The Egyptian Rheumatologist xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/ejr

Frequency of vitamin D inadequacy among Saudi males visiting a Rheumatology Outpatient Clinic of a tertiary hospital in Al-Qassim region: Effect of vitamin D supplementation

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ARTICLE INFO

Article history:
Received 8 April 2017
Accepted 30 April 2017
Available online xxxx

Keywords:
Vitamin D
Deficiency
Inadequacy
Insufficiency
Supplementation

ABSTRACT

Background: Vitamin D inadequacy (deficiency and insufficiency) has become an epidemic with the assumption that women in Arab countries are at a higher risk due to their clothing style of wearing dark colored suits or a veil. *Aim of the work:* To determine the frequency of vitamin D inadequacy among young adult and early middle-aged males in Al-Qassim region and to study the effect of vitamin D supplementation. *Patients and methods:* Sixty Saudi males visiting Rheumatology Outpatient Clinic of a tertiary hospital in Al-Qassim region were enrolled and evaluated for musculoskeletal state including assessment of chronic diffuse musculoskeletal pains using Numeric Rating Pain Scale (NRPS) and functional evaluation of lower limb proximal muscle power using chair–rise performance test. Serum 25(OH)D was evaluated. Vitamin D supplementation was provided for symptomatic subjects. Follow-up clinical evaluation as well as serum 25(OH)D measurement after 12 weeks vitamin D3 supplementation was performed. *Results:* The mean age of the patients was 43.2 ± 6.4 years. 54 (90%) had vitamin D inadequacy; 42 (70%) deficiency and 12 (20%) had insufficiency. Significant increase in baseline serum 25(OH)D (13.92 ± 5.67 ng/ml) after 12 weeks of supplementation (35.94 ± 4.11 ng/ml) with significant decrease in NPRS (7.42 ± 2.12 vs 2.06 ± 2.04) ($p < 0.001$), as well as significant improvement of functional status scores of chair–rise performance test (93.95 ± 23.56 vs 203.1 ± 58.6 ($p < 0.001$). *Conclusion:* Vitamin D inadequacy is a major health problem not only in elderly people or women with in-door residency and dark-colored clothes, but also in Saudi male young adults in Al-Qassim region.

1. Introduction

Vitamin D is in fact not a vitamin but a fat-soluble hormone as vitamins cannot be created by the human body but they come from dietary sources whereas hormones like vitamin D are produced in the body itself [1]. It belongs to the family of steroid hormones and has its nuclear hormone receptor [2]. Vitamin D has a documented role in supporting bone and teeth health; it enhances the intestinal absorption of calcium and phosphorus and transports it to the bones and teeth, and regulates how much calcium remains in the body [3,4]. It is also essential for maintaining muscle mass [5]. Thus, ensuring adequate vitamin D intake may help reduce the incidence of both osteoporosis and sarcopenia [6]. Moreover, it plays an important role in modulating the immune system and helping regulate cell growth. Vitamin D_3 (cholecalciferol) is produced mostly in the skin under the influence of ultraviolet B radiation. Only a few foods, such as oily fish, contain significant amounts of vitamin D naturally [7].

In adults, vitamin D deficiency can cause a skeletal mineralization defect with consequent osteomalacia [8], osteopenia/osteoporosis, increased risk of fracture [7,9,10] and has long been associated with sarcopenia and proximal muscle weakness [11]. There is evidence that vitamin D insufficiency might also be associated with rheumatoid arthritis [12], systemic lupus erythematosus [13], Behcet's disease [14] and osteoarthritis [15].

