Vitamin D in the Middle East and North Africa

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A B S T R A C T

Purpose: The Middle East and North Africa (MENA) region registers some of the lowest serum 25-hydroxyvitamin D [25(OH)D] concentrations, worldwide. We describe the prevalence and the risk factors for hypovitaminosis D, completed and ongoing clinical trials, and available guidelines for vitamin D supplementation in this region.

Methods: This review is an update of previous reviews published by our group in 2013 for observational studies, and in 2015 for randomized controlled trials (RCTs) from the region. We conducted a comprehensive search in Medline, PubMed, and Embase, and the Cochrane Library, using MeSH terms and keywords relevant to vitamin D, vitamin D deficiency, and the MENA region, for the period 2012–2017 for observational studies, and 2015–2017 for RCTs. We included large cross-sectional studies with at least 100 subjects/study, and RCTs with at least 50 participants per arm.

Results: We identified 41 observational studies. The prevalence of hypovitaminosis D, defined as a 25-hydroxyvitamin D [25(OH)D] level below the desirable level of 20 ng/ml, ranged between 12–96% in children and adolescents, and 54–90% in pregnant women. In adults, it ranged between 44 and 96%, and the mean 25(OH)D varied between 11 and 20 ng/ml. In general, significant predictors of low 25(OH)D levels were female gender, increasing age and body mass index, veiling, winter season, use of sun screens, lower socioeconomic status, and higher latitude.

We retrieved 14 RCTs comparing supplementation to control or placebo, published during the period 2015-2017: 2 in children, 8 in adults, and 4 in pregnant women. In children and adolescents, a vitamin D dose of 1000–2000 IU/d was needed to maintain serum 25(OH)D level at target. In adults and pregnant women, the increment in 25(OH)D level was inversely proportional to the dose, ranging between 0.9 and 3 ng/ml per 100 IU/d for doses ≤ 2000 IU/d, and between 0.1 and 0.6 ng/ml per 100 IU/d for doses ≥ 3000 IU/d. While the effect of vitamin D supplementation on glycemic indices is still controversial in adults, vitamin D supplementation may be protective against gestational diabetes mellitus in pregnant women. In the only identified study in the elderly, there was no significant difference between 600 IU/day and 3750 IU/day doses on bone mineral density. We did not identify any fracture studies.

The available vitamin D guidelines in the region are based on expert opinion, with recommended doses between 400 and 2000 IU/d, depending on the age category, and country.

Conclusion: Hypovitaminosis D is prevalent in the MENA region, and doses of 1000–2000 IU/d may be necessary to reach a desirable 25(OH)D level of 20 ng/ml. Studies assessing the effect of such doses of vitamin D on major outcomes, and confirming their long term safety, are needed.

1. Introduction

One of the earliest reports on low 25-hydroxyvitamin D [25(OH)D] concentrations in the Middle East was in a group of apparently healthy young university students from Saudi Arabia, in the early eighties (Sedrani et al., 1983). The vitamin D field has since witnessed an explosion in publications, with a larger number of systematic reviews and meta-analyses than original publications, in the last decade (Holick, 2007; El-Hajj Fuleihan et al., 2015; Ross et al., 2011; Holick et al., 2011; Van Schoor and Lips, 2017; Sperati et al., 2013; Keum and Giovannucci, 2014; Bolland et al., 2014; Mao et al., 2013; Ford et al., 2014; Stubbs et al., 2015; Avenell et al., 2014; Weaver et al., 2016; Zheng et al., 2013; Bjelakovic et al., 2014; Chowdhury et al., 2014; Lips, 2010).

The Middle East North Africa (MENA) region spans latitudes from 15 to 39° N. At such latitudes, it would be anticipated that vitamin D synthesis from the skin should be possible over 300/364 days of the year (Tavera-Mendoza and White, 2007). However, some of the lowest reported serum 25(OH)D levels, the metabolite that reflects vitamin D nutritional status, are from this region (Arabi et al., 2010; Bassil et al., 2013; Hoteit et al., 2014; El-Rassi et al., 2012). A recent systematic review of 195 studies, involving over 168,000 participants from 44 countries, revealed mean values < 50 nmol/l (20 ng/ml) in 37% of studies, with higher proportions in the Middle East and Asia (Hilger et al., 2014). Environmental and lifestyle factors account for substantial variations in serum 25(OH)D levels, amounting to 7.5–37.5 nmol/l (3 to 15 ng/ml).

In this paper we describe 3 case presentations illustrating presentations for low vitamin D in the region. We then synthesize information based on a comprehensive literature search obtained from: reviews and studies on the prevalence of hypovitaminosis D, vitamin D randomized trials (completed and ongoing), vitamin D and overview guidelines, in the MENA region. The MENA countries, as defined by the World Bank, include: Algeria, Bahrain, Djibouti, Egypt, Jordan, Iran, Iraq, Kuwait, Lebanon, Libya, Malta, Morocco, Oman, Palestine/Israel, Qatar, Kingdom of Saudi Arabia (KSA), Syria, Tunisia, United Arab Emirates (UAE), and Yemen (MENA Countries Definition World Bank, n.d.). Details on literature search, abstract and title screen, eligibility criteria, calculation of weighted mean (WM) and pooled standard deviation (SDp), are presented in Appendix I (Arabi et al., 2010; Bassil et al., 2013; MENA Countries Definition World Bank, n.d.; Chakhtoura et al., 2017a, 2017b; Green, 2011; *Weighted Mean Calculation*, n.d.; *Pooled Standard Deviation Calculation*, n.d.).

2. Case presentations

2.1. Osteomalacia in a postmenopausal woman mimicking osteoporosis

A 52-year-old post-menopausal white female presented with worsening low back and hip pain of one year duration. She had difficulty getting up from the chair and climbing upstairs, and was unable to perform her daily activities. She reported avoiding dairy products, spent little time outdoors, had been veiled for many years, and was on no medications. Her physical exam was notable for diffuse musculoskeletal tenderness and inability to stand up from a sitting position. Her laboratory evaluation revealed hypocalcemia, calcium (Ca) of 6.9 mg/dl (normal 8.5–10.5), a normal albumin, hypophosphatemia, phosphorus (PO$_4$) of 2.5 mg/dl (normal 2.9–5), an elevated alkaline phosphatase (ALKP) of 820 IU/l (normal 35–120), a 25(OH)D level of < 5 ng/ml with a parathyroid hormone (PTH) level of 250 pg/ml (normal 10–65). Skull films revealed multiple lucent areas in the skull vault and parietal areas. Her bone mineral density (BMD) at the lumbar spine had a T-score of −2.46, and at the hip of −2.42. The biochemical profile was consistent with osteomalacia, although this diagnosis was not established by histomorphometry. Workup for malabsorption including stool fat, and a duodenal biopsy to rule out sprue, was negative.

She was treated with calcium, 600 mg po tid, plus high-dose vitamin D 600,000 IU intramuscularly twice within 2 months, and had a rapid and impressive clinical improvement. Her difficulty with ambulation improved within 1 week of start of therapy. Her serum Ca and PO$_4$ normalized within a month, but her ALKP and PTH took over a year to normalize. Her BMD showed increments of 40% at the spine and 35% at the hip at 4 months, 63% and 39% at 10 months, and 62% and 52% at 15 months, at these sites, respectively (Al-Ali and El-Hajj Fuleihan, 2000). Treatment of osteomalacia is extremely rewarding, with dramatic clinical improvement, accompanied by rapid increments and normalization of BMD, reflecting mineralization of osteomalacic bone. Such presentation has become relatively uncommon in Lebanon, but is still seen in the Gulf States, where concealed clothing style is the custom.

