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REVIEW

Impact of vitamin D replacement in adults and elderly in the Middle East and North Africa: a systematic review and meta-analysis of randomized controlled trials

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Abstract
Summary In the Middle East and North Africa (MENA), a vitamin D dose ≥2000 IU/day may be needed to allow to the majority of the population to reach the target 25-hydroxyvitamin D (25(OH)D) level ≥20 ng/ml. Data in the region on the effect of vitamin D supplementation on various skeletal and extra-skeletal effects are scarce.
Introduction Hypovitaminosis D is prevalent worldwide, more so in the Middle East and North Africa (MENA). This study aims to determine the effects of vitamin D replacement on the mean difference in 25-hydroxyvitamin D [25(OH)D] level reached and other outcomes, in the MENA.
Methods This is a meta-analysis of randomized trials from the MENA, administering vitamin D supplementation for at least 3 months, without language or time restriction. We conducted a comprehensive search in seven databases until July 2015. We abstracted data from published reports, independently and in duplicate. We calculated the mean difference (MD) and 95 % CI of 25(OH)D level reached for eligible comparisons, and pooled data using RevMan version 5.3.
Results We identified 2 studies in elderly and 17 in adults; for the latter, 11 were included in the meta-analysis. Comparing a high vitamin D dose (>2000 IU/day) to placebo (nine studies), the MD in 25(OH)D level achieved was 18.3 (CI 14.1; 22.5) ng/ml; p value < 0.001; I^2 = 92 %. Comparing an intermediate dose (800–2000 IU/day) to placebo (two studies), the MD in 25(OH)D level achieved was 14.7 (CI 4.6; 24.9) ng/ml; p value 0.004; I^2 = 91 %. Accordingly, 89 and 71 % of participants, in the high and intermediate dose groups, respectively, reached the desirable level of 20 ng/ml. The risk of bias in the included studies was unclear to high, except for three studies.
Conclusion In the MENA region, vitamin D doses ≥2000 IU/day may be needed to reach the target 25(OH)D level ≥20 ng/ml. The long-term safety and the efficacy of such doses on various outcomes are unknown.

Keywords Meta-analysis · Meta-regression · Middle East and North Africa · Vitamin D

Protocol registration number on PROSPERO CRD42014010488

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Introduction

Hypovitaminosis D is a worldwide problem [1, 2]. While normal mean 25-hydroxyvitamin D (25(OH)D) levels in adults and elderly are observed in North America, Asia Pacific, and Europe (20.4–28.9 ng/ml) [1], the Middle East and North Africa (MENA) region registers the lowest values (13.6–15.2 ng/ml), for the same age category, despite plentiful sunshine [1–3].

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In adults, the classical risk factors for hypovitaminosis D are related to older age, female gender, higher latitude, and dark skin pigmentation [4]. Other risk factors, specific to the MENA, have been identified, including multiparity, concealed clothing style and veiling, season (winter in the Mediterranean region, summer in gulf countries), lower socioeconomic status, urban living, and the lack of governmental regulation of food fortification [4, 5]. Furthermore, genetic factors may play a contributory role [6, 7].

Several scientific societies have issued guidelines on vitamin D replacement in the general population. The IOF was the only society to specifically recognize the Middle East as a region with a high prevalence of hypovitaminosis D, and thus requiring higher doses, of 2000 IU/day [8]. While the Institute Of Medicine (IOM) defined the recommended dietary allowance (RDA) for vitamin D in adults from North America as a dose of 600 IU/day allowing ≥97.5 % of participants to reach a desirable 25(OH)D level ≥20 ng/ml [9], the Endocrine Society (ES) guidelines suggested to use higher doses of 1500–2000 IU/day in adults and elderly, in order to reach their target 25(OH)D level of 30 ng/ml [10].

The objectives of this paper are to: (1) Determine the mean difference in 25(OH)D level reached with low (<800 IU), intermediate (800–2000 IU), or high (>2000 IU) daily dose of vitamin D in the MENA and estimate the proportion of individuals reaching a 25(OH)D level ≥20 ng/ml at the end of the intervention; (2) Compare the effect of vitamin D supplementation, by dose category, on skeletal and extra-skeletal outcomes; (3) Define the dose response of vitamin D in individuals in this region and identify the potential predictors affecting 25(OH)D level reached following intervention.

Methods

This is a systematic review and meta-analysis, implemented according to the Cochrane group guidelines for such analysis [11]. The protocol of this review was registered on PROSPERO (CRD42014010488) [12].

a. Eligibility criteria

Inclusion criteria

- Participants

– Individuals from the MENA countries, based upon the World Bank definition: Algeria, Bahrain, Djibouti, Egypt, Jordan, Iran, Iraq, Kuwait, Lebanon, Libya, Malta, Morocco, Oman, Palestine/Israel, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates (UAE), and Yemen [13].
– Apparently healthy, community-dwelling individuals, or individuals with mild diseases who have no reason to have altered vitamin D metabolism, such as chronic liver or kidney diseases.
– Age >18 years.

- Intervention

– Vitamin D of any dose, given orally, daily, weekly, or monthly, with or without calcium supplementation, for at least 3 months.

- Type of studies

– Randomized controlled trials (RCTs)

Exclusion criteria

– Studies conducted in pregnant women.
– Studies conducted in adults with osteomalacia, or institutionalized/hospitalized individuals, those with chronic illnesses (kidney, liver, or heart failure) or conditions or drug therapy that affect vitamin D metabolism (anticonvulsants, steroids, anti-fungal, malabsorption, bypass surgery).
– Studies administering vitamin D at a frequency of less than once monthly, or as fortified food, or active vitamin D.

b. Search strategy

We conducted a comprehensive search in February 2014, and an update in July 2015, in the following electronic databases: MEDLINE (1946 till present), EMBASE, PubMed, Cochrane Library, in addition to Popline, Index Medicus for WHO Eastern Mediterranean (IMEMR), and Global Health Library. We applied no time or language limitation. We used MeSH terms and keywords relevant to vitamin D and MENA countries. We applied an RCT filter (Appendix 1). In addition, in 2014, we searched trials registries, the ClinicalTrial.gov., and the WHO International Clinical Trials Registry, for registered and potentially completed trials. Finally, we screened the references lists of all systematic reviews of RCTs on the topic, published in the last 10 years. We considered only published trials.