The desirable 25(OH) D levels, and thus hypovitaminosis D, have been a matter of great debate lately. There is agreement on 20 ng/mL as a minimum desirable serum concentration of 25 (OH)D [4]. It has been suggested that the most beneficial serum

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
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http://dx.doi.org/10.1016/j.ejr.2017.04.010
1110-1164/

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concentration of vitamin D begins at 30 ng/mL (75 nmol/L) [7]. Alshahrani et al. suggested that 25(OH)D serum levels between 20 ng/mL and 32 ng/mL were insufficient [16]. Vitamin D inadequacy (including both deficiency and insufficiency) has become a prevalent epidemic in many parts of the world including sunny countries of which the sun is a natural source as in the Kingdom of Saudi Arabia (KSA) where the average sunlight is 2200 kWh/m^2, due to its location within the earth's equatorial sun belt where more solar radiation hits the earth. It has been estimated that around one billion persons worldwide have vitamin D deficiency or insufficiency [7].

Many Factors can affect vitamin D levels including nutrition deficient in vitamin D; increased demands as during pregnancy and breastfeeding; decreased absorption in gastrointestinal diseases; liver failure; age-related issues including decreased intestinal absorption of vitamin D, reduced synthesis of the active form in the kidney and skin thinning and atrophy with more difficulty synthesizing vitamin D from the sun; obesity as vitamin D is metabolized in the adipose tissue of obese people, thus reducing its bioavailability; skin type/color as people with darker skin have more melanin in their skin, which is a natural sunscreen that blocks UVB and consequently less vitamin D is produced each minute; amount of exposed skin: the more skin exposed, the more vitamin D produced; the excessive use of makeup and sun block creams while outdoors; clothing issues as wearing clothing that conceals the body from sunlight and females wearing dark-colored clothes (abaya), with a head scarf (hijab) or face veil (neqab) [4,17].

The aim of the present work was to determine the frequency of vitamin D inadequacy among young adult and early middle-aged males in Al-Qassim region and to study the effect of 12 weeks vitamin D supplementation on symptomatic subjects with chronic musculoskeletal complaints

2. Patients and methods

Sixty Saudi males (20–50 years of age) attending the Rheumatology Outpatient Clinic of a tertiary hospital in Al-Qassim region either visiting the clinic for any complaint or patients with chronic musculoskeletal complaints referred from other outpatient clinics of various departments of the hospital. Thorough history-taking including a detailed history of chronic diffuse musculoskeletal complaints (persistent generalized body aches or diffuse bony pains /widespread nociceptive pain/ fatigue/asthenia/sense of muscle weakness/difficulty climbing stairs or rising from chair), and clinical evaluation of musculoskeletal state was performed. *Baseline* assessment of diffuse musculoskeletal body pains was performed using Numeric Rating Pain Scale (NRPS) [18], subjective rating or ability to stand from a sitting position was rated (0–10) and functional evaluation of proximal muscle power/strength of lower limbs was by chair–rise performance test [19]. Laboratory investigations included serum calcium, phosphorous, albumin, alkaline phosphatase and thyroid function tests, parathyroid hormone levels. Serum 25 hydroxyvitamin D 25(OH)D was performed for all patients at baseline. The study conforms to the 1995 Helsinki declaration and was approved by the ethical committee of the Hospital. All patients gave their informed consent prior to their inclusion.

Patients were divided into 2 groups: group A ($\leq$40 years) = Young adults (20–40 years) and group B (>40) = Early middle-aged (41–50 years). Those with any autoimmune rheumatic diseases, fibromyalgia syndrome, chronic diseases that affect vitamin D status as malabsorption, chronic liver or renal diseases, thyroid disease, hyperparathyroidism or hypercotisolism and those using vitamin D supplements or drugs that can affect vitamin D metabolism as anticonvulsants or corticosteroids were excluded. Serum calcium, phosphorous, albumin, alkaline phosphatase and parathyroid hormone levels were determined by standard laboratory procedures.

Quantitative determination of serum 25-hydroxyvitamin D by electrochemiluminescence binding assay (Vitamin D total assay for 25-hydroxyvitamin D, Elecsys and Cobas® REF 05894913 190 V5 LOT 184690, Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim, Germany. www.roche.com). This assay employs a vitamin D binding protein as capture protein to bind vitamin D3 and D2. Vitamin D was considered deficient $\leq$20 ng/ml, insufficient between 21–29 ng/ml and normal $\geq$30 ng/ml.

