels ($P = 0.03$, $r = -0.183$).

When comparing between patients with hypovitaminosis, 25-OHD less than 40 ng/ml, and patients with desirable 25-OHD levels, we found that radiographic grading of OA was significantly higher in the hypovitaminosis group ($t = 2.024$, $P = 0.045$); WOMAC was also significantly higher in the hypovitaminosis group ($t = 3.226$, $P = 0.002$) and NRS was also higher in the hypovitaminosis group ($t = 4.468$, $P < 0.0001$) (Table 2).

Table 1 Patient characteristics

|	Range	Mean ± SD
Age	40–77	52.42 ± 9.80
Disease duration (years)	1–21	4.96 ± 3.82
Daily sun exposure duration (min)	20–120	54.61 ± 21.69
WOMAC	12–80	45.47 ± 17.09
25-OHD (ng/ml)	10.62–71.82	35.77 ± 14.6
PTH (pg/ml)	17–146	47.27 ± 25.96
Alkaline phosphatase (U/l)	31–453	97.46 ± 53.13
Phosphorus (mg/dl)	2.5–12.6	4.39 ± 1.51
Calcium (mg/dl)	6–10.55	8.23 ± 1.95
	Number (%) (total = 140)	
Female patients	110 (78.6)	
Male patients	30 (21.4)	
Patients with deficient 25-OHD	90 (64.3)	

25-OHD, 25-hydroxy vitamin D; PTH, parathormone; WOMAC, western ontario and mcmaster universities osteoarthritis index.

Figure 1
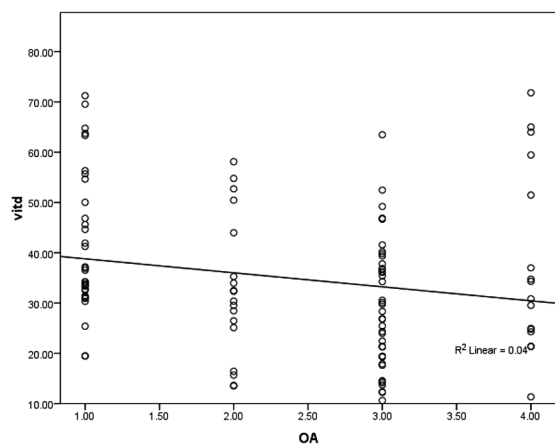
Showing significant negative correlation between 25-hydroxy vitamin D and radiographic osteoarthritis (OA) (Kellgren–Lawrence grade).

Figure 2
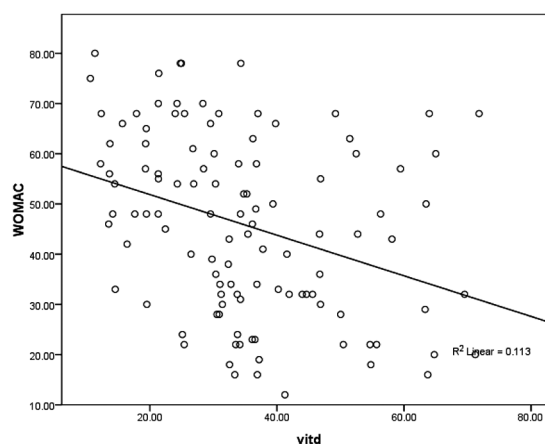
Showing significant negative correlation between 25-hydroxy vitamin D and radiographic Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Table 2 Different correlations with 25-hydroxy vitamin D

	Correlation coefficient (r)	P
Age	−0.236	0.013*
Kellgren–Lawrence grade	−0.20	0.036*
WOMAC	−0.337	0.0001***
Sun exposure duration	0.646	>0.0001***
NRS	−0.580	>0.0001***
History of falls	−0.409	0.0001***

NRS, numerical rating scale; WOMAC, western ontario and mcmaster universities osteoarthritis index; *P < 0.05, statistically significant; **P < 0.01, highly significant; ***P < 0.0001, very highly significant.

Discussion

OA is a disease with very rich and ancient historical background from prehistoric times to the present day; it can be traced back in time from paleopathological findings in skeletal remains. OA is frequently referred to as the oldest ever known disease. Indeed, evidence of its presence can be found in dinosaur skeletons of up to 70 million years old [30]; in addition, Egyptian royal mummies radiographs demonstrate degenerative joint disease findings [31].

Among joints usually affected, knee OA is the most prevalent type of OA and is estimated that 80% of all adults at or above the age of 65 years exhibit radiographic evidence of knee OA. It is twice as relevant in women as in men [32]. Because of this, we held our study on female patients who are even more liable for both OA and hypovitaminosis D.