2.2. Rickets in infancy

JAH is a 14-month old male admitted to the pediatric Intensive Care Unit at the age of 4 months for a severe lower respiratory infection requiring intubation. On routine blood chemistry found to have a serum Ca of 4.5 mg/dl (normal 8.5–10.5), PO$_4$ was 4.2 mg/dl (normal for age 3.5–6.6), ALKP was 833 IU (normal for age 20–385) and a PTH was 357 pg/ml (normal 15–76). 25(OH)D concentration was < 3 ng/ml and 1,25 (OH)$_2$D3 was 105 pg/ml (normal 20–46). X-rays of wrists and knees showed changes of rickets (Fig. 1A, B). The patient had an excellent clinical, biochemical, and radiographic (Fig. 1C) response to vitamin D, with gradual rise in calcium to 10.5 mg/dl and 25(OH)D level to 40.4 ng/ml. The clinical and radiologic presentation may be similar or more severe (Fig. 1D) in patients homozygous for the H397P mutation in the ligand binding domain of the VDR, otherwise known as vitamin D resistant rickets, or vitamin D dependent rickets type 2 (VDDR2), where parents are heterozygous (Malloy and Feldman, 2010). In contrast however, such patients are refractory to even large doses of alfacalcidol and calcium, and may have alopecia. Due to frequent consanguinity in the Middle East, this condition is more prevalent than in western populations.

2.3. Asymptomatic low vitamin D level in a pregnant woman

A 32-year-old Lebanese pregnant lady was referred for evaluation and management of a low 25(OH)D level of 18 ng/ml, at 11 weeks of gestation. She is gravida 1 para zero, and has a non-significant past medical history. Early during her pregnancy, she was started on calcium carbonate 500 mg and cholecalciferol 600 IU twice a day, in addition to a prenatal multivitamin. She does not take dairy products. Upon presentation, she was completely asymptomatic. The patient was prescribed cholecalciferol 10,000 IU weekly throughout her pregnancy, and repeat 25(OH)D level at delivery was 32 ng/ml, with the same assay. Such presentation with borderline low 25(OH)D level is a common presentation, not only in pregnant women, but also in adolescents, adults, and elderly from the Middle East. The impact of such levels, as opposed to clear vitamin D deficiency, on major outcomes is unclear.

3. Prevalence of low 25(OH)D concentrations by age category and their predictors

In a previous review, we had noted that rickets and osteomalacia still occur in this sunny area (Bassil et al., 2013). We had also reported that hypovitaminosis D, defined as a serum 25(OH)D below 20 ng/ml, prevailed, with proportions between 30 and 90% depending on the age, gender, and country (Bassil et al., 2013). Prolonged breastfeeding without vitamin D supplementation and low dietary calcium intake were recognized risk factors for rickets and hypovitaminosis D in children. Advancing age, female gender, multiparity, clothing style, season, socio-economic status and urban living were predictors of
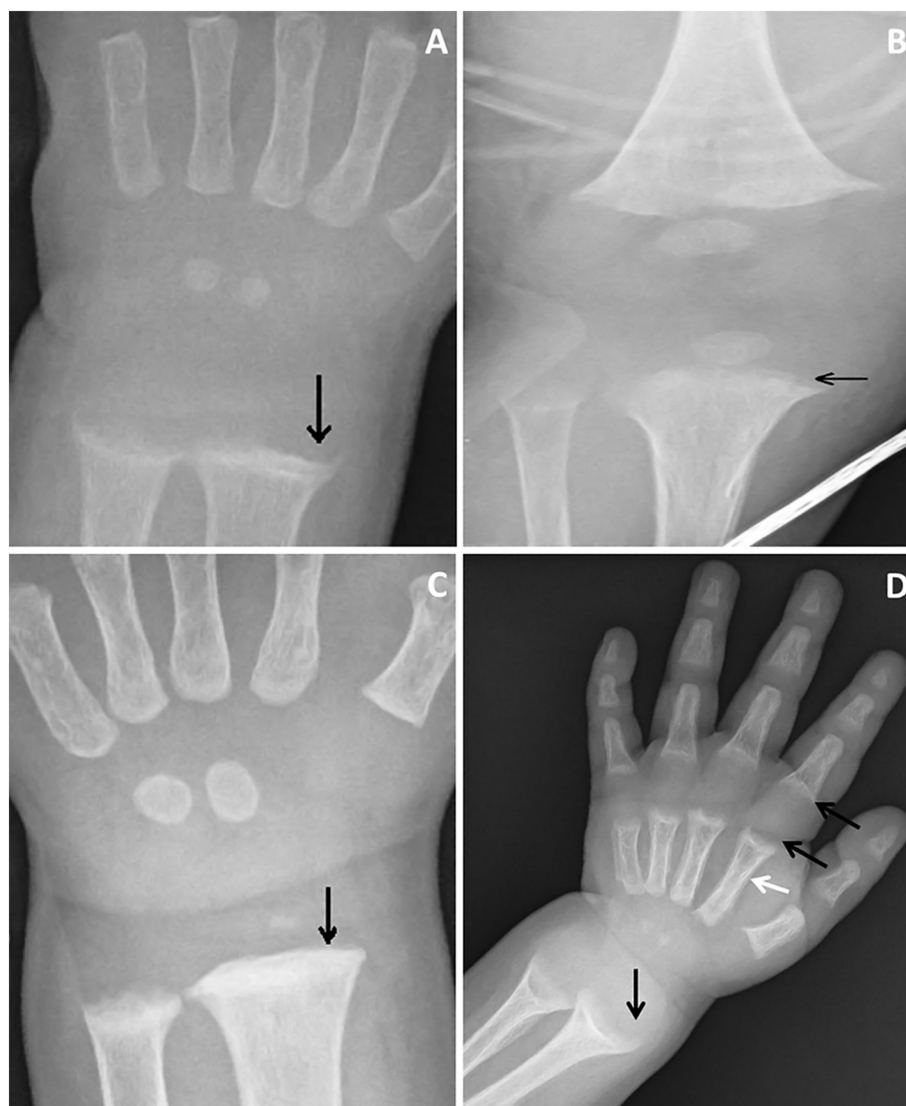
Fig. 1. Four panel figure of radiographs from a 4-month old boy with nutritional rickets (A–C), and a 2 year old girl with vitamin D dependent rickets type 2 (D). Wrist (A), and knee (B) radiographs reveal cupping and fraying of the metaphysis of the long bones (black arrow). Wrist radiograph (C) post-treatment demonstrates healing at the level of the radius (black arrow) with persistent changes at the ulna. Radiographic changes, with severe cupping extending from the radius to the metacarpals and phalanges (D), may be more severe in patients with vitamin D dependent rickets type 2 (black and white arrows).

hypovitaminosis D in adults (Bassil et al., 2013).

To update the above, we conducted a systematic search in Medline, PubMed, and Embase, using MeSH terms and keywords relevant to vitamin D, vitamin D deficiency, and focusing on the 20 countries of the MENA region, as per the World Bank definition (MENA, n.d.). We have limited the search to years 2012–2017, in view of our previous reviews on the topic, latest published in 2013 (Arabi et al., 2010; Bassil et al., 2013). The search resulted in 4012 articles that were screened by title and abstract, of which 182 were reviewed in full text, and 41 with a sample size of at least 100 participants were selected and summarized here-in (Appendix I, search methodology) (Arabi et al., 2010; Bassil et al., 2013; MENA, n.d.; Chakhtoura et al., 2017a, 2017b; Green, 2011; Weighted Mean Calculation, n.d.; Pooled Standard Deviation Calculation, n.d.). The studies included 1 from Algeria, 3 from Bahrain, 2 from Egypt, 10 from Iran, 3 from Jordan, 10 from KSA, 1 from Kuwait, 1 from Lebanon, 3 from occupied Palestine/Israel, 1 from Morocco, 1 from each of Qatar, Syria, and Tunis, and 3 from UAE. A unified assessment for the prevalence of hypovitaminosis D, by age categories, based on the studies selected, was challenging in view of the variability in the 25(OH)D cut-offs, season and assays used in the various studies

(Appendix II) (Hoteit et al., 2014).