Patients with positive clinical history and evidence for chronic diffuse musculoskeletal complaints/widespread musculoskeletal pain on NRS and/or lower limb proximal muscle weakness evidenced by reduced score of chair-rise test were enrolled/recruited following their consent to a 2nd phase study of vitamin D supplementation. Those with inadequate 25(OH)D received oral cholecalciferol supplementation according to the following regimen: loading doses of 50,000 IU/w for 6 consecutive weeks (a total dose of 300,000 IU), followed by a maintenance dose of 1000 IU/d for another 6 weeks. Serum levels of 25(OH)D measurement after 12 weeks supplementation was performed [20]. Those with insufficient 25(OH)D levels but were asymptomatic received oral cholecalciferol supplementation according to the previously described protocol [21] with no follow-up as regards pain or muscle power; symptomatic patients with inadequate 25(OH)D received supplementation and were followed-up using the NRPS and chair – rise performance test after 12 weeks.

3. Results

Mean age of the 60 patients was 43.2 ± 6.4 years (median 44; range 20–50 years); Group A (n = 13; 21.7%) and Group B (n = 47; 78.3%). Mean level of serum 25(OH)D was 16.72 ± 8.23 ng/ml (median 15.5 ng/ml; range 4–36 ng/ml). Fifty-four (90%) had vitamin D inadequacy; 42 (70%) deficiency and 12 (20%) had insufficiency and 6 (10%) had adequate 25(OH)D. In group A, 9 (21.4%) were deficient, 2 (16.7%) insufficient and 2 (33.3%) adequate; among group B 33 (78.6%) were deficient, 10 (83.3%) insufficient and 4 (66.7%) were adequate.

A flow-chart for path of participants throughout the study is presented in Fig. 1. 6 (10%) with adequate serum 25(OH) D level received no supplementation and were not followed-up; of the 12 (20%) with vitamin D insufficiency: 4 (6.66%) were asymptomatic: received oral cholecalciferol supplementation with serum 25(OH) D level measurement after 12 weeks with no reassessment and 8 (13.33%) were symptomatic: received oral cholecalciferol supplementation with serum 25(OH) D level measurement after 12 weeks and clinical reassessment; symptomatic patients with deficiency (70%) received the supplementation and were followed by vitamin D level measurement after 12 weeks and clinical reassessment.

At initial presentation, 50 (83.3%) patients were symptomatic with a combination of 2 or more related symptoms (chronic diffuse musculoskeletal pain/ persistent widespread musculoskeletal aches, generalized bony pains, vague body pains, easy fatigue, asthenia, sense of muscle weakness, frequent falls). Upon follow-up, 30 (50%) patients reported one or more of the above-mentioned musculoskeletal complaints. The difference was significant ($p < 0.001$). 21 (35%) reported difficulty in chair rising in the first assessment but only 5 (8.33%) following 12 weeks of cholecalciferol supplementation ($p < 0.001$).

A significant negative correlation was present between the serum 25(OH) D level and the body mass index (BMI) (R = −0.66,

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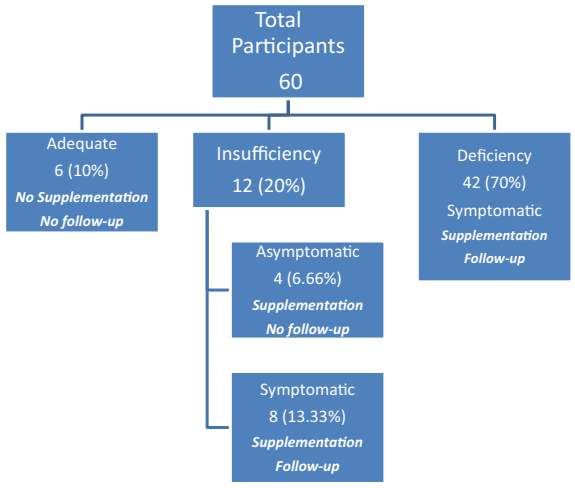

Fig. 1. A flow-chart for path of participants throughout the study.

