Dermato-Endocrinology 5:2, 274–298; April/May/June 2013; © 2013 Landes Bioscience

Hypovitaminosis D in the Middle East and North Africa

Prevalence, risk factors and impact on outcomes

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Keywords: risk factors, prevalence, osteomalacia, rickets, musculoskeletal outcomes, infections, pleotropic, genetics polymorphisms, region specific guidelines, policy

Abbreviations: 25(OH)D, vitamin D; BMI, body mass index; BMD, bone mineral density; GC, DBP, vitamin D binding protein; HMO, Health Maintenance Organization; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IOF, International Osteoporosis Foundation; IOM, Institute of Medicine; LCMS, liquid chromatography mass spectrometry; ME, Middle East; MENA, Middle East North Africa; MetS, metabolic syndrome; NGO, non-governmental organization; PTH, parathyroid hormone; SES, socio-economic status; SLE, systemic lupus erythematosis; SNPs, single nucleotide polymorphisms; TB, tuberculosis; T1DM, type 1 diabetes milletus; T2DM, type 2 diabetes milletus; UAE, United Arab Emirates; UNICEF, United Children's Fund; VDR, vitamin D receptor

Background: The Middle East and North Africa (MENA) region registers some of the highest rates of hypovitaminosis D worldwide.

Aim: We systematically reviewed the prevalence of hypovitaminosis D, rickets and osteomalacia, their predictors and impact on major outcomes, in the region.

Results: Rickets and osteomalacia still occur in this sunny region. Hypovitaminosis D prevails, with rates varying 30–90%, considering a desirable serum 25 hydroxy-vitamin D [25(OH)D] of 20 ng/ml. Advancing age, female gender, multiparity, clothing style, season, socio-economic status and urban living are recognized predictors of hypovitaminosis D in adults. Prolonged breastfeeding without vitamin D supplementation and low dietary calcium intake are the recognized risk factors for rickets and hypovitaminosis D in children. Associations with pain score and disease activity in rheumatologic disorders, viral load and interleukins in hepatitis C, BMI, lipids and insulin sensitivity, blood pressure, heart failure and mortality are described. Sun exposure in adults decreased prevalence of metabolic syndrome in one study. Few randomized vitamin D trials revealed that the majority of mothers or children failed to achieve a desirable 25(OH)D level, even with doses by far exceeding current recommendations. A trial in adolescent girls reveals substantial bone and lean mass increments.

Methods: Medline, Pubmed and Embase search engines, entering keywords and concepts, combined with individual countries of interest, were used. Search was limited years 2000–2012; and review articles were used for the period preceding year 2000.

Conclusion: Hypovitaminosis D is prevalent in MENA. The lack of populations based studies, gaps in studies in infants, pre-pubertal children and pregnant women, hinder the development of region specific guidelines and constitute a major obstacle to impact this chronic and most often subclinical disease.

Introduction

Vitamin D is a steroid hormone that modulates a wide range of molecular and cellular functions, most readily recognized are its beneficial effects on musculoskeletal parameters. Rickets and osteomalacia represent short-term latency manifestation of vitamin D deficiency and osteoporosis the long-term latency manifestation of more subtle chronic deficiencies.[1,2] An increasing body of evidence also supports non-traditional, extra-skeletal, benefits of vitamin D on the immune system, fuel metabolism, cardiovascular system diseases and cancer.[2-5] In addition, associations with decreased mortality have been described.[6]

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Submitted: 01/15/13; Revised: 05/10/13; Accepted: 05/21/13
http://dx.doi.org/10.4161/derm.25111

While rickets is almost eradicated in western populations, its prevalence remains unacceptably high in Asia, Africa and the Middle East and resurgence is also registered in ethnic minority groups in some Northern European countries.[7,8] Conversely, hypovitaminosis D is prevalent worldwide, but is again most notable in Asia and surprisingly the Middle East, despite its plentiful sunshine.[1,3] Although such observations stem mostly from non-population based studies, they have for the most part been consistent across reviews over the last decade.[9-14] Such findings are explained by the prevalence of specific risk factors for hypovitaminosis D in this region. These include the classic predictors, in addition to conservative concealed clothing style in women in general and in men from gulf countries in particular. The, lack of governmental regulation for food fortification with vitamin D in the region has also been noted.