The weighted means for serum 25(OH)D levels were between 13 and 18 ng/ml in children from Iran, Lebanon, and KSA, between 11 and 13 ng/ml in pregnant women from KSA and Iran, and between 13 and 24 ng/ml in adults in these 3 countries (Fig. 2). Adults from Bahrain had the lowest weighted mean 25(OH)D level of 13 ng/ml (Fig. 2).

In the pediatric age group, 90% of neonates in Bahrain and 94% in Jordan had a 25(OH)D below 20 ng/ml, while 65% in Saudi Arabia had a 25(OH)D level below 10 ng/ml (Appendix II) (Hoteit et al., 2014; Al-Mahroos et al., 2013; Khalesi et al., 2012; Khuri-Bulos et al., 2013; Fouda et al., 2017; Mohamed and Al-Shehri, 2013; Djennane et al., 2014; Shady et al., 2015; Ebrahimi et al., 2014; Kelishadi et al., 2014; Nikooyeh et al., 2017; Nichols et al., 2012; Al-Daghri et al., 2015; Al-Daghri et al., 2016; Al Shaikh et al., 2016; Kaddam et al., 2017; Sulimani et al., 2016; Korchia et al., 2013; Bezrati et al., 2016; Narchi et al., 2015; Rajah et al., 2012; Al-Sahlawi et al., 2014; Botros et al., 2015; Khalessi et al., 2015; Naseh et al., 2017; Al-Ajlan et al., 2015; Golbahar et al., 2013; Ardeshir Larijani et al., 2014; Esteghamati et al., 2014; Jaddou et al., 2012; Alfawaz et al., 2014; Ardawi et al., 2012; Tuffaha et al., 2015; Zhang et al., 2016; El Maghraoui et al., 2012;
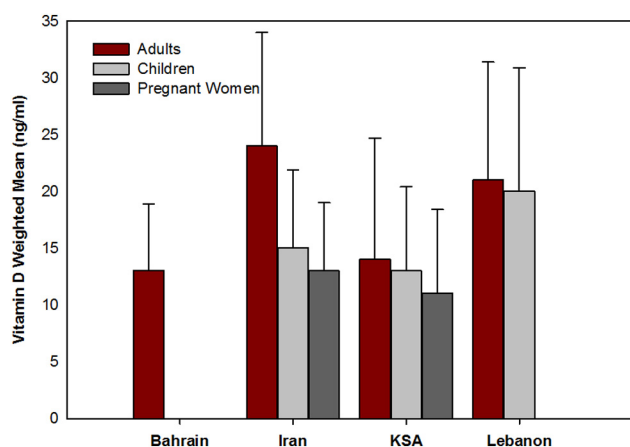
Fig. 2. Weighted means (± pooled SD) for serum 25-hydroxy-vitamin D levels by age group in 4 countries in the Middle East. In adults, the weighted means are based on 2 studies from each of Bahrain (N = 1150), Iran (N = 6842) and KSA (N = 4305) and one from Lebanon (N = 5091, spanning two periods, 2000–2004, and 2007–2008); in children the weighted means are based on 3 studies from Iran (N = 2809) and KSA (N = 5143) and one from Lebanon (N = 494, spanning the 2 same periods); and in pregnant women 3 from Iran (N = 351) and 2 from KSA (N = 1612).

Saliba et al., 2012a; El-Menyar et al., 2012; Sayed-Hassan et al., 2014; Sridhar et al., 2016; Hosseini et al., 2014; Saliba et al., 2012b). Predictors of low neonatal vitamin D included maternal 25(OH)D level, maternal vitamin D supplementation, time spent outdoors, gestational-neonatal age, and season.

In pregnant and lactating women, 54–96% of subjects in studies from Bahrain, Egypt, Iran and KSA had a 25(OH)D level below 20 ng/ml, and the proportions ranged from 27 to 68% for a cut-off below 10–12 ng/ml, in the 3 studies from KSA and Iran (Appendix II) (Hoteit et al., 2014).

In children and adolescents, the proportion of subjects with a 25(OH)D level below 15–20 ng/ml ranged between 12%–62% in studies from Algeria, Iran, Bahrain, Egypt, Iran, occupied Palestine-Israel, Jordan, KSA, and Lebanon. The highest proportions were reported in studies from KSA and UAE reaching proportions of 96% and 99% for this cut off, respectively, and 33–66% for a cut-off below 10–12 ng/ml in these countries (Appendix II) (Hoteit et al., 2014).

By far, the largest number of selected studies was in adults, spanning an age range of 18–65 years, where the proportion of subjects with a 25(OH)D level below 20–25 ng/ml ranged between 37% and 96%, depending on the age group and country, including Bahrain, Egypt, Iran, Jordan, KSA, Kuwait, Lebanon and Syria. The highest proportion of 96% was reported in a population based household survey in the spring in 2039 young adults from Jordan where the Liquid Chromatography Mass Spectrometry (LCMS/MS) vitamin D assay was used. The proportion of subjects with 25(OH)D levels below 10–12 ng/ml varied between 31 and 67% in studies from Bahrain, Iran, Jordan, KSA, Morocco, and Syria (Appendix II) (Hoteit et al., 2014).

In the elderly, the prevalence of levels below 20 ng/ml was between 38% and 77% in elderly from Egypt, Iran, and Lebanon, and 65% in KSA for a level range of 0–28 ng/ml for KSA (Appendix II) (Hoteit et al., 2014).

Consistent predictors of low 25(OH)D levels across the lifecycle included increasing age, female gender, high weight or body mass index (BMI), low physical activity, low intake of calcium or vitamin D supplements, concealed clothing, low sun exposure duration, winter season, lower education or socio-economic status, and urban residence (Hoteit et al., 2014; Al-Mahroos et al., 2013; Khalesi et al., 2012; Khuri-Bulos et al., 2013; Fouda et al., 2017; Mohamed and Al-Shehri, 2013; Djennane et al., 2014; Shady et al., 2015; Ebrahimi et al., 2014; Kelishadi et al., 2014; Nikooyeh et al., 2017; Nichols et al., 2012; Al-

Daghri et al., 2015; Al-Daghri et al., 2016; Al Shaikh et al., 2016; Kaddam et al., 2017; Sulimani et al., 2016; Korchia et al., 2013; Bezrati et al., 2016; Narchi et al., 2015; Rajah et al., 2012; Al-Sahlawi et al., 2014; Botros et al., 2015; Khalessi et al., 2015; Naseh et al., 2017; Al-Ajlan et al., 2015; Golbahar et al., 2013; Ardeshir Larijani et al., 2014; Esteghamati et al., 2014; Jaddou et al., 2012; Alfawaz et al., 2014; Ardawi et al., 2012; Tuffaha et al., 2015; Zhang et al., 2016; El Maghraoui et al., 2012; Saliba et al., 2012a; El-Menyar et al., 2012; Sayed-Hassan et al., 2014; Sridhar et al., 2016; Hosseini et al., 2014; Saliba et al., 2012b). Added to that is smoking status in adults and maternal weight at delivery (Appendix II) (Hoteit et al., 2014).