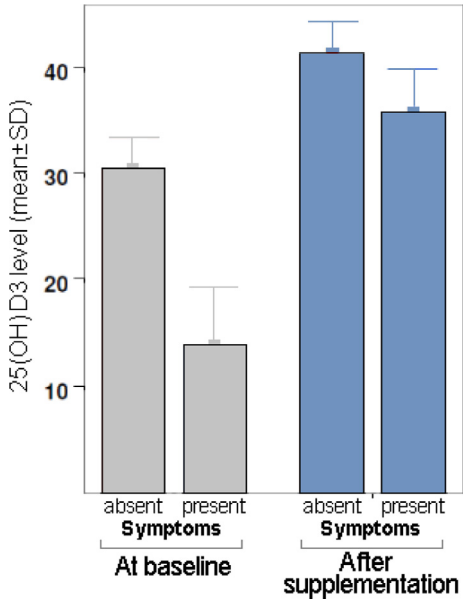

Fig. 2. Serum 25(OH)D in asymptomatic and symptomatic participants before and after supplementation.

p < 0.001), fasting blood glucose (FBG) (R = −0.42, p < 0.001), glycosylated hemoglobin (R = −0.41, p < 0.001), total cholesterol (R = −0.39, p = 0.002), LDL-cholesterol (R = −0.35, p = 0.006), triglycerides (R = −0.52, p < 0.001), phosphorus (R = −0.65, p < 0.001) and parathormone (PTH) (R = −0.47, p < 0.001) levels and a positive correlation with serum calcium (R = 0.67, p < 0.001). There was also a negative correlation between baseline 25(OH)D and vitamin D change (R = −0.66, p < 0.001). Linear regression analysis showed that 25(OH)D level before supplementation was a significant predictor for vitamin D change (β −0.517, R^2 = 0.478, CI −0.67 to −0.36, p < 0.001).

At base line, serum 25(OH)D was significantly reduced in symptomatic (13.92 ± 5.67 ng/ml; median 14, range 4–26 ng/ml) participants compared to those asymptomatic (30 ± 2.83 ng/ml; 30, 27–36 ng/ml) (p < 0.001). *After 12 weeks supplementation*, mean serum 25(OH) D was still significantly reduced in symptomatic (35.94 ± 4.11 ng/ml; 37, 30–45 ng/ml) compared to those asymptomatic (41.50 ± 3.11 ng/ml; 41.5, 38–45 ng/ml) (p = 0.011) (Fig. 2). 25(OH)D of symptomatic patients significantly increased after supplementation (p < 0.001) (Table 1). The change in serum 25(OH)D between asymptomatic (13.25 ± 3.3 ng/ml 13.5, 9–17 ng/ml) and symptomatic (22.02 ± 4.24 ng/ml; 22, 14–33 ng/ml) participants was significant (p < 0.001), and the difference between group A (25 ± 4.59 ng/ml; 25, 18–33 ng/ml) and group B (21.28 ± 3.85 ng/ml; 21.5, 14–31 ng/ml) was significant (p = 0.011) (Table 2).

The NRPS at baseline (7.42 ± 2.12; 7, 3–10) significantly decreased after supplementation (2.06 ± 2.04; 2, 0–6)(p < 0.001) and the functional status significantly improved; subjective ability to rise from sitting position (at baseline 4.26 ± 4.46; 0, 0–10 and after supplementation 2.12 ± 2.55; 0, 0–7)(p < 0.001) as well as chair–rise performance test (at baseline 93.95 ± 23.56; 85.7, 66.66–150 and following supplementation 203.1 ± 58.6; 200 (100–300) (p < 0.001) (Figs. 3 and 4).

Table 1
Comparison of serum 25(OH)D before (pre) and after supplementation (post) in symptomatic patients.