The aim of this paper is to systematically review the prevalence of rickets, osteomalacia and hypovitaminosis D, in the Middle East and North Africa (MENA) region, evaluate relevant predictors and describe the impact of low vitamin D status on relevant outcomes in studies from the region. Implications of the vitamin D guidelines issued by the Institute of Medicine and the Endocrine Society in 2011 will be put in perspective taking into consideration the status of vitamin D in the MENA.[15,16]

Magnitude of the Problem and Predictors of Low Vitamin D Status

Rickets and osteomalacia. Rickets and osteomalacia are conditions that can result from severe vitamin D deficiency, hypophosphatemia or mineralization defects. This paper focuses on those resulting from vitamin D deficiency, best captured by measurement of serum 25 hydroxy-vitamin D [25(OH)D] level. Rickets is a childhood condition caused by serious vitamin D deficiency and is characterized by soft and weak bones, slowed growth and skeletal development and convulsions. Rickets, by definition, is a disorder which begins in childhood. If this problem occurs later in life it is known as osteomalacia. In a review on rickets worldwide, covering 30 y from 1968–1998, Prentice et al. noted that Asia, the Middle East and Africa, a region spanning latitudes from 5° to 40° North, registered the highest rates. The reported rates for clinical or radiological rickets were 70% in Mongolia (1998), 66% in Tibet (1994), 44% in Ethiopia (1987), 27% in Yemen (1987), 15% in Iran (1975), 10% in Turkey (1994) and 9% in Nigeria (1998), compared with 1.6% in Manchester minorities mostly Pakistanis.[7,8] Similarly, a review by our group underscored the lack of adequate population based studies and reported rates to be 10–100 folds higher than those in western populations.[11] These include a prevalence of 27% in children < 5 y in North Yemen, 10% in a field sample from rural Egypt, 1% Kuwait if < 2 yrs (1981–86), 0.5% of Saudis < 2 y (1997–1999) and 6% in Turkey in 1998 down to < 1% in 2008, the latter following a National Vitamin D supplementation program.[11] Rickets accounted for a substantial number of pediatric hospital admissions, 50% of children hospitalized with pneumonia in Yemen, 11% of infant's admissions with acute illness in Jordan, 6.5% of newborn admissions in Kuwait and 1.8% of pediatric admissions in 1986–88 in Saudi Arabia.[9,11] Non-skeletal manifestations of rickets included convulsions in 4–79% of patients, acute chest infections and asthmatic bronchitis in 66% of 500 cases in Saudi Arabia, broncho-pneumonia in 43% of 200 Iranian children and 44% of 250 children from Kuwait. An acute infection or respiratory diseases were the presenting manifestation in 20–60% of cases presenting with rickets in smaller studies from Turkey, Egypt, Jordan and Saudi Arabia, while gastroenteritis accounted for 8–56% of reasons for admission in hospitals in Middle East. Dilated cardiomyopathy was reported in three infants from Asia, one from Turkey and two from UAE.[11] Predictors of rickets included, low maternal vitamin D status, prolonged breast feeding, low socioeconomic status (SES), educational level and crowding. It has been recognized that primary vitamin D deficiency does not adequately describe nutritional rickets explained in some African, Middle Eastern and Asian countries and that concomitant low calcium intake and possibly disturbances of phosphate metabolism, renal compromise and iron deficiency may also play an important role in the pathophysiology of the disease.[9]

In our current search, we retrieved 13 publications on rickets, but only 8 were on nutritional rickets. Case series were published in Iran, Saudi Arabia, Kuwait, United Arab Emirates, Qatar and Egypt, with sample sizes ranging 21 to 283 subjects and age ranging from infants all the way to adolescents, with the majority being infants and toddlers.[22-30] In a study of 98 rachitic children from Egypt and Turkey, mean age 11.7 y, mean 25(OH)D was 14.3 (± 11.2) ng/ml in patients from Egypt and 10.1 (± 7.9) ng/ml in Turkey, compared with mean levels above 20 ng/ml in controls, underscoring a combined etiology that includes insufficient calcium intake, in the pathophysiology of rickets and possibly other factors, especially in Egypt.[29] Similarly, in a small study of 16 Emirati children from Abu Dhabi (24°), nutritional rickets from vitamin D deficiency was reported in eight subjects, with a mean 25(OH)D of 7 (± 2) ng/ml and a mixed etiology with combined calcium deficiency in the rest with a mean 25(OH)D of 17 (± 8) ng/ml.[31] Common risk factors included multiparity, prolonged breast feeding, delayed intake of semi-solids, maternal education and complete wrapping of the child.[28]