4. Vitamin D assay variation: a pressing need for standardization

The exponential rise in vitamin D publications is paralleled by a similar increase in the number and use of 25(OH)D assays available. Such high test volume necessitated a gradual shift from the kit based radio-immunoassays to the rapid, automated, platform assays, in most clinical and many research laboratories. The Vitamin D External Quality Assessment Scheme (DEQAS), recently reported 26 different assay methods being used in over 1100 laboratories, from 53 countries worldwide, with automated platform assays taking the lion's share (Carter et al., 2017). However, such shift has come at a large price, considering the variability in intra- and interassay performance, and differences in accuracy between methods, making comparison across studies, such as performed in this review, most challenging. Thus the pressing need for clinical and research laboratories to all engage in continuous calibration, recalibration and standardization (Carter et al., 2017; Barake et al., 2012; Binkley and Carter, 2017). The most reliable and accurate method is LCMS (Carter et al., 2017), when performed, but such technology is costly, and seldom used in commercial assays, and even research laboratories in the MENA region. Indeed, based on information obtained from a major vitamin D quality assurance programs DEQAS (*DEQAS Vitamin D External Quality Assessment Scheme*, n.d.), 22 laboratories in the MENA region currently partake in DEQAS: 14 from Iran, 14 from occupied Palestine/Israel, 2 each from Lebanon, KSA, and UAE (personal communication Graham Carter for DEQAS and Dr Hubert Vesper for VDCSP). Only one laboratory in Qatar is using the LCMS/MS methodology, and only one laboratory, based at our institution, partakes in the CDC VDSP (*Laboratory Quality Assurance and Standardization Program*, n.d.; Vitamin D CDC Certified Laboratories, 2017).

Our laboratory has been a participant in DEQAS for almost 2 decades, and consistently received certification. DEQAS uses few pooled sera and assesses measurements performed at one point in time. The CDC VDSCP is striving to improve the analytical performance of vitamin D assays and ultimately improve clinical and public health practice. It uses 40 unmodified, single donor samples measured over the course of a year to evaluate assay performance. Because of the more rigorous protocol and stringent evaluation criteria, obtaining certification by CDC VDSCP is more challenging. Between August 2016 and May 2017, our laboratory received a total 160 unknown samples from the VDSP (some duplicates to also assess precision), that were run for 25(OH)D levels using a platform automated assay (Elecsys Cobas) and the laboratory reported values that were compared against a reference value assigned for each sample, as obtained from measurements performed at the Centers for Disease Control and Prevention (Stepman et al., 2011; Mineva et al., 2015). Although the mean precision was quite tight, 4.7(2.7%, 95 CI [1.3–9.1%], the mean bias of 13.7% (SD = 36.8%), 95 CI [1.8–25.6%] exceeded the mean desirable bias range set by the VDSCP of ± 5%., with individual values falling much farther off. Indeed, only 24% of the samples fell within this recommended bias range (Fig. 3). Thus, even though our laboratory passes DEQAS challenges it was not able to obtain VDSCP certification, which may well to be reflect of the different purposes of these programs. The goal of clinical laboratories is to provide accurate and
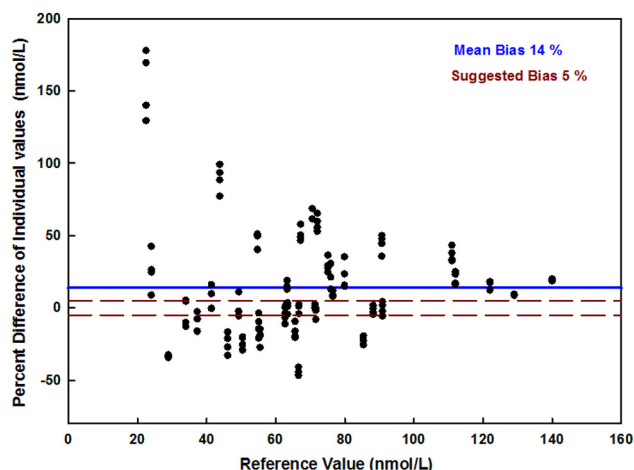
Fig. 3. Percent bias in 160 samples run as part of Center of Diseases C (CDC) Vitamin D Standardization Program (VDSP). The percent bias of the individual reported values is shown for all 160 samples run at our institution over 4 quarters in 2016–2017 using the platform automated Roche Elecsys assay compared with reference values defined by the CDC VDSP reference. Percent bias formula: [(reported value − reference value) / reference value] × 100. Although the mean % bias in our samples was 14%, many individual values fell outside that recommended bias range of −5% to +5% (range framed by dotted lines).

reliable vitamin D measurements to help physicians and public health officials in clinical and public health decision making. Factors affecting the accuracy and reliability of vitamin D measurements are related to the extraction methods to extract the vitamin D metabolite from its binding protein, the detection of 25(OH)D2 metabolite, cross-reactivity with 3-epi-25OHD3 and other vitamin D metabolites, and matrix interferences. These factors can result in a percent bias ranging between −25% to +25%, based on means group of laboratories using the same assay (*DEQAS Vitamin D External Quality Assessment Scheme*, n.d.). In our study, we did observe a high variability in bias among individual samples provided by the CDC VDSCP (Fig. 3). Since the samples provided by CDC are from individual donors, one can assume that similar variability in accuracy exists when measuring patient samples. Programs such as DEQAS combine sera to conduct their program, and this could result in samples showing a high bias being diluted with samples showing a low bias making it difficult to detect high variability in bias among different patients and could explain why certification through DEQAS can be achieved while certification through CDC VDSCP is more difficult to achieve. Clinical practice is based on single measurements performed on individual patients. The high variability in accuracy of measurements in patients is a pressing issue, the resolution of which is crucial to allow the successful pooling of 25(OH)D results across studies, the implementation of meta-analyses, and the development of evidence based vitamin D guidelines (Barake et al., 2012; Binkley and Carter, 2017; Binkley and Sempos, 2014).

5. Randomized trials of vitamin D supplementation in different age categories

We had previously conducted a systematic review on vitamin D randomized trials across all age groups, in the region (Chakhtoura et al., 2017a, 2017b).

The 4 trials in children and adolescents (El-Hajj Fuleihan et al., 2006; Ghazi et al., 2010; Mayan et al., 2015; Neyestani et al., 2014), mean age of 9.8–16.6 years, baseline 25(OH)D level 7.9–25 ng/ml, showed that a vitamin D dose of 1400–2000 IU/d would be needed to maintain a desirable 25(OH)D level ≥ 20 ng/ml in the majority of the population (Ross et al., 2011; Chakhtoura et al., 2017b). One study demonstrated substantial improvements in body lean mass and total hip

bone mineral content (BMC), in girls only, both in the low dose (400 IU/d) and the high dose (2000 IU/d) arms, compared to placebo, and in total hip area, in the high dose group only (El-Hajj Fuleihan et al., 2006). Interestingly, the latter effect persisted at 1 year after the discontinuation of the intervention (Ghazal et al., 2016). The risk of bias in these trials varied widely (Chakhtoura et al., 2017b).