Serum 25(OH)D (ng/ml) in symptomatic patients (n = 50) mean ± SD [median (range)]		p
At baseline	13.92 ± 5.67 [14 (4–26)]	**<0.001**
After supplementation	35.94 ± 4.11 [37 (30–45)]	

Bold values are significant at p < 0.05.

Table 2
Comparison of serum 25(OH)D change between asymptomatic and symptomatic participants and between the two age groups of the study.

Parameter Mean ± SD [median (range)]	Serum 25(OH)D change (ng/mL)	p
Asymptomatic (n = 10)	13.25 ± 3.3 [13.5 (9–17)]	**<0.001**
Symptomatic (n = 50)	22.02 ± 4.24 [22 (14–33)]	
Group A (≤40 years) (n = 13)	25.0 ± 4.59 [25 (18–33)]	**0.011**
Group B (>40 years) (n = 47)	21.28 ± 3.85 [21.5 (14–31)]	

Bold values are significant at p < 0.05.

4. Discussion

Vitamin D is a steroid hormone that modulates a wide range of molecular and cellular functions, most readily recognized are its beneficial effects on musculoskeletal parameters [22]. Patients with osteomalacia often complain of isolated or global bone discomfort along with aches and pains in their joints and muscles [8]. These patients may be misdiagnosed with fibromyalgia, dysthymia, degenerative joint disease, arthritis or chronic fatigue syndrome [23].

Vitamin D deficiency is now recognized as a pandemic [24] and a concentration <20 ng/mL is an indication of deficiency, 21–29 ng/mL, is considered insufficiency and >30 ng/mL is sufficient [5]. It has been suggested that the optimal serum 25(OH) D levels may be even higher, >32 ng/mL [21]. Some raise the recommended level to ≥40 ng/ml in people with skin type IV, V and VI as they need more sunshine to produce vitamin D, and are at a higher risk of becoming vitamin D deficient [25]. The Kingdom of Saudi Arabia (KSA) is among the countries with the highest number of sunny days per year [26]. Environment, tradition, and religion in KSA call for conservative clothing for both men and women. The traditional dress habits evolved around reducing sun exposure in the hot months and protection from the cold during nights in the desert and colder months. With reduced outdoor activities, the population is now less exposed to the sun [27].

In the present study, vitamin D status was investigated in young adults and early middle-aged Saudi males with their relatively free

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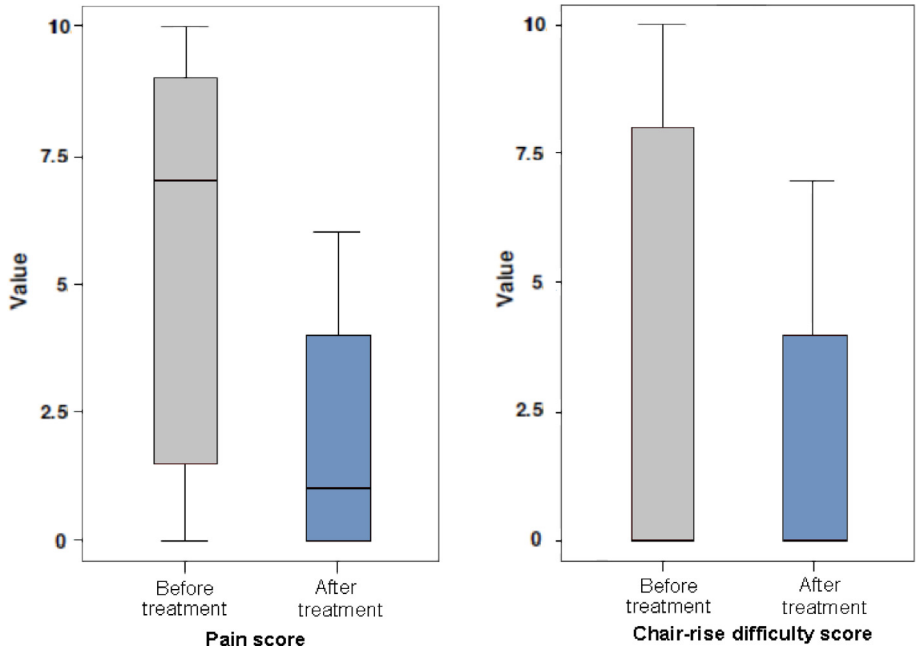

Fig. 3. Pain score and subjective chair-rising difficulty before and after oral cholecalciferol supplementation in the patients with chronic musculoskeletal complaints.