Osteomalacia, the adult manifestation of rickets, may be asymptomatic and go undetected, thus making true prevalence studies very difficult. The diagnosis is usually made on basis of the classic clinical profile of bone pain, fractures and proximal myopathy, combined with confirmatory laboratory tests including a low 25(OH)D, usually below 5–10 ng/ml (25–50 nmol/L), low serum calcium and phosphate levels and a high alkaline level. However, the patient may not have hypocalcemia due to correction of serum calcium level from secondary hyperparathyroidism. Moreover, hypovitaminosis D can be misdiagnosed as fibromyalgia, chronic fatigue syndrome or simply depression.[32,33] The above 25(OH)D cut-offs are not diagnostic of osteomalacia, as demonstrated in a study in Caucasian subjects.[34] We are unaware of such studies in MENA. Convulsions and hypocalcemic cardiomyopathy are also very rare manifestation of severe hypocalcemia from rickets or any other causes.[35] To-date, most publications on osteomalacia are limited to case reports or case series, made on basis of a clinical diagnosis.[36,37] The condition can mimic osteoporosis, with severe bone demineralization due to severe vitamin D deficiency, hyperparathyroidism, vertebral compression fractures, T-scores ranging from −5 to −4, with normalization after aggressive vitamin D therapy.

Hypovitaminosis D. Despite limitations caused by the lack of methodological standardization, in general, a serum 25(OH)D at concentration less than 25 nmol/L (10 ng/mL) is a useful marker of the risk of clinical deficiency, but the terminology and cut-offs used to define less than desirable vitamin D status is controversial. It includes terms such as insufficiency, inadequate level, sub-optimal level and hypovitaminosis D and may result in subclinical conditions with chronic latent manifestations, the most recognized of which is osteoporosis. The 25(OH)D cut-offs to define this condition vary and have most recently been framed by the 2011 desirable levels of the Institute of Medicine Report set at 20 ng/ml (50 nmol/L),[16] and the Endocrine Society Guidelines set at 30 ng/ml (75 nmol/L).[15] Most studies have however predated these recommendations and used variable cut-offs.

In a review conducted by the nutrition working group of the IOF, hypovitaminosis defined as 25 (OH)D level below 30 ng/ml (75 nmol/L) was prevalent in all regions of the world, whereas levels below 10 ng/ml (25 nmol/L) were most common in South Asia and the Middle East. Predictors of low 25(OH)D levels included older age, female sex, higher latitude, winter season, darker skin pigmentation, less sun exposure, dietary habits and absence of vitamin D fortification.[12] The high prevalence of hypovitaminosis D worldwide, and not only in risk groups, was again underscored in a recent review, Asia and the Middle East being at particular risk, albeit with high variability between studies within the ME.[13,14] The latest attempt at a global representation of vitamin D status in healthy populations, commented on the lack of representative studies, large gaps in information in children, adolescents worldwide and in adults in Central and South America, as well as Africa.[14]

One of the original studies on hypovitaminosis D in the Middle East was conducted in apparently healthy 104 male Saudi university students, who had a mean 25(OH)D of 12.8 (± 6.3) ng/ml with 35% < 10 ng/ml.[38] The high prevalence of hypovitaminosis D in Saudi subjects has been validated in numerous studies. **Table 1** summarizes key findings from studies of good or very good quality retrieved from our search, for adults from the MENA region.[39-81] The overwhelming majority of studies revealed 25(OH)D levels in the low teens [25(OH)D 10–15 ng/ml], even considering population-based studies. Consistent predictors across these studies for lower values were age, albeit with differing findings, some studies showing older age to be a risk factor,[57,67,69] while others point to younger age,[41,42,77] female gender in adults[41,61,63,72,75,82] and children,[83-89] winter season, sunlight exposure and veiling,[40,41,44,56,60,63,66,75,78,81,90,92] except in some studies from gulf countries where summer registers lowest values in studies from the United Arab Emirates,[75,77] pollution,[43] low calcium or vitamin D dietary intake,[67,77,80,81,90,92] and exclusive breast feeding in infants.[88] Other predictors included high BMI and/or increased adiposity,[39,60,66-68,72,93] and lower SES status or educational level.[44,60,64,68,80,83] The impact of menopause was not consistent across studies, whereas premenopausal women had higher levels in the study from Saudi Arabia,[67] the opposite was found in UAE.[77] **Table 1** details studies conducted in adults, **Table 2** in children, **Table 3** in mothers-neonates, by country, and highlights are underscored here-in.

Adults in middle east. *Iran.* The mean 25(OH)D level in several cross-sectional studies of good to very good quality was in the low teens [25(OH)D 10–15 ng/ml],[39,40,42-45] and the majority of these studies used randomized cluster sampling that was population based, be it at city level or nation level.