Similarly, we had identified 19 RCTs in adults and elderly (Chakhtoura et al., 2017a; Hosseini et al., 2014; Ahmadi et al., 2013; Al-Sofiani et al., 2015; Al-Zahrani et al., 2014; Begay and Danshiyour, 2012; Breslavsky et al., 2013; El-Hajj Fuleihan et al., 2016; Firouzabadi et al., 2012; Gendelman et al., 2015; Ghavamzadeh et al., 2014; Golan et al., 2013; Moghassemi and Marjani, 2014; Nasri et al., 2014; Rashidi et al., 2009; Sharifi et al., 2014; Salehpour et al., 2012; Taheri et al., 2014; Tehrani et al., 2014). The risk of bias in the trials was unclear to high, except for few (Chakhtoura et al., 2017a). The response of 25(OH)D levels to vitamin D supplementation was blunted at high doses (Chakhtoura et al., 2017a), similarly to findings in Western studies (Ross et al., 2011; Cashman et al., 2011). Starting at a baseline 25(OH)D level of 8.6–15.5 ng/ml, a vitamin D dose ≥ 2000 IU/d allowed for the majority of subjects to increase their 25(OH)D level to a desirable level of 20 ng/ml (Chakhtoura et al., 2017a). In the meta-regression, baseline 25(OH)D level and vitamin D dose were significant predictors of the achieved 25(OH)D level post-intervention (Chakhtoura et al., 2017a).

We had also identified 10 trials in pregnant women (Chakhtoura et al., 2017b; Sabet et al., 2012; Dawodu et al., 2013; Shakiba and Iranmanesh, 2013; Soheilykhah et al., 2013; Etemadifar and Janghorbani, 2015; Karamali et al., 2015; Samimi et al., 2016a, 2016b; Shahgheibi et al., 2016; Vaziri et al., 2016). Nine studies were from Iran and one from the UAE (Chakhtoura et al., 2017b). The risk of bias was unclear to high, with the exception of 2 studies (Chakhtoura et al., 2017b). Starting at a mean baseline 25(OH)D level of 7–11 ng/ml, a daily vitamin D dose of 1800–3600 IU was needed to allow for the majority of the subjects to reach a 25(OH)D level of 20 ng/ml (Chakhtoura et al., 2017b).

To update the above systematic review (Chakhtoura et al., 2017a; Chakhtoura et al., 2017b), we conducted a comprehensive search spanning from 2015 to 2017, and only included trials with at least 50 participants per arm (Appendix I) (Arabi et al., 2010; Bassil et al., 2013; MENA Countries Definition World Bank, n.d.; Chakhtoura et al., 2017a; Chakhtoura et al., 2017b; Green, 2011; *Weighted Mean Calculation*, n.d.; *Pooled Standard Deviation Calculation*, n.d.). The search yielded 1280 citations after removal of duplicates. We screened the full text of 242 papers, and identified 14 relevant trials (Shahgheibi et al., 2016; Vaziri et al., 2016; Saad et al., 2018; Talaat et al., 2016; Taheri et al., 2015; Tepper et al., 2016; Zarrin et al., 2017; Kamelian et al., 2017; Jozanikohan and Kazemi Saleh, 2015; Mohammad-Alizadeh-Charandabi et al., 2015; Shehata, 2016; Rahme et al., 2017; Mojibian et al., 2015; Behjat Sasan et al., 2017).

5.1. Children and adolescents

The current update identified 2 trials in children, with a variable risk of bias from low to high. The study from KSA, randomized children, mean age 8.2 (3.5) years, to 400 IU/d (group 1), 45,000 IU weekly over 2 months then 400 IU/d (group 2), or 2000 IU/d for 3 months then 1000 IU/d for a total of 12 months (group 3) (Talaat et al., 2016). The mean (SD) 25(OH)D level increased from 12.9–14.3(5.4) ng/ml at baseline, to reach 47.7(21.4) ng/ml and 36.2 (7.0) ng/ml at 4 months, in group 2 and 3, respectively, and then decreased to 23.1(12.7) ng/ml in group 2, while it was maintained at 37.7(5.3) ng/ml in group 3 (Talaat et al., 2016). In contrast, it dropped from a high baseline of 21.7(9.5) to 17.0(9.4) ng/ml at 4 months, and 10.2(8.3) ng/ml at 12 months in the low dose group 1 (Talaat et al., 2016). Such findings confirm our previous report that a vitamin D dose of 1000–2000 IU/d may be necessary to maintain a 25(OH)D level ≥ 20 ng/ml, in children

and adolescents from this region (Chakhtoura et al., 2017b). A study from Egypt demonstrated that 300 IU/kg/day of vitamin D increased serum 25(OH)D level from 26.3 (12.7) ng/ml to 45.9(17.2) ng/ml, and resulted in a significant 6 unit drop in the Childhood Autism Rating Scale (CARS), in children (mean age 5.4 years) with vitamin D insufficiency at baseline, compared to placebo (Saad et al., 2018). Given the scarcity of vitamin D trials in children with autistic disorders (Mazahery et al., 2016), further trials are needed to confirm the protective effect of vitamin D supplementation in this specific population.

5.2. Pregnant women

In the current update, we identified 4 studies all from Iran, with an unclear (Shahgheibi et al., 2016; Vaziri et al., 2016; Behjat Sasan et al., 2017) or high risk of bias (Mojibian et al., 2015). Two of these studies were already described in our previous systematic review, and described here for completion, as they were published during the period 2015–2017 (Shahgheibi et al., 2016; Vaziri et al., 2016).

5.2.1. Vitamin D supplementation and 25(OH)D level

Two studies only reported on the change in 25(OH)D level following supplementation (Vaziri et al., 2016; Mojibian et al., 2015). The first compared an equivalent daily dose of around 3570 IU/d to 400 IU/d, and reported increments in the mean 25(OH)D level, from a mean baseline of 15 ng/ml, to 27 ng/ml in the low dose group, and to 38 ng/ml in the high dose group (Mojibian et al., 2015). The second reported increments, from a baseline 25(OH)D level of 12 ng/ml, of 6.4 ng/ml using a vitamin D dose of 2000 IU/d, while no change was detected in the placebo group (Vaziri et al., 2016). The increment in 25(OH)D level were 3 ng/ml/100 IU/d vitamin D for the lowest dose, and 0.3–0.6 ng/

ml/100 IU for the highest doses (Table 1) (Vaziri et al., 2016; Mojibian et al., 2015). Such findings are comparable to those from our previous review (Chakhtoura et al., 2017b).

5.2.2. Vitamin D supplementation and other skeletal and non-skeletal parameters

Two studies (mean baseline 25(OH)D level 13.5–17.4 ng/ml), administered high doses of vitamin D, ranging from 3570 to 5000 IU/d, and compared that to placebo or a low dose (400 IU/d), started in the first and continued until the third trimester or delivery. Both studies reported a protective effect of a high vitamin D dose, compared to a low dose or placebo, on the incidence of Gestational Diabetes Mellitus (GDM), with a calculated relative risk (RR) of 0.3–0.5 (Shahgheibi et al., 2016; Mojibian et al., 2015). These results are consistent with findings from our previous review (Chakhtoura et al., 2017b), and another recent one that was based mostly on data from Iran (Akbari et al., 2017). During pregnancy, vitamin D supplementation (at an equivalent daily dose of 1000–7142 IU) improved glycemic indices, when it was compared to no supplementation (Akbari et al., 2017), or when comparing a high (> 2000 IU/d) to a low dose (< 800 IU/d) (Chakhtoura et al., 2017a). However, these results were all derived from trials conducted in the same country (Iran) and the majority was conducted by the same research group (Chakhtoura et al., 2017b; Akbari et al., 2017).