c. Study selection

Three reviewers (MC, SEG, KS) screened the retrieved citation for potential eligibility. The selection of each article was implemented in duplicate and independently by teams of two reviewers. We obtained the full texts of citations judged as potentially eligible by at least one reviewer. Teams of two reviewers screened the full text in duplicate, and independently. We resolved disagreements by discussion with a content expert (GEHF). We

conducted a calibration exercise on a sample of abstracts and full texts in order to standardize reviewers' screening.

d. Data analysis

We performed data collection in duplicate and independently, using standardized pilot tested data abstraction forms. Data collection included the following variables: author, publication year, city, country and latitude, sampling method, intervention details, number of participants, age, body mass index (BMI), baseline and post-intervention 25(OH)D level, vitamin D assay, co-morbidities, compliance and adverse events, in addition to data on other pre-specified skeletal and extra-skeletal outcomes.

e. Risk of bias assessment

We assessed in duplicate the risk of bias (ROB) for the 25(OH)D level outcome in the included studies, using the Cochrane Collaboration's tool for bias assessment [11]. We resolved disagreement by discussion with experts (GEHF, EA). We assessed publication bias by performing a funnel plot of the included studies [11].

f. Standard meta-analysis

For each predefined outcome in each comparison, we conducted a random-effects meta-analysis, when at least two studies were available, in adults and elderly separately. In each comparison, we calculated the mean difference (MD) and 95 % CI of 25(OH)D level achieved following the intervention, using RevMan (version 5.3). Similarly, we calculated the MD and relative risk (RR) for the other continuous and categorical outcomes, respectively. For comparison purposes, we calculated the weighted mean (WM) and pooled standard deviation (SDp) of the vitamin D dose and 25(OH)D level (Appendix 2). In addition, in each dose category, using the WM 25(OH)D level achieved, and assuming normality of the distribution of 25(OH)D level, we calculated the proportion (%), and 95 % CI, of subjects reaching a 25(OH)D ≥20 ng/ml, at the end of the intervention; 95 % CI was calculated using an online calculator [14].

We conducted subgroup analyses based on baseline 25(OH)D level, BMI, and the supplementation duration. We performed a complete case analysis. We assessed statistical heterogeneity between studies using the I^2 and chi square, with significance at p value ≤0.05.

g. Meta-regression

We performed a random-effects meta-regression to identify the predictors of the achieved 25(OH)D level, using data derived from intervention and placebo/control arms of the included adult and elderly studies. We calculated within studies variances and the inverse of standard error $(SE)^2$, based on study arm standard deviations (SD). We calculated between studies variances on STATA version 12. We considered the predictors identified in previous meta-regressions of trials from Western countries, in single variable and then in multivariable analysis, taking into consideration that the evaluation of each predictor requires the presence of 10 units of analysis [15] (Appendices 2 and 3).

Results

The search strategy identified 4961 citations, and 4280 citations after duplicate removal. We considered 228 citations as potentially eligible, for which we screened the full text. Figure 1 shows the review flow diagram. We excluded 209 articles, and included 2 studies in elderly (mean age >65 years) and 17 studies in adults (mean age 18–65 years).

The included studies were from Iran (n = 12), Israel (n = 3), Saudi Arabia (n = 2), Lebanon (n = 1), and the UAE (n = 1). Vitamin D supplementation was administered for at least 3 months (n = 11 in adults) or for a maximum of 12 months (n = 2 in elderly, n = 1 in adults) (Table 1).

The ROB was unclear to high (Appendices 4 and 5). Only three studies were at low risk of bias across all domains [16–18], and the study by Al-Sofiani followed closely [19]. Publication bias was assessed in adults in the high vitamin D dose versus placebo comparison (total of nine trials). The inverted funnel plot of the MD in 25(OH)D level achieved did not suggest a clear publication bias (data not shown).

In elderly, we identified two studies. Breslavsky et al. administered an intermediate vitamin D3 dose (1000 IU/day) versus placebo to vitamin D-deficient diabetic elderly subjects over 12 months [20]. While the baseline 25(OH)D levels were 12.9 (10.7) and 10.8 (6.6) ng/ml in the intermediate and placebo groups, respectively, the respective achieved 25(OH)D levels were 17.6 (11.5) and 14 (5.9) ng/ml; p value 0.299 [20]. El Hajj Fuleihan et al. compared a low vitamin D3 dose (600 IU/day) to a high dose (3750 IU/day), in overweight elderly subjects with vitamin D insufficiency over 12 months [18]. The baseline 25(OH)D level was 20.3 (7.5) ng/ml, and the achieved 25(OH)D levels were 36 (9.7) and 26 (6.9) ng/ml in the high- and low-dose groups, respectively (p value <0.001). As reported by the authors, 98 and 83 % of individuals reached a 25(OH)D level ≥20 ng/ml, in the high- and low-dose groups, respectively [18] (Table 2). We could not pool the results of these two studies as the vitamin D doses fell into two different categories.

In adults, we identified 17 studies [16, 17, 19, 21–34]. Nine studies compared the effect of a high vitamin D dose