Jordan. Quite opposing results were found in two large, recent, population based studies graded as very good. The first included 4590 subjects and revealed a surprising high mean 25(OH)D level of 73 ng/ml in males and 40 ng/ml in females,[57] levels that remain unmatched in any other study or population. Conversely, a study of 2032 women, age 15–49 y revealed a median vitamin D of 11 ng/ml, 96% of subjects had levels below 20 ng/ml, and 60% were below a cut-off of 12 ng/ml.[56] While the former study used a Biosource assay, the latter used the gold standard LCMS assay to measure vitamin D. Aside from assay differences, reasons for such wide discrepancies remain unexplained.

Lebanon. Several studies including a population-based study conducted in elderly subjects revealed mean 25(OH)D levels varying between the low-high teens [25(OH)D 12–18 ng/ml].[60,61,94] In an interesting sub-set analysis of a large international study in post-menopausal women, Lebanese Muslim women had lower levels than Christian women, findings that could in part be explained by dress style and higher BMI in Muslims.[60]

Occupied palestine/israel. In general 25(OH)D mean levels were higher than those recorded in other countries in Middle East, including those reported in several large scale studies that took advantage of Health Maintenance Organization (HMO) or Non-Governmental Organization (NGO) databases, averaging around 20 ng/ml.[51,53,54] One ecological study revealed vitamin D levels to be highest in Ashkenazi Jews and lowest in Arabs.[55]

Saudi arabia. While several large sample population based studies as well as smaller studies revealed a high prevalence of hypovitaminosis D in Saudi Arabia (> 80% below 20 ng/ml),[64,66,70] few smaller studies revealed replete levels.[72,74] In a sample of 1,172 women from of population-based survey of 40 primary health care centers around the city of Jeddah, 80% of subjects had a 25(OH)D level below 20 ng/ml. Mean levels in pre-menopausal women were 17 and in post menopausal women were 13 ng/ml.[67] Similarly a mean level of 12 ng/ml was found in a sample of 834 adults men, age 42 y.[64]

United arab emirates. The mean levels from the three studies listed in **Table 1** are close to 10 ng/ml, with inverse seasonal pattern.[75-77]

Adults in north africa. Studies from this region are scarce, limited to Morocco and Tunisia. Two hospital-based studies conducted in women in Rabat revealed a 25(OH)D level in the mid-high teens.[78,79] Studies in Moroccan immigrants revealed similarly low levels.[95,96] A study of 100 immigrants with mean age of 49 y, showed a mean 25(OH)D of 11 ng/ml and 90% of subjects had mean levels below 20 ng/ml.[96] Findings were not different in Tunisian women, with mean levels again noted in mid-teens.[80,81]

Children and adolescents in the middle east. As detailed in **Table 2**[30,82-91,93,97-104] most studies reported mean 25(OH)D levels in teens or close to 20 ng/ml, thus again revealing a large proportion of apparently healthy children, that is 30–75%, to have 25(OH)D levels below this deemed desirable cut-off.

Iran. Registered the largest number of studies with wide variations in 25(OH)D levels, in general being lower in winter, in girls and in older children. The proportion of subjects with 25(OH)D level below 20 ng/ml was 33% in 7,112 infants and toddlers in Tehran (36° North) in early summer,[87] 3% in a sample of 513 young school children, age 6–7 y in Isfahan (33° North) in the summer,[91] up to 78% in school adolescents from Tehran in the spring,[89] and 46% in high school students.[84] Mean levels were quite low in the winter in 1,111 older school children from Tehran, measured at 11 ng/ml in boys and 8 ng/ml in girls,[86] and surprisingly high in middle school girls in Isfahan in winter.[30]

Jordan. Two studies conducted in hospital based clinics in Amman, in toddlers and pre-school children, one in summer and the other in the winter, revealed that one-third of subjects had mean 25(OH)D levels below 20 ng/ml,[88,97] while a community based sample in 93 children mean age 60 mo, in the summer of 2007, revealed the proportion to be even higher at 82%.[98]

Lebanon. Two separate studies reported mean 25(OH)D levels in mid-teens conducted in school adolescents from greater Beirut.[83,99,100] Between 30–40% had a mean 25(OH)D levels below 20 ng/ml, proportions being higher in the winter and in girls.