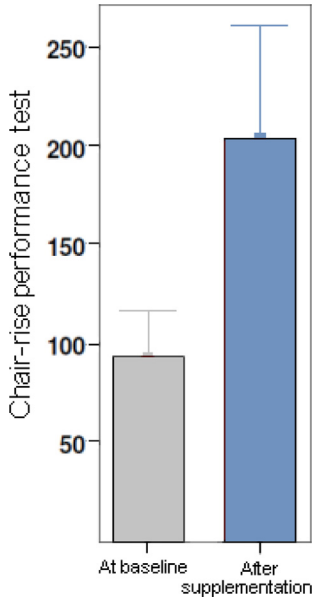

Fig. 4. Chair-rise Performance Test before and after oral cholecalciferol supplementation in the patients with chronic musculoskeletal complaints.

outdoor frequent physical activity with light-colored clothing; It is undergone in Al-Qassim Province located in a relatively high altitude above sea level and in a rather central latitude allowing presumably better sun exposure of residents of this area. 54 (90%) suffered from vitamin D inadequacy with 70% deficient being more pronounced in those above 40 years. Vitamin D significantly correlated with the serum calcium level and negatively with the presence of type 2 diabetes mellitus, fasting blood sugar, glycosylated hemoglobin, total cholesterol, LDL cholesterol, serum triglycerides, serum phosphorus and parathyroid hormone.

Those with vitamin D insufficiency who were asymptomatic received oral cholecalciferol supplementation as subclinical vitamin D deficiency may contribute to the burden of chronic diseases [21]. Symptomatic patients with inadequate 25(OH)D received vitamin D3 supplementation. Serum 25(OH)D levels significantly raised following supplementation in both asymptomatic and symptomatic participants. There was a significant decline in pain scores and a significant decrease in the patients' difficulty rising from chair with less need for help and significant improvement in the test scores following vitamin D supplementation.

Similarly, previous studies showed low levels of vitamin D in KSA. The frequency of vitamin D inadequacy among healthy Saudi population residing in Al-Qassim region in 122/180 (67.8%); 28.3% were deficient, 39.4% insufficient while 32.2% had normal vitamin D level. Commonest symptom of vitamin D deficiency was bone pain (20%) and fatigue (11.1%) and the study concluded that vitamin D inadequacy is a major public health problem in Saudi population [28]. Furthermore, in 488 Saudi subjects living in Riyadh with comparable gender distribution, 130 (29%) had vitamin D deficiency and 101 (22.7%) insufficiency. They concluded that vitamin D deficiency is common in healthy Saudi adults [29]. Again, in a study involving 834 men aged 20–74 years living in Jeddah, deficiency was present in 87.8% and insufficiency in 9.7%. Deficiency was common among older and obese Saudi Arabian men with no education and sedentary lifestyle sampled during summer and spring [30]. Alsammak and coworkers evaluated vitamin D levels in a cohort of healthy subjects in the Eastern region of KSA and showed an increased prevalence of vitamin D deficiency between Saudi Arabians both males and females [31]. Earlier in 2009, Sadat-Ali and colleagues, evaluated vitamin D levels among 100 healthy young or middle-aged Saudi men and in 100 males aged 50 years or older living in the Eastern Province and found that in the younger age group, 28% had low 25OHD levels; 10% deficient and 18% insufficient. In the older age group, 37% had low 25OHD; 12% deficient and 25% insufficient [32].