In this study, we found that hypovitaminosis D was prevalent in our patient sample of knee OA. Serum 25-OHD deficiency was observed in 90 (64.3%) patients. The mean serum 25-OHD was 35.77 ± 14.6 (range 10.62–71.82) ng/ml. This is already in agreement with most of the studies dealing with OA, starting with Kuwaiti study conducted by Al-Jarallah *et al.* [23]; they found that the mean value of 25-OHD level was 11.4 8 6.07 ng/ml and 92 (92.9%) patients were 25-OHD deficient. In addition, Heidari *et al.* [22] found that serum 25-OHD deficiency was observed in 39.8% of patients versus 32% of their controls.

In our study, we found that serum 25-OHD was negatively significantly correlated with age of the patients (P = 0.013, r = −0.236); this is expected because aging patients have less activity, less sun exposure, and lower 25-OHD levels [33]. 25-OHD was positively highly significantly correlated with daily hours of sun exposure (P < 0.0001, r = 0.646); this is also expected as sun exposure increases the body synthesis of 25-OHD.

In addition, in this study, we found a negative significant correlation between serum 25-OHD levels and radiological degree of OA (P = 0.036, r = −0.20) (Fig. 1); this is in agreement with the results obtained by Heidari *et al.* [22], but the main difference is that they did not found this significant correlation in all patients, just in the younger group less than 60 years old. In this age group, knee OA was significantly associated with serum 25-OHD deficiency, which remained significant after adjusting for age and sex [adjusted odds ratio (OR) = 2.26, 95% confidence interval (CI) 1.15–4.4, P = 0.018]. A greater association was observed in patients aged below 55 years (OR = 2.63, 95% CI 1.16–5.95, P = 0.01), whereas the association between OA and serum 25-OHD deficiency in patients aged 60 years or above did not reach a significant level.

In other study conducted by Bergink *et al.* [20], 'Rotterdam Study', they found that low dietary 25-OHD intake was associated with increased risk for knee OA progression over a mean follow-up time of 6.5 years and concluded that low dietary 25-OHD intake increases the risk of progression of knee OA, particularly in patients with low baseline Bone Mineral Density (BMD), and that 25-OHD status seems to affect the incidence and progression of knee OA. In addition, they suggested that improving the 25-OHD status in the elderly could protect against the development and worsening of knee OA, especially in those with low BMD [20].

Another study conducted on 880 randomly selected patients (TASOAC study) found that sunlight exposure and serum 25-OHD levels are both associated with decreased knee cartilage loss (assessed by radiograph or MRI). This study used the whole range of 25-OHD levels rather than predefined cut points and implied that achieving 25-OHD sufficiency may prevent and/ or retard cartilage loss in knee OA [21].

In another longitudinal study on elderly women, the risk for incidental hip OA increased by OR of 3.34 (95% CI 1.13–9.86) in patients with low serum 25-OHD levels over an average follow-up period of 8 years, and it was concluded that low serum levels of 25-OHD appear to be associated with an increased risk for progression of OA of the knee [17]. However, Felson *et al.* [19] found that a low 25-OHD level is unrelated to worsening of knee OA. However, other effects of 25-OHD those are not visible such as cartilage loss or radiographic progression may be important to our understanding of disease pathogenesis and may be associated with a possible therapeutic or preventive role of 25-OHD in OA [19]. In another cross-sectional study conducted in Kuwait Al-Jarallah *et al.* [23], it was found that serum level of 25-OHD was not related to the severity of the knee radiograph grading or to the functional assessment in patients with primary knee OA.

Interestingly, in our study, we found negative significant correlation between serum 25-OHD levels, WOMAC ($P < 0.0001$, $r = -0.337$) (Fig. 2), and NRS for pain ($P < 0.0001$, $r = -0.580$). Even the correlation with pain was more strong and more significant than radiological findings (Kellgren–Lawrence grade); this is in agreement with the study by Muraki et al. [34] who, in their cross-sectional study using a large-scale population, found that 25-OHD is associated with pain rather than radiographic change.

We can conclude from our study that hypovitaminosis D is prevalent in our patient sample, even more prevalent in female patients than in male patients; in addition, we can suggest that getting better serum 25-OHD levels will improve the patient sufferance from primary knee OA regarding improving pain and functional assessment of OA as well as it may be a factor aiding in retarding the ongoing degenerative process. Further studies are needed with more number of patients and healthy controls to clarify the role of 25-OHD as a contributing risk factor for development of primary OA.

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