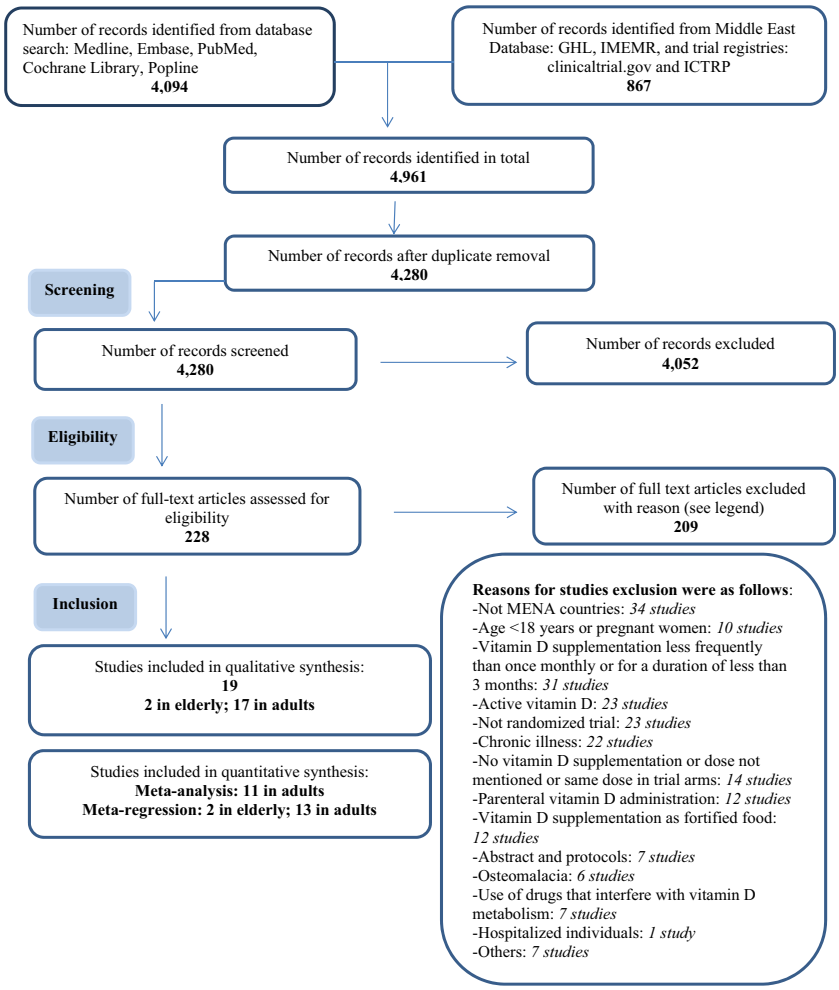

Fig. 1 Flow diagram of the different phases of the systematic review. Results in other age categories and pregnant women are not reported in this paper. *IMEMR* Index Medicus for WHO Eastern Mediterranean, *GHL* Global Health Library; *ICTRP* WHO International Clinical Trials Registry

versus placebo [16, 17, 19, 28–32, 34], and two studies compared the effect of an intermediate dose versus placebo [27, 33] on the achieved 25(OH)D level. Data from these studies were pooled in a meta-analysis for each comparison. The remaining six studies were not included, given that their supplementation doses fell into different comparisons [21, 22] or 25(OH)D level pre and/or post-intervention was not reported [23–26] (Table 1). Only two studies were conducted in healthy non-obese adults [23, 27], six studies were conducted in diabetic patients [17, 19, 22, 28–30], and the remaining were in patients with various co-morbidities: polycystic ovary syndrome [24, 26, 31, 32] obesity [33], multiple sclerosis [21], non-alcoholic fatty liver disease [16], pre-diabetes [34], and pain syndromes [25]. All study subjects had a mean BMI >25 kg/m^2. Only four studies administered calcium concomitantly with vitamin D [26, 31, 32, 34]. Thirteen studies were conducted on vitamin D-deficient individuals (baseline level 8.6–20 ng/ml); one study was conducted on vitamin D-insufficient individuals (baseline level 24–25.5 ng/ml) [25], and one study was conducted on vitamin D-replete individuals (baseline level 33.6–42.3) [29] (Table 1).

Standard meta-analysis

High vitamin D dose (>2000 IU/day) versus placebo comparison

Nine studies were included [16, 17, 19, 28–32, 34], with a total number of participants of 342 in the high-dose group and 328 in the placebo group. The intervention lasted for 3–4 months, except for one trial that extended over 6 months [31]. The WM 25(OH)D level at baseline was 15.3 ng/ml. The WM vitamin D supplementation dose was 4856 IU/day. The MD in 25(OH)D level achieved between high dose and placebo groups was 18.3 (14.1; 22.5) ng/ml (p value <0.001), favoring the high dose, with a high heterogeneity (I^2 = 92 %) (Fig. 2a). The calculated WM 25(OH)D level achieved post-intervention was 38 (SDp = 14.4) ng/ml. The estimated proportion of participants reaching a 25(OH)D level ≥20 ng/ml in the high-dose group was estimated at 89 (86–92) % (Table 2).

Subgroup analysis showed a significantly higher MD in the achieved 25(OH)D level of 25.7 (16.8; 34.5) ng/ml, with a 3-month supplementation, compared to a MD of 10.5 (9.5;

Table 1 Characteristics of included studies in adults and elderly by treatment arm