One study demonstrated a protective effect of a high vitamin D dose, 50,000 IU every 2 weeks, started early in the second trimester, on the rate of pre-eclampsia, with a RR 1.94 (1.02–3.71), in the control arm compared to the high dose arm (Behjat Sasan et al., 2017). This is consistent with findings from previous reviews on the topic from studies conducted in Western countries (De-Regil et al., 2016; Hypponen et al.,

Table 1

Summary of 25(OH)D levels before and after supplementation in trials published during the Period 2015–2017,[a] with at least 50 participants per arm.

Author year/country	Dose	Mean age (years)	Gender (% female)	Duration	Baseline 25(OH)D (ng/ml)	Achieved 25(OH)D (ng/ml)	Δ 25(OH)D (ng/ml)	Δ 25(OH)D/ 100 IU/d (ng/ml)	25(OH)D level assay
Infants and children									
Saad et al., 2018	300 IU/kg/d	5	22	4 mo	26	46	20	NA	ELISA
Egypt	PBO	6			27	28	1		
Talaat et al., 2016	400	8	51	12 mo	22	10	−12	NA	CLIA
KSA	45,000 IU/w (2 mo) than 400 IU/d	9			14	23	9		
	2000 IU/d (3 mo) then 1000 IU/d	8			13	38	25		
Pregnant women									
Mojibian et al., 2015	400 IU/d	27	100	12 w GA till delivery	15	27	12	3	ELISA
Iran	50,000 IU/2 w (3570 IU/d)	28			15	38	23	0.6	
Vaziri et al., 2016	2000	32	100	26–28 w GA until delivery	12	18	6	0.3	CLIA
Iran	PBO	26			13	12	−1	NA	
Adults									
Taheri et al., 2015	2000	30	100	3.7 mo	9	28	19	0.9	EIA
Iran	C	29			9	9	0	NA	
El-Hajj Fuleihan et al., 2016	600	71	57	12 mo	20	26	6	0.9	LCMS
Lebanon	3750	71	54		21	36	15	0.4	
Tepper et al., 2016	100,000 IU bimonthly (6666 IU/d)	48	0	12 mo	16	26	10	0.1	NR
Occupied Palestine-Israel	PBO				15	21	6	NA	
Zarrin et al., 2017[b]	1000	48	53	3 mo	19	–	11	1.1	ELISA
Iran	PBO	48	51		15	–	−2	NA	
Kamelian et al., 2017[b]	7142	39	69	9 mo	8	–	32	0.4	CLIA
Iran	PBO	41	63		8	–	9	NA	

Abbreviations: C: control; CLIA: Chemiluminescence Immunoassay; EIA: Enzymatic Immune Assay; ELISA: Enzyme Linked Immunosorbent Assay; GA: gestational age; LCMS: Liquid Chromatography Mass; mo: months; Spectrometry; NA: not applicable; NR: not reported; PBO: Placebo; w: weeks.

[a] This is an update of a previous systematic review on vitamin D randomized controlled trials conducted in the MENA region. For further details, refer to the main text and to previous publications (Chakhtoura et al., 2017a, 2017b).

[b] Achieved 25(OH)D level not reported but the change in 25(OH)D level reported.

2013).

The effect of vitamin D supplementation on neonatal and infant anthropometrics was assessed in one trial, that administered vitamin D (2000 IU/d), starting at 26–28 weeks gestation, or placebo (Vaziri et al., 2016). It revealed no significant difference between groups (Vaziri et al., 2016). There was also no significant difference in BMD in a sub-group of the population who underwent this measurement, both in the mothers and their neonates (Vaziri et al., 2016). To-date, the effect of vitamin D supplementation during pregnancy on neonatal anthropometric and bone parameters is still a matter of debate. While the neutral results described here-in replicate findings of a study from Brazil, that administered 200 IU of vitamin D with 600 mg of calcium daily, or placebo (Diogenes et al., 2015), other trials from the UK showed a potential beneficial effect with a vitamin D dose of 1000 IU/d, with a trend for a higher neonatal bone mineral content (BMC) at forearm (Congdon et al., 1983), or a higher whole body BMC, in neonates born in the winter season (Cooper et al., 2016). Indeed, baseline 25(OH)D level vitamin D dose administered, and the timing at which supplementation was started, seem to be important modulators of response, and this needs to be taken into consideration.

5.3. Adults and elderly

The current update identified 8 trials: 5 from Iran (Taheri et al., 2015; Zarrin et al., 2017; Kamelian et al., 2017; Jozanikohan and Kazemi Saleh, 2015; Mohammad-Alizadeh-Charandabi et al., 2015), 1 from Egypt (Shehata, 2016), one from occupied Palestine/Israel (Tepper et al., 2016), and one from Lebanon (El-Hajj Fuleihan et al., 2016; Rahme et al., 2017). The latter was included in our previous review (Chakhtoura et al., 2017a), since we had access to primary data, but it was not published then, and is described herein (Table 1) (El-Hajj Fuleihan et al., 2016; Taheri et al., 2015; Tepper et al., 2016; Zarrin et al., 2017; Kamelian et al., 2017). The risk of bias in the included trials was unclear (Taheri et al., 2015; Tepper et al., 2016; Kamelian et al., 2017; Jozanikohan and Kazemi Saleh, 2015) to high (Zarrin et al., 2017; Mohammad-Alizadeh-Charandabi et al., 2015), with the exception of 2 RCTs considered at low risk of bias (El-Hajj Fuleihan et al., 2016; Shehata, 2016). Three studies were conducted exclusively in women (Taheri et al., 2015; Mohammad-Alizadeh-Charandabi et al., 2015; Shehata, 2016), one study exclusively in men (Tepper et al., 2016) and the others included both genders (El-Hajj Fuleihan et al., 2016; Zarrin et al., 2017; Kamelian et al., 2017; Jozanikohan and Kazemi Saleh, 2015). The mean BMI was $\geq 25 \text{ kg/m}^2$ in all studies (El-Hajj Fuleihan et al., 2016; Taheri et al., 2015; Tepper et al., 2016; Zarrin et al., 2017; Kamelian et al., 2017; Shehata, 2016). Several trials were conducted in individuals with diseases not expected to affect vitamin D metabolism, such as pre-diabetes (Zarrin et al., 2017), asymptomatic bacterial vaginosis (Taheri et al., 2015), coronary artery disease (Jozanikohan and Kazemi Saleh, 2015). All the studies compared vitamin D supplementation (low < 1000 IU/d (Mohammad-Alizadeh-Charandabi et al., 2015; Shehata, 2016), intermediate dose 1000–2000 IU/d (Taheri et al., 2015; Zarrin et al., 2017), or high dose > 2000 IU/d (Tepper et al., 2016; Kamelian et al., 2017; Jozanikohan and Kazemi Saleh, 2015) to placebo, except one study that compared a low (600 IU/d) to a high (3750 IU/d) vitamin D dose (El-Hajj Fuleihan et al., 2016).

5.3.1. Serum 25(OH)D levels before and after vitamin D supplementation

Data are derived from 6 studies (El-Hajj Fuleihan et al., 2016; Taheri et al., 2015; Tepper et al., 2016; Zarrin et al., 2017; Kamelian et al., 2017; Jozanikohan and Kazemi Saleh, 2015). Mean baseline 25(OH)D level was < 10 ng/ml in 2 studies (Taheri et al., 2015; Kamelian et al., 2017), 10–20 ng/ml in one (Tepper et al., 2016), and between 20 and 30 ng/ml in 2 other studies (El-Hajj Fuleihan et al., 2016; Zarrin et al., 2017). One study did not report on baseline 25(OH)D levels, but specified that all the participants had a level < 30 ng/ml (Jozanikohan and

Kazemi Saleh, 2015). The increment in 25(OH)D level per 100 IU/d was inversely proportional to the administered dose, similar to our previous findings (Chakhtoura et al., 2017a), ranging between 0.9 and 1.1 ng/ml per 100 IU/d for doses ≤ 2000 IU/d, and between 0.1 and 0.4 ng/ml per 100 IU/d for doses ≥ 3000 IU/d (Table 1) (El-Hajj Fuleihan et al., 2016; Taheri et al., 2015; Tepper et al., 2016; Zarrin et al., 2017; Kamelian et al., 2017).