Hypovitaminosis D was also reported to be common among young Lebanese people (72.8%) in a study by Gannagé-Yared et al. [33] and was more prevalent in women particularly in the veiled ones. The current results came in contrast to the findings of Holick [3] about better UV exposure in high altitudes, but in agreement with a study held in Argentina found a higher prevalence of 25(OH) D deficiency in indigenous population versus

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mixed population boys, suggesting that dark skin, high altitudes, could contribute to this problem. An inverse association between vitamin D and glucose concentration in apparently healthy children was also found [34].

A link between low levels of vitamin D and incidence of acute and chronic pain has been suggested. A growing body of evidence, both clinical and laboratory, point to a potential relationship between low levels of 25-hydroxy vitamin D and a variety of chronic pain states and effectiveness of vitamin D supplementation [35].

In a Brazilian study, subjects >60 years receiving a 6-month calcium/vitamin D supplementation had significantly higher 25(OH)D levels and increase in strength of hip flexors and knee extensors than the calcium/placebo group. Cholecalciferol supplementation is safe and efficient in enhancing 25(OH)D levels and muscle strength in the elderly, in the absence of any regular physical exercise practice [36]. In 150 patients with persistent, nonspecific musculoskeletal pain aged 10–65 years, vitamin D was deficient especially in men; 28% had severe deficiency and 55% were <30 years [23]. Goswami et al. supplemented 28 healthy Asian Indians with low serum 25(OH)D and after 8 weeks the levels increased in all. At 1 year, though the mean 25(OH)D level was significantly higher than the baseline, all subjects were deficient. Thus, for sustained improvement in 25(OH)D levels supplementation has to be ongoing after the initial cholecalciferol loading [37]. In a study by Arvold et al., those with vitamin D deficiency received 50,000 units of vitamin D3 weekly or a placebo for 8 weeks with a significant improvement in pain assessment scores [38]. In a study from the Netherlands on vitamin D-deficient non-Western immigrants with nonspecific persistent musculoskeletal complaints receiving high dose vitamin D were more likely to report an improvement in self-assessment pain and ability to walk stairs 6 weeks after treatment [39]. High dose vitamin D3 50000 IU is effective in achieving sufficient serum 25(OH)D among populations who tend to have lower baseline serum levels. Migrants especially dark-skinned are at a high risk for vitamin D deficiency in Australia [40]. In a recent study, 68 patients with chronic low back pain for 3 months and 25(OH) D3 levels <30 ng/ml showed an improved pain intensity and functional ability after vitamin D supplementation for 6 months compared to baseline in addition to normalization of the level [41].

In conclusion, vitamin D inadequacy is a very common health problem in Saudi males living in Al-Qassim Province despite their free outdoor activity and lack of conservative dark clothing; many of the encountered chronic musculoskeletal complaints are attributed to vitamin D inadequacy; vitamin D supplementation and restoring adequate stores can be crucial in improving pain intensity and improving functional ability and muscle strength. Health education campaigns for increasing outdoor physical activity, fortification of food and dairy products, screening for vitamin D status, as well as vitamin D supplementation needs to be addressed and encouraged.

Statistical analysis: Data were summarized using means and standard deviation (SD) or medians with ranges as applicable, whereas categorical variables were presented as percentages and counts. Differences in the 25(OH) D levels between groups were tested using independent *t*-test or Mann–Whitey Test as appropriate, Analysis of Variance (ANOVA) or its nonparametric equivalence, the Kruskal–Wallis test. Categorical variables were also compared using Chi-square test. Simple linear logistic regression was performed to examine the association between the serum 25 (OH)D before supplementation and vitamin D change. The data were analyzed using SPSS (Statistical Package for the Social Sciences), version 15.0, Chicago, Illinois. P values $\leq$0.05 were considered significant.

Conflict of interest

None.

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Please cite this article in press as: Fayed HL, Saleh AH. Frequency of vitamin D inadequacy among Saudi males visiting a Rheumatology Outpatient Clinic of a tertiary hospital in Al-Qassim region: Effect of vitamin D supplementation. The Egyptian Rheumatologist (2017), http://dx.doi.org/10.1016/j.ejr.2017.04.010