Author	City, Country Latitude	Sampling method/setting	Intervention Duration	Ca supp	Nb of subjects randomized per arm	Nb of subjects lost to follow-up	Gender (% Male per arm)	Age mean (SD) or median (range) (years)
Ahmadi et al. [30]	Isfahan, Iran 32.6° N	Isfahan Endocrine and Metabolism Research Center	*I* = D3 50,000 IU weekly (=7142 IU/day) *C* = PBO Duration = 3 months	No	*I* = 30 *C* = 30	*I* = 2 *C* = 7	*I* = 42.9 *C* = 30.4	*I* = 58.3 (11.1) *C* = 57.1 (10.7)
Al-Sofiani et al.[19]	Riyadh, Saudi Arabia 24.6° N	Primary care clinic at King Khalid University Hospital	*I* = D3 5000 IU/day *C* = PBO Duration = 3 months	No	*I* = 11 *C* = 11	*I* = 1 *C* = 1	75 (both arms)	*I* = 54.8 (9.2) *C* = 55 (12)
Al-Zahrani et al.[28]	Riyadh, Saudi Arabia 24.6° N	Outpatient Diabetes Clinics King Abdul-Aziz Medical City	*I* = D3 45,000 IU weekly for 2 months and a single 45,000 IU in the last month (=4785 IU/day) *C* = Control Duration = 3 months	No	*I* = 100 *C* = 100	*I* = 9 *C* = 8	*I* = 62 *C* = 36	*I* = 56.9 (9.4) *C* = 52.5 (8.1)
Begay et al. [26]	Isfahan, Iran 32.6° N	NA	*I1* = Ca + D3 400 IU/day + clomiphene *I2* = Clomiphene + PBO Duration = 3 months	Yes	*I1* = 22 *I2* = 22	NA	0	*I1* = 26 (20–43) *I2* = 29 (23–26)
Breslavsky et al. [20]	Wolfson, Israel 32.03° N	HTN outpatient clinic at E. Wolfson Medical Center	*I* = D3 1000 IU/day *C* = PBO Duration = 12 months	No	*I* = 24 *C* = 23	*I* = 5 *C* = 10	*I* = 45.8 *C* = 47.8	*I* = 66.8 (9.2) *C* = 65.8 (9.7)
El Hajj et al.[18]	Beirut, Lebanon 33.8° N	Outpatient clinics AUB-MC, HDF, RHUH	*I1* = D3 3750 IU/day *I2* = D3 600 IU/day Duration = 12 months	Yes	*I1* = 129 *I2* = 128	*I1* = 19 *I2* = 16	*I1* = 43 *I2* = 46	*I1* = 71.2 (4.8) *I2* = 71.0 (4.7)
Firouzabadi et al. [31]	Yazd, Iran 31.8° N	OB-GYN Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Science	*I* = D3 100,000 IU/month (=3333 IU/day) *C* = Control Duration = 6 months	Yes	*I* = 50 *C* = 50	NA	0	*I* = 27.9 (4.1) *C* = 28.5 (4.2)
Gendelman et al.[25]	Kfar Saba, Israel 32.74° N	Pain unit of the Meir Medical Center	*I* = D3 4000 IU/day *C* = PBO Duration = 3 months	No	*I* = 40 *C* = 40	*I* = 4 *C* = 2	*I* = 22 *C* = 16	*I* = 56.8 (13.1) *C* = 57.3 (13.8)
Ghavamzadeh et al. [22]	Urmia Iran 37.5° N	Diabetes clinic of Taleqani hospital	*I* = D3 400 IU/day *C* = PBO Dietary vitamin D *I* = 120 IU/day *C* = 118 IU/day Duration = 3.5 months	No	*I* = 60 *C* = 60	*I* = 33 *C* = 34	41.2 (both arms)	*I* = 52.3 (10.6) *C* = 49.3 (10)
Golan et al.[21]	Haifa, Israel, 32.8° N	MS clinic	*I1* = D3 75,000 IU every 3 weeks plus 800 IU daily (=4370 IU/day) *I2* = D3 800 IU/day Duration = 12 months	No	*I1* = 19 *I2* = 21	*I1* = 6 *I2* = 8	*I1* = 23 *I2* = 15.4	*I1* = 47.7 (11.6) *I2* = 46.3 (9.2)
Hoseini et al. [34]	Isfahan, Iran 32.6° N	Pre diabetics at Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences	*I* = D 50,000 IU weekly or every other week if serum 25(OH)D less or more than 30 ng/ml, respectively. (average 5300 IU/day) *C* = Control Duration = 3 months	Yes	*I* = 22 *C* = 16	*I* = 1 *C* = 1	*I* = 19 *C* = 47	*I* = 46.3 (6.5) *C* = 48.9 (6.1)
Moghassemi and Marjani [23]	Gorgan, Iran 36.8° N	Different health centers	*I* = D3 2000 IU/day *C* = Placebo Duration = 3 months	No	*I* = 38 *C* = 38	4 from the whole study	0	*I* = 52.7 (4.6) *C* = 51.9 (9.9)
Nasri et al. [29][b]	Shahrekord,			No	*I* = 30	NA		

Table 1 (continued)

Author	City, Country Latitude	Sampling method/setting	Intervention Duration	Ca supp	Nb of subjects randomized per arm	Nb of subjects lost to follow-up	Gender (% Male per arm)	Age mean (SD) or median (range) (years)
	Iran 32.3° N	Endocrinology clinic at Shahrekord University of Medical Sciences	*I* = D3 50,000 IU weekly (=7142 IU/day) *C* = Placebo Duration = 3 months		*C* = 30		28.3 (both arms)	55 (10.7) (both arms)
Rashidi et al. [24]	Tehran, Iran 35.6° N	Patients referred to Vali-e-Asr Reproductive Health Research Center	D 400 IU/day *I1* = Ca + D *I2* = Ca + D + MTF *I3* = MTF Duration = 3 months	Yes	*I1* = 20 *I2* = 20 *I3* = 20	0	0	*I1* = 24.9 (3.6) *I2* = 25.8 (4.6) *I3* = 26.9 (4.4)
Sadiya et al. [17]	Ajman, UAE 25.3° N	Rashid Centre for Diabetes and Research, a tertiary outpatient diabetes care clinic	*I* = D3 6000 IU/day *C* = Placebo Duration = 3 months	No	*I* = 45 *C* = 42	0	*I* = 20 *C* = 16.7	*I* = 49 (8) *C* = 48 (8)
Sharifi et al.[16]	Ahvaz, Iran 31.3° N	Outpatient clinic of Jundishapur University of Medical Sciences	*I* = D3 50,000 IU every 14 days (3571 IU/day) *C* = Placebo Duration = 4 months	No	*I* = 30 *C* = 30	*I* = 3 *C* = 4	*I* = 48 *C* = 50	*I* = 40.3 (8.6) *C* = 43.9 (9.5)
Salehpour et al. [33]	Tehran, Iran 35.6° N	Heart and Vascular Lab in Tehran University of Medical Sciences	*I* = D3 1000 IU/day *C* = Placebo Dietary vitamin D: *I*: = 21 IU/day *C* = 15 IU/day Duration = 3 months	No	*I* = 42 *C* = 43	*I* = 3 *C* = 5	0	*I* = 38 (7) *C* = 37 (8)
Taheri et al. [27]	Tehran, Iran 35.6° N	Gynecology clinic of Tehran Imam-Khomeini hospital	*I* = D3 2000 IU/day[c] *C* = Placebo Duration = 3.5 months	No	*I* = 116 *C* = 113	3 from the whole study	0	*I* = 29.4 (5) *C* = 29.8 (4.4)
Tehrani et al. [32]	Isfahan, Iran 32.6° N	Obstetrics and gynecology clinic of Alzahra hospital	D3 50,000 IU every 2 weeks (=3571 IU/day) 2 arms received vitamin D: *I1* = Ca + D *I2* = Ca + D + MTF *I3* = MTF *I4* = Placebo Duration = 4 months	Yes in 2 arms	*I1* = 20 *I2* = 20 *I3* = 20 *I4* = 20	NA	0	*I1* = 31.3 (4.6) *I2* = 28.7 (4.5) *I3* = 27.4 (2.2) *I4* = 27.2 (6.5)