5.3.2. Vitamin D supplementation and other skeletal parameters

Vitamin D at a dose of 50,000 IU/week for 9 months in 119 Iranian women and men resulted in a significant increase in FGF23 level, compared to placebo (Kamelian et al., 2017). An adequately powered study of 221 elderly overweight Lebanese individuals, with a baseline femoral T-score of −1.7 (0.8), demonstrated that vitamin D3 at daily equivalent doses of 600 IU or 3570 IU yielded similar increments in BMD at one year, despite a significant difference in the achieved 25(OH)D level, 36 (9.7) ng/ml in the high dose arm and 26 (7) ng/ml in the low dose arm (Rahme et al., 2017).

5.3.3. Vitamin D supplementation and extra-skeletal parameters

Three studies assessed the effect of vitamin D supplementation on metabolic and glycemic indices, as primary outcomes (El-Hajj Fuleihan et al., 2016; Tepper et al., 2016; Zarrin et al., 2017). Significant improvement in the fasting blood glucose, insulin and HOMA-IR levels in pre-diabetic Iranian patients were noted in subjects receiving vitamin D3 1000 IU/d over 3 months, compared to placebo (Zarrin et al., 2017). Another study conducted on a similar population from occupied Palestine/Israel, administered a higher vitamin D dose, 100,000 IU bi-monthly, and did not show any significant difference in glycemic indices between arms (Tepper et al., 2016). Finally, the above described study in Lebanese overweight elderly did not detect any significant difference in indices of insulin resistance, including HOMA-IR, in the high compared to the low vitamin D dose groups (El-Hajj Fuleihan et al., 2016). In trials conducted in women of reproductive age, vitamin D supplementation allowed an improvement in premenstrual syndrome (Shehata, 2016), a higher rate of cure of asymptomatic bacterial vaginosis (Taheri et al., 2015), and a lower rate of oral contraception discontinuation (Mohammad-Alizadeh-Charandabi et al., 2015).

Clinical trials of vitamin D supplementation and its impact on skeletal and extra-skeletal parameters, and surrogate outcomes, from the MENA, are still scarce. There are no studies on fall or fracture. Findings on metabolic and glycemic parameters are conflicting (El-Hajj Fuleihan et al., 2016; Tepper et al., 2016; Zarrin et al., 2017). While our previous systematic review showed a significant improvement in HOMA-IR with a high vitamin D dose, in studies extending over ≤ 4 months (Chakhtoura et al., 2017a), results of the current studies were conflicting, possibly related to differences in the risk of bias, race (Persian versus Arab) and study duration; the protective effect of vitamin D supplementation was only detected in short term studies, and not in those extending over 12 months (El-Hajj Fuleihan et al., 2016; Tepper et al., 2016). Indeed, this controversy is not specific to the MENA region, but constitutes a challenge worldwide (Mirhosseini et al., 2017; Lee et al., 2017). The recent scientific statement of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) on vitamin D supplementation for the prevention and management of chronic non-skeletal diseases concluded that "no evidence exists, so far, that administering vitamin D could reduce type 2 diabetes or obesity in the general population" (Cianferotti et al., 2017). Such statement is consistent with the Institute of Medicine 2009 report regarding the effect of vitamin D supplementation on various outcomes including cancer/neoplasms, cardiovascular disease and hypertension, diabetes and metabolic syndrome, falls and physical performance, immune functioning and autoimmune disorders, infections, neuropsychological functioning, and preeclampsia (Ross et al., 2011).

Table 2

Summary of vitamin D replacement guidelines in the general population, identified in the MENA region.

Author year/journal	Country	Guidelines developing group[a]	Desirable 25(OH) D level	Recommendations
A vitamin D targeted guidelines				
Raef et al., 2011 Ann Saudi Med	KSA	Osteoporosis Working Group of King Faisal Specialist Hospital and Research Centre	NA	- 18–50 years: 400–800 IU/d - 51–70 years: 800 IU/d - > 70 years: 800 IU/d
Al-Daghri et al., 2017 Arch Osteoporos	KSA	Prince Mutaib Chair for Biomarkers of Osteoporosis: 12 local and 2 expert advisers from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)	- Sufficiency: 25(OH) D ≥ 20 ng/ml - Adequacy for frail, osteoporotic elderly: 25(OH)D > 30 ng/ml	- Pregnant women: 1000–2000 IU/d - Post-menopausal women: 1000–2000 IU/d
Haq et al., 2018 J Steroid Biochem Mol Biol	UAE	Not defined explicitly, but authors included experts in endocrinology and metabolism, biochemistry and public health	–30 ng/ml as per the Endocrine Society	- Children and adolescents: 600–1000 IU/d - > 18 years: 800–2000 IU/d - Pregnant women: 1500–2000 IU/d
B osteoporosis guidelines				
Lebanese Society for Osteoporosis and Metabolic Bone disorders (OSTEOS), 2012	Lebanon	*Guidelines developed by*: OSTEOS *Guidelines endorsed by*: Lebanese Society of Endocrinology; Lebanese Society of Obstetrics and Gynecology; Lebanese Association of Orthopedic Surgeons; Lebanese Society of Radiology; Lebanese Society of Rheumatology; Lebanese Society of Family Medicine; Lebanese Society of Internal Medicine; Lebanese Society of General Practitioners	30–60 ng/ml	- Children-adolescents and low-risk adults under 50 years of age: 600–1000 IU/d - High-risk and older adults: 1000–2000 IU/d, with potential for consideration of higher doses
Maalouf et al., 2007 J Musculo-skelet Neuronal Interact	MENA	Not defined explicitly, but authors included experts in osteoporosis, endocrinology and metabolism	No clear statement	- Women 50–70 year: ≥ 400 IU/d - Women > 70 years: ≥ 600 IU/d

Abbreviations: 25(OH) D: 25-hydroxyvitamin D; ESCEO: European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; KSA: Kingdom of Saudi Arabia; MENA: Middle East and North Africa; NA: not available; OSTEOS: Lebanese Society for Osteoporosis and Metabolic Bone disorders; UAE: United Arab Emirates.

[a] None of the documents describe the methodology used in the guideline development process.

6. Available vitamin D replacement guidelines for MENA - who to screen and replacement doses

The search strategy identified 70 citations for Medline, 60 for Pubmed, and 171 for Embase. After screening titles and abstracts, we considered 5 citations as eligible, targeting the general population (Table 2) (Raef et al., 2011; Al-Daghri et al., 2017; Haq et al., 2018; Lebanese Society of Osteoporosis and Metabolic Bone Disorders, 2012; Maalouf et al., 2007). Two guidelines included recommendations on vitamin D replacement, as part of osteoporosis guidelines (Raef et al., 2011; Maalouf et al., 2007), and recommended a vitamin D dose ranging between 400 and 800 IU/d, depending on the age category. The Lebanese Society for Osteoporosis and Metabolic Bone disorders (OS-TEOS) recommends a vitamin D dose of 600–1000 IU/d for children, adolescents and low risk adults (< 50 years), and a dose of 1000–2000 IU/d for older and high risk adults (Lebanese Society of Osteoporosis and Metabolic Bone Disorders, 2012). Two other guidelines, from KSA and UAE, were exclusively dedicated to vitamin D supplementation, and recommended 800–2000 IU/d, depending on age category and reproductive status (Al-Daghri et al., 2017; Haq et al., 2018). None of these guidelines were based on a rigorous systematic review on vitamin D dose response in the MENA region, but rather, they were mostly based on expert opinion and review of the evidence from Western studies, regarding target 25(OH)D level, and recommended doses (Table 2) (Raef et al., 2011; Al-Daghri et al., 2017; Haq et al., 2018; Lebanese Society of Osteoporosis and Metabolic Bone Disorders, 2012; Maalouf et al., 2007).