Saudi arabia. A school-based study reveals 25(OH)D levels in mid-high teens in children, being lower in girls than boys, whereas mean levels were below 10 ng/ml in a study of adolescents recruited from primary health care centers in Ryadh.[82,85]

United arab emirates. In study of 183 children, age 1–12 y, selected from an urban ambulatory clinic in Abu Dhabi, there was a decrease in 25(OH)D levels with age from infancy to early adolescence; 21% of girls and 16% of boys had a 25(OH)D below 10 ng/ml, and the proportions were 46% and 32% respectively for a cut-off below 20 ng/ml.[101] Levels were lower in mother and infants from 2 hospital based studies, where 61% of the mothers and 82% of the 78 infants tested had hypovitaminosis D (serum 25(OH)D < 10 ng/ml).[90,104]

Qatar. In a small study of 65 school girls, age 9–15 y, 25(OH)D levels were below 20 ng/ml in 98%.[105] The weighted average for 25(OH)D was 17.5 ng/ml level in 458 subjects, age < 16 y, attending a primary health clinic and was less than 20 ng/ml in 69%.[103]

We could not identify any studies conducted in children and adolescents for countries in North Africa.

Pregnant women and neonates. A systematic review of first trimester normative 25(OH)D levels, of 18 studies across the world, revealed mean 25(OH)D levels ranging between 29 and 73 nmol/L in white Caucasian women and between 15–26 nmol/L in Turkish and Moroccan and other non-western women in Netherlands.[106] Similarly, a high prevalence of low 25(OH)D levels was reported in ethnic minority groups in western countries, the prevalence ranged between 59–84% in the Netherlands, exceeded 50% in the UK, averaged 61% in New Zealand, was above 80% in Australia, using a cut-off of 10 ng/ml; and it was 5–30% in the US at a cut-off of 15 ng/ml.[7] Investigations in Saudi Arabia, Kuwait, United Arab Emirates and Iran reveal that 10–60% of mothers and 40–80% of their neonates had undetectable low 25(OH)D levels (0–25 nmol/L) at delivery.[106] Such low levels may be associated with poor maternal and neonatal outcomes, as has been documented in women from western countries. Indeed, Caucasian women with low 25(OH)D levels had a higher risk of pre-eclampsia and Cesarean sections, but we are unaware of any such studies in the ME or Asia.[106] More recently, children of women with low 25(OH)D levels in third term had smaller anthropometric parameters.[107] In Iran, neonates born to mothers with low 25(OH)D levels have lower cord 25(OH)D levels, and in one study were more likely to have lower birth weight, height, Apgar score and may be at risk for the development of rickets.[106] Unfortunately, the few studies conducted in the MENA were not population-based and thus not necessarily representative of vitamin D nutritional status of pregnant women and their neonates in the region. But the few studies available, revealed a 25(OH)D level below 20 ng/ml in mothers in all 6 studies and below 10 ng/ml in two of them and even lower levels in neonates and cord blood.[108-112] Predictors for low maternal 25(OH)D levels included dress code, winter season, dietary habits and avoidance of sun exposure.[92,108]

Is there a Genetic Basis for Low Vitamin D Levels and Rickets in the MENA?

Lifestyle factors, namely sunlight exposure, diet and use of supplements, are well recognized major determinants of circulating 25(OH)D levels, in general,[1] including subjects from the MENA, as detailed above. Interestingly, it has been recently underscored that genetic factors may contribute up to 50% of inter-individual variability in serum 25(OH)D levels (**Fig. 1**).[113] Several genetics determinants of vitamin D status were recently described in a large genome wide association study of over 30,000 individuals of European descent from 15 cohorts.[114] In addition, single nucleotide polymorphisms (SNPs) at or near 6 pre-specified vitamin D pathways candidate genes were considered. These include the vitamin D receptor (VDR), 1-α-hydroxylase *(CYP27B1)*, 25-hydroxylase *(CYP2R1),* 24-hydroxylase *(CYP24A1),* vitamin D binding protein *(GC, DBP)* and 27- and 25-hydroxylse *(CYP27A1)* genes. The discovered genetic polymorphisms included variants near genes involved in cholesterol synthesis (*DHCR7)*, hydroxylation *(CYP2R1* and *CYP24A1)* and vitamin D transport *(GC)*, and these may identify individuals at high risk of vitamin D deficiency.[114] African Americans are a subgroup at higher risk for low vitamin D levels. A recent study investigating associations between 94 three single nucleotide polymorphisms (SNPs) in 5 vitamin D pathway genes (GC, VDR, CYP2R1, CYP24A1, CYP27B1) and serum 25(OH)D in 379 African American and 379 Caucasian controls, revealed statistical associations for 3 SNPS, 2 in the vitamin D transport pathway and one in the hydroxylation pathway, only in African Americans.[115]

Table 1. Overview of Studies on 25(OH) D Values in Adults in Middle East and North Africa

Country	Author/Yr	Sampling Method City (Latitude)	N Gender/Age	Exclusion criteria specified	Assay type/ Manufacturer	Season Yr	Predictors for