Author	BMI mean (SD) or median (range) (kg/m^2)	Baseline 25(OH)D mean (SD) or median (range) (ng/ml)	Achieved 25(OH)D mean (SD) or median (range) (ng/ml)	Vitamin D assay	Co-morbidities	Compliance	AE or serious AE
Ahmadi et al. [30]	*I* = 28.4 (4.1) *C* = 29.4 (4.8)	*I* = 14.1 (7.8) *C* = 16.1 (6.1)	*I* = 71.2 (26.5) *C* = 17.6 (18.5)	Direct competitive chemiluminescence Manufacturer: NA	DM, HTN DL, diabetic nephropathy	NA	No AE
Al-Sofiani et al.[19]	*I* = 28.8 (26.7,30.9) *C* = 33.3 (27.3,35.6)	*I* = 10.2 (8.9,11.6) *C* = 15.5 (9.5, 15.9)	*I* = 36.5 (29.8,39.8) *C* = 11.8 (9.2, 13.7)	Liaison CLIA	All diabetics	97 %	NA
Al-Zahrani et al.[28]	*I* = 31.3 (4.6) *C* = 32.0 (5.7)	*I* = 10.3 (6.33) *C* = 8.8 (6.1)	*I* = 33.2 (12.7) *C* = 22 (15.1)	Liaison DiaSorin	DM (all) HTN DL	NA	NA
Begay et al. [26]	NA	NA	NA	NA	PCOS	NA	NA

Table 1 (continued)

Author	BMI mean (SD) or median (range) (kg/m^2)	Baseline 25(OH)D mean (SD) or median (range) (ng/ml)	Achieved 25(OH)D mean (SD) or median (range) (ng/ml)	Vitamin D assay	Co-morbidities	Compliance	AE or serious AE
Breslavsky et al. [20]	*I* = 27.9 (5.2) *C* = 30.6 (5.1)	*I* = 12.9 (10.7) *C* = 10.8 (6.6)	*I* = 17.6 (11.5) *C* = 14.0 (5.9)	Competitive protein-binding method Manufacturer: NA	DM (all) HTN DL	NA	2 fractures (hip, radial) 1 diarrhea 1 cholecystectomy 1 weakness 1 respiratory infection
El Hajj et al.[18]	*I1* = 30.6 (4.4) *I2* = 29.7 (4.6)	*I1* = 20.6 (7.9) *I2* = 20.1 (6.9)	*I1* = 36.0 (9.7) *I2* = 26.0 (6.9)	LCMS, ThermoFisher Scientific, Franklin, Massachusetts	CVD, CAD, CHF, HTN, DL	*I1* = 93.5 *I2* = 91.7	Various serious adverse events[a]
Firouzabadi et al. [31]	*I* = 26.9 (2.1) *C* = 26.9 (2.3)	*I* = 13.2 (6.6) *C* = 13.5 (6.4)	*I* = 24.8 (6.5) *C* = 13.8 (6.5)	RIA Manufacturer: NA	PCOS (all)	NA	NA
Gendelman et al.[25]	NA	*I* = 24.0 (13.1) *C* = 25.5 (13.0)	NA	Immunoassay, Diaorin	Pain syndromes	NA	No AE
Ghavamzadeh et al. [22]	*I* = 28.9 (0.86) *C* = 27.9 (0.93)	*I* = 8.6 (9.5) *C* = 8.9 (10.6)	*I* = 18.6 (14) *C* = 8.4 (14.5)	CLIA, Diasorin Liaison	DM (all)	NA	NA
Golan et al.[21]	*I1* = 25.2 (6.2) *I2* = 26.2 (7.4)	*I1* = 20.0 (10–28.8) *I2* = 20.0 (6.9–28.8)	*I1* = 40 (22.6–63.8) *I2* = 22.6 (12–30.4)	CLIA, Diasorin	MS (on INFβ) (all)	NA	NA
Hoseini et al. [34]	*I* = 30.4 (4.3) *C* = 28.6 (2.6)	*I* = 31.0 (15.7) *C* = 17.9 (7.33)	*I* = 47.6 (22.5) *C* = 13.9 (5.6)	Direct competitive CLIA, IDS, Boldon, UK	Pre-DM (all)	NA	NA
Moghassemi and Marjani [23]	*I* = 30.0 (6) *C* = 30.8 (5.3)	*I* = 13.8 (6.0) *C* = 13.3 (7.9)	NA	EIA Manufacturer: NA	None	NA	No AE
Nasri et al. [29][b]	*I* = 29.3 (4.4) *C* = 28.8 (4.5)	*I* = 33.6 (20.8) *C* = 42.3 (25.6)	*I* = 65.7 (22.8) *C* = 46.4 (37.7)	ELISA Manufacturer: NA	DM (all)	NA	NA
Rashidi et al. [24]	*I1* = 25.7 (3.9) *I2* = 27.8 (3.8) *I3* = 25.2 (3.90)	NA	NA	NA	PCOS	NA	NA
Sadiya et al. [17]	*I* = 38.0 (6.1) *C* = 37.6 (7.8)	*I* = 11.4 (3.7) *C* = 12.2 (4.5)	*I* = 30.9 (12.1) *C* = 11.5 (5.2)	Chemiluminescence method, Diasorin Liaison	DM and obese (all)	NA	No AE
Sharifi et al.[16]	*I* = 31.3 (28.6, 32.5) *C* = 29.3 (26.8, 31.9)	*I* = 11.5 (8.8, 28.4) *C* = 16.8 (11.7, 24.8)	*I* = 30.0 (25.8, 46.6) *C* = 19.2 (14.7, 26.7)	RIA, Roche	NAFLD (all)	*I* = 94.4 *C* = 92.2	No AE
Salehpour et al. [33]	*I* = 30.1 (3.9) *C* = 29.5 (4.4)	*I* = 14.7 (12) *C* = 18.8 (12.8)	*I* = 30.0 (8.8) *C* = 20.6 (12.4)	EIA, Immunodiagnostic Systems Ltd., Boldon, UK	Obese	*I* = 87.1 *C* = 87.4	NA
Taheri et al. [27]	*I* = 25.9 (4.8) *C* = 26.2 (4.6)	*I* = 10.1 (7.4) *C* = 9.3 (6.4)	*I* = 29.7 (18.1) *C* = 9.9 (7.7)	EIA, UK-made IDS	NA	NA	NA
Tehrani et al. [32]	*I1* = 26.3 (2.5) *I2* = 27.8 (3.3) *I3* = 26.8 (2.2) *I4* = 27.3 (1.3)	*I1* = 19.5 (3.2) *I2* = 18.7 (2.7) *I3* = 20.1 (3.2) *I4* = 20.0 (2.9)	*I3* = 20.1 (3.2) *I2* = 29.4 (2.3) *I1* = 31.5 (2.4) *I4* = 20.0 (2.9)	ELISA, Euroimmun Germany	PCOS	NA	NA

A trial is considered conducted in elderly if >50 % of participants are >65 years old

AE adverse events, *AUB-MC* American University of Lebanon - Medical Center, *CAD* coronary artery disease, *CLIA* chemiluminescence immunoassay, *CVD* cerebrovascular disease, *CHF* congestive heart failure, *DL* dyslipidemia, *DM* diabetes mellitus, *HDF* Hotel Dieu de France, *HTN* hypertension, *INF-ß* interferon-ß, *MTF* metformin, *MS* multiple sclerosis, *NAFLD* non-alcoholic fatty liver disease, *OB-GYN* Obstetrics and Gynecology, *PBO* placebo, *PCOS* polycystic ovary syndrome, *RHUH* Rafic Hariri University Hospital, *RIA* radioimmunoassay, *UAE* United Arab Emirates, *I1* intervention 1 group, *I2* intervention 2 group, *C* control group, *NA* not available

[a] In the low-dose group: death, stroke, thrombophlebitis, hemorrhoids, glaucoma, disk disease; in the high-dose group: death, kidney stone, hypertensive crisis, retinal detachment, knee arthroplasty

[b] Same trial in Behradmanesh 2013

[c] Type of vitamin D being D3 was taken from published protocol

Table 2 Summary of results in elderly and adults

Age category (*N* studies)	Dose category	Number of subjects in each dose category	Baseline 25(OH)D (ng/ml)[a]	Increase in 25(OH)D level per 100 IU/day vitamin D (ng/ml)[b]	Proportion ≥20 ng/ml (%) (95 % CI)
Elderly (2 studies)	Low[c] (600 IU/day)	110	20	1	83 (76–90)
	Intermediate[d] (1000 IU/day)	19	12.9	0.5	40 (18–62)
	High[c] (3750 IU/day)	112	20	0.4	98 (95–100)
Adults (12 studies)	Low[e] (400 IU/day)	27	8.6	2.5	54 (35–73)
	Intermediate[f] (1750 IU/day)	153	11.5	1	71 (64–78)
	High[f] (4850 IU/day)	342	15.5	0.5	89 (86–92)

[a] Baseline level of participants if one study arm identified or weighted mean baseline level of studies included in the meta-analysis

[b] Calculated as follows: [(WM 25(OH)D level achieved − WM 25(OH)D level at baseline)/vitamin D dose IU/day] × 100

[c] Results from a single randomized controlled trial El Hajj Fuleihan (2016)

[d] Results from a single randomized controlled trial Breslavsky (2013)

[e] Results from a single randomized controlled trial Ghavamzadeh (2014)

[f] Results derived from meta-analysis

11.4) ng/ml, when supplementation extended >3 months (*p* value <0.001). Subgroup analyses by BMI and baseline 25(OH)D levels did not yield significant results.

Intermediate vitamin D dose (800–2000 IU/day) versus placebo comparison

Two studies compared the effect of an intermediate vitamin D dose versus placebo on the achieved 25(OH)D level over 6 months [27, 33]. The total number of participants was 153 in the intermediate dose group and 150 in the placebo group. The WM 25(OH)D level at baseline was 11.5 ng/ml. The dose was 1000 IU/day in one of them [33] and 2000 IU/day in the other one [27], with a WM vitamin D dose of 1750 IU/day. The MD in 25(OH)D level reached was 14.7 (4.6; 24.9) ng/ml (*p* value 0.004), favoring the intermediate dose, with a high heterogeneity (I^2 = 91 %) (Fig. 2b). The WM 25(OH)D level reached in the intermediate dose group was 29.8 (SDp = 16.2) ng/ml at the end of the intervention. We estimated the proportion of participants reaching a 25(OH)D level

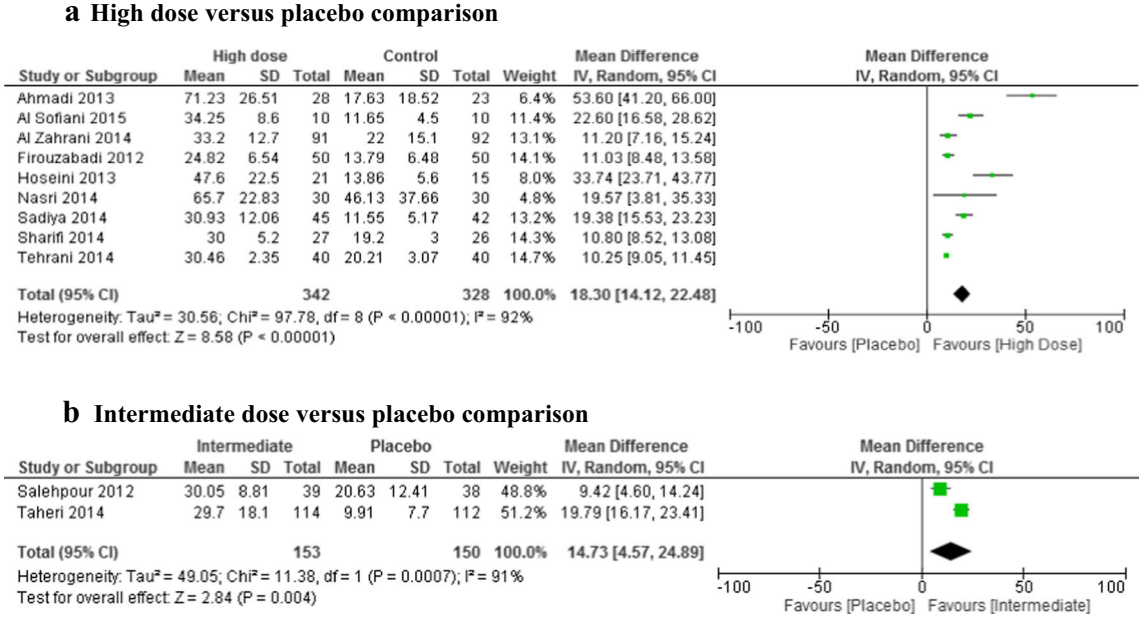

Fig. 2 The effect of high- and intermediate-dose vitamin D supplementation on 25(OH)D level, compared to placebo in adults. **a** The vitamin D-equivalent daily doses administered in the high-dose groups were as follows: Ahmadi 2013 = 7140 IU/day; Al-Sofiani 2015 = 5000 IU/day; Al-Zahrani 2014 = 6428 IU/day; Firouzabadi 2012 = 3333 IU/day; Hoseini 2013 = 7140 IU/day; Nasri 2014 = 7140 IU/day; Sadiya 2014 = 6000 IU/day; Sharifi 2014 = 3571 IU/day; and Tehrani 2014 = 3571 IU/day. **b** The vitamin D equivalent daily doses administered in the intermediate dose groups were as follows: Salehpour 2012 = 1000 IU/day; Taheri 2014 = 2000 IU/day

≥20 ng/ml in the intermediate dose group to be 71 (64–78) % (Table 2).

We did not identify any study comparing the effect of different vitamin D doses on fracture risk. The effect on bone mineral density (BMD) was assessed in one study from Lebanon [18]. While no significant dose effect was detected in lumbar spine and hip BMD, there was a significant difference in the whole-body subtotal BMD, favoring the high dose (manuscript in preparation) [18].

A high vitamin D dose resulted in a significant drop in systolic blood pressure, MD −3.0 (−5.7, −0.4) (p = 0.03), and a significant increase in the homeostatic model assessment of insulin resistance HOMA-IR, MD 1 (0.3, 1.6) (p = 0.003). For results on other outcomes, refer to Appendix 6.

The adverse events (AEs) of vitamin D replacement, including kidney stones, hypercalcemia, hypercalciuria, and hypervitaminosis D, were poorly reported in individual studies. While the studies in elderly reported on AEs [18, 20] (Table 1), in adults, three studies administering a high dose reported "no AEs" [16, 17, 30] and all the other studies did not provide any relevant information.

Meta-regression analysis

The meta-regression analysis included 30 arms (17 intervention, 13 placebo arms) from studies conducted in adults and elderly. Since the assessment of the effect of each covariate requires the presence of 10 units of analysis (study or study arms) [15, 35], we were powered to assess the effect of only three covariates.

We conducted a univariate (Fig. 3) followed by a multivariate random-effect meta-regression including the three most robust predictors of the 25(OH)D level, identified at the univariate level. Vitamin D dose and baseline 25(OH)D level were persistently significantly associated with the 25(OH)D level achieved post-intervention, whereas the duration category was not (Table 3). As per the final model, the increase in 25(OH)D level was around 0.4 ng/ml per 100 IU/day vitamin D and 0.8 ng/ml per 1 ng/ml increase in baseline 25(OH)D level. This model explained 87 % of the variability in 25(OH)D level achieved.

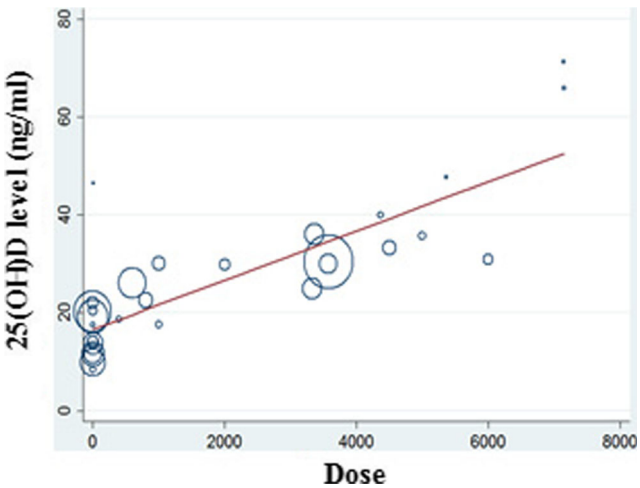

Fig. 3 Single variable random-effects meta-regression of the effect of the vitamin D dose (IU/day) on the 25(OH)D level achieved (ng/ml)

Discussion

This systematic review identified 19 vitamin D trials in adults and elderly, from the Middle Eastern countries, but none from North Africa. More than half of the included studies compared a high dose of vitamin D (equivalent daily dose 3333–7140 IU/day) to either placebo or a low vitamin D dose. All but one trial administered vitamin D3 preparations.

As expected, we demonstrated a dose-dependent increase in the MD and in the estimated WM 25(OH)D level achieved post-intervention. However, the increments per 100 IU/day of vitamin D were lower as the total daily dose increased, suggesting a plateau in the dose response at higher doses. Intermediate and high doses of vitamin D increased 25-hydroxyvitamin D level by 0.5–1 ng/ml for each 100 IU/day vitamin D. Studies from Western countries have assessed the increase in 25(OH)D level in response to escalating doses of vitamin D. Gallagher et al. assessed the effect of a wide range of vitamin D3 (400–4800 IU/day) in white post-menopausal women from Nebraska (baseline 25(OH)D level 15 ng/ml) [36]. The calculated increments per 100 IU/day vitamin D varied between 1.6 ng/ml for the lowest dose and 0.6 ng/ml for the highest dose. Furthermore, the vitamin D dose response curve showed a plateau at 45 ng/ml, at a dose ≥3200 IU/day [36]. A previous meta-analysis by Shab-bidar et al. comparing vitamin D doses to placebo, showed in a subgroup analysis, that the MD in 25(OH)D level achieved was lower with doses >800 IU/day [MD 13.7 (28.1–37) ng/ml], compared to those equivalent to 800 IU/day [MD 15.7(42.4–57.4) ng/ml] [37]. Previous meta-regression analyses conducted by the IOM and other groups from Europe showed that after logarithmic transformation of the dose, the response to vitamin D supplementation is blunted at doses ≥1200 IU/day, and reaches a plateau at a level of 28–32 ng/ml [8, 38]. These results unequivocally confirm that, in adults, the achieved 25(OH)D level increases in parallel to the increase in the vitamin D dose administered. However, the increments in 25(OH)D level, per 100 IU/day vitamin D, tend to reach a plateau at high doses.

Subgroup analysis by the supplementation duration yielded significant result, favoring a shorter duration. In fact, some vitamin D trials have shown that 25(OH)D level reaches a peak at 3–6 months, then it tends to drop by the end of the intervention [21, 36, 39]. Compliance may be a contributory factor, but this variable was poorly reported in the included

studies. Furthermore, studies that extended for 3 months administered a higher vitamin D dose (5000–7140 IU/day), than the dose in longer duration studies (400–3500 IU/day).

Based on our findings, an intermediate vitamin D dose of 800–2000 IU/day, that is two to three times the dose recommended by the IOM RDA in adults and elderly (600–800 IU/day), is needed to allow for two thirds of the population to reach a 25(OH)D level ≥20 ng/ml. This dose remains below the upper limit of intake set by the IOM at 4000 IU/day, and it is not expected to be associated with any risk of vitamin D toxicity. Unfortunately, the documentation of adverse events in the identified studies was sketchy, at best, with the exception of studies in elderly, and most studies lasted for ≤12 months. Data on the effect of vitamin D supplementation on skeletal outcomes were scarce. None of the included studies assessed fracture risk, and only one study showed improvement in whole-body subtotal BMD with a high vitamin D dose (manuscript in preparation) [18]. Several included studies evaluated the effect of vitamin D on extra-skeletal outcomes; a high vitamin D dose resulted in a significant improvement in systolic blood pressure and insulin resistnae measured by HOMA-IR. Despite the plethora of observational studies associating vitamin D deficiency with various non-classical outcomes, auto-immune and cardio-vascular diseases, infections, and cancer, intervention studies from Western and non-Western countries are still needed to determine the optimal vitamin D dose and target level to prevent such diseases [40–42].

Our meta-regression identified the dose and the baseline 25(OH)D level as significant predictors of the 25(OH)D level achieved post-intervention. The increase in 25(OH)D level approximated 0.4 ng/ml per 100 IU/day vitamin D. This increase is similar to increments estimated with high doses in the standard meta-analysis, and to the increments ranging between 0.2 and 0.5 ng/ml per 100 IU/day vitamin D described in previous meta-regressions, using a linear model, and pooling the results of trials from Western countries (Appendix 3) [37, 39, 43]. Results on other predictors, including age, BMI, and concomitant calcium supplementation were also consistent with previously published data. However, we were not powered to reach statistical significance. These findings suggest that the vitamin D dose response curve in the MENA region may be similar to the one characterized in Western countries, but the higher requirements may be driven by various factors, most importantly the lower baseline 25(OH)D levels, latitude, concomitant calcium supplementation, and BMI.

Our review has several limitations that are mostly related to the inherent limitations of the identified studies. A large number of trials (12/19) are from Iran. Therefore, the results may not be representative of all MENA. A high heterogeneity was detected in the meta-analysis. This was related to differences in the baseline

Table 3 Multivariate random-effect meta-regression

Model 1				Model 2			
Independent variable	β	p value	Model characteristics	Independent variable	β	p value	Model characteristics
Constant	6.4	0.068	p value <0.001 Tau^2 26.7	Constant	5.3	0.077	p value <0.001 Tau^2 25.6
Vitamin D dose (100 IU/day)	0.4	<0.001	I^2 res 92.4 Adjusted R^2 87.1	Vitamin D dose (100 IU/day)	0.4	<0.001	I^2 res 91.8 Adjusted R^2 87.6
Baseline 25(OH)D (ng/ml)	0.8	<0.001		Baseline 25(OH)D (ng/ml)	0.8	<0.001	
Duration (>3 months compared to 3 months)	−1.5	0.514					

Model 1: Multivariate random-effects meta-regression including variables significantly associated with the 25(OH)D level achieved at the end of the intervention, in single variable analysis, at p value 0.1

Model 2: Multivariate random-effects meta-regression including variables significantly associated with the 25(OH)D level achieved at the end of the intervention, in single variable analysis, at p value 0.1, after removing the duration

characteristics of the included participants and in the dose administered (i.e., a high dose could vary from 3570 to 7140 IU/day). A high heterogeneity is one of the factors that result in downgrading the level of evidence derived from a meta-analysis of RCTs [44]. In addition, several factors that could have affected the effect size of the intervention were poorly described. Dietary vitamin D intake was infrequently reported, season and clothing style were not mentioned, except in few studies, and none of these quantified sun exposure accurately. Compliance to vitamin D supplementation was described only in four studies. Furthermore, only two studies were conducted in healthy non-obese subjects. The variability in vitamin D assays used in the included studies remains a major limiting factor, in view of the high discrepancies in accuracy and precision between assays [45] and the impact this may have on the ultimate results. Finally, the quality of several included studies was low, related to selection, reporting, and other bias.

This is the first meta-analysis in the MENA assessing the dose response of vitamin D in this population specifically. It allows exploring the applicability of the IOM recommendations in the region. The search methodology was very extensive, including five databases, and two others relevant to the region, in addition to clinical trials registries. This review sheds light on the availability and on the quality of vitamin D trials in the region. It identifies several knowledge gaps relevant to this topic and allows one to set priorities for future research agenda.

Conclusion

In the MENA region, the IOM RDA of 600 IU/day is not sufficient to bring 25(OH)D to the desirable level of 20 ng/ml; higher doses of 1750–2000 IU/day may be needed. In addition to the dose, the baseline 25(OH)D level significantly affects the response to vitamin D replacement. These findings provide the needed information to formulate MENA specific vitamin D guidelines. Additional long term safety and high quality trials using intermediate to high vitamin D doses are needed, and further evidence on the effect of vitamin D on various skeletal and extra-skeletal outcomes is still required.

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Compliance with ethical standards

Conflicts of interests Marlene Chakhtoura, Elie A Akl, Sara El Ghandour, Khaled Shawwa, Asma Arabi, Ziyad Mahfoud, Robert H Habib, Hassan Hoballah, and Ghada El Hajj Fuleihan declare that they have no conflict of interest.

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