7. Ongoing trials

Our search on ClinicalTrials.Gov identified 7 ongoing studies conducted in adults (3 from KSA, one from Iran, one from Qatar and one from occupied Palestine/Israel, Appendix III). Two studies are conducted on patients with multiple sclerosis (n = 240 and 200), and assess the effect of vitamin D supplementation (50,000 IU/week) over one year, on disease relapse rate, and the extended disability state scale score. One study is conducted in diabetic patients (n = 180) and evaluates the effect of vitamin D, given as a monthly loading dose of 120,000 IU over 6 months, compared to placebo, on the change in HbA1c, and other metabolic parameters. Two other studies target patients at high risk of diabetes (n = 200) or those with impaired glucose tolerance (n = 500), and administer a high vitamin D dose (4000–5000 IU/d), or placebo. Their primary outcome is insulin resistance and the incidence of diabetes, respectively. The remaining 2 studies (n = 1080 and 432) compare the effect of different doses of vitamin D on 25(OH)D level and other mineral and muscle parameters.

We identified 2 ongoing studies in pregnant women. One of them from Lebanon (n = 280), administers 2 vitamin D doses, a low (daily equivalent dose of 660 IU) versus a high dose (daily equivalent dose of 2850 IU), started early in the second trimester and continued until delivery. The latter study is powered for 2 primary outcomes: the proportion of women reaching the IOM desirable level of 20 ng/ml and neonatal bone mineral content, assessed by DXA at 4 weeks (± 2 weeks) after birth. The other study from occupied Palestine/Israel compares 2 lower vitamin D doses (400 IU/d versus 2000 IU/d), and assesses the impact of supplementation on tibial and radial bone density, using quantitative US.

Although two of the described studies (one in adults and one in pregnant women) had an estimated completion date in 2012 and 2014, we could not identify any results on clinicaltrials.gov, nor in PubMed, Medline, and Embase.

8. Discussion

Nutritional rickets is still seen in our region, due to peculiar lifestyle factors, and genetic rickets is more likely to occur than in other regions, due to high consanguinity rates. There are no population based studies in the MENA region to derive specific statistics.

Our systematic review confirms the high prevalence of silent hypovitaminosis D in the MENA region, and that vitamin D at doses higher

than those recommended by the IOM would be necessary to raise serum 25(OH)D levels to the desirable range of 20 ng/ml defined, in western populations (Arabi et al., 2010; Bassil et al., 2013; Chakhtoura et al., 2017a, 2017b).

However, the clinical significance of 25(OH)D levels in the teens to below 20 ng/ml, such as commonly seen and illustrated in case 3, is totally unclear. Similarly, unknown is the desirable 25(OH)D range due to the scarcity of vitamin D RCTs investigating the impact of its replacement on major health outcomes in this region.

The predictors of low 25(OH)D levels highlighted in this report are well described and include extremes of age, female gender (some studies reported higher levels in women due to the higher likelihood of using vitamin D supplements), pregnancy, latitude, UVB/sun exposure, pollution, concealed clothing style, high BMI, lower socioeconomic status, skin pigmentation, race, and ethnicity (Holick, 2007; Bassil et al., 2013). Seasonal variations of vitamin D are well described, with lower serum 25(OH)D levels in the winter, except for countries from the Gulf states, where they are lower in the summer due to longer in-door dwelling to avoid the scorching heat. In addition, genetic factors, namely polymorphisms in key genes of the vitamin D pathway, modulate vitamin D status in western populations and possibly the Middle East (Wang et al., 2010; Ahn et al., 2010; Arabi et al., 2017). The recognition of these consistent predictors justifies vitamin D supplementation strategies to prevent progression to symptomatic osteomalacia or rickets, which although becoming increasingly rare, is certainly not extinct in the region.

We recognize several limitations of our systematic review, mostly stemming from the original studies available. None of the observational studies or trials was truly population-based, as detailed in Appendix II (Hoteit et al., 2014; Al-Mahroos et al., 2013; Khalesi et al., 2012; Khuri-Bulos et al., 2013; Fouda et al., 2017; Mohamed and Al-Shehri, 2013; Djennane et al., 2014; Shady et al., 2015; Ebrahimi et al., 2014; Kelishadi et al., 2014; Nikooyeh et al., 2017; Nichols et al., 2012; Al-Daghri et al., 2015; Al-Daghri et al., 2016; Al Shaikh et al., 2016; Kaddam et al., 2017; Sulimani et al., 2016; Korchia et al., 2013; Bezrati et al., 2016; Narchi et al., 2015; Rajah et al., 2012; Al-Sahlawi et al., 2014; Botros et al., 2015; Khalessi et al., 2015; Naseh et al., 2017; Al-Ajlan et al., 2015; Golbahar et al., 2013; Ardeshir Larijani et al., 2014; Esteghamati et al., 2014; Jaddou et al., 2012; Alfawaz et al., 2014; Ardawi et al., 2012; Tuffaha et al., 2015; Zhang et al., 2016; El Maghraoui et al., 2012; Saliba et al., 2012a; El-Menyar et al., 2012; Sayed-Hassan et al., 2014; Sridhar et al., 2016; Hosseini et al., 2014; Saliba et al., 2012b). Although we only selected relatively large studies (trials with ≥ 50 participants per arm, and observational studies with ≥ 100 participants), sample size calculations and power analyses were missing from several reports. There was a large heterogeneity in 25(OH)D assays used, and only few studies reported 25(OH)D results obtained with the superior method of LCMS/MS. This is an important limitation considering the high variability in 25(OH)D assays and for many limited accuracy. Indeed, none of the reports mentioned participation in an external vitamin D quality assurance program, and the number of participating laboratories, with the exception of a couple of countries, in DEQAS and VDSP was quite low. The risk of bias of RCTs was high, with the exception of a few (El-Hajj Fuleihan et al., 2016; Saad et al., 2018; Shehata, 2016), and although it was not independently assessed by 2 co-authors, this causes serious concerns regarding the internal validity of the trials reported. In studies where mean 25(OH)D levels were not reported, we assumed that the mean and median are the same. Reporting of patients' compliance and adverse events was scarce, and data on the safety of moderate to high vitamin D doses is therefore still lacking.

In summary, most RCTs identified the impact of vitamin D supplementation on serum 25(OH)D levels as the main outcome, and no study has evaluated its effect of supplementation on fractures or falls. Furthermore, the few guidelines available are mostly based on expert opinion. Given the large variability in fracture risk worldwide (Ballane et al., 2014; Kanis et al., 2012), and the high prevalence of hypovitaminosis D in the MENA region, the significance of which is unclear, large randomized controlled trials from the MENA region are needed to confirm the applicability of findings from Western countries, and to enable the rigorous development of region-specific vitamin D guidelines.

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Conflicts of interest statement

Nothing to disclose.

Transparency document

The Transparency document associated with this article can be found, in online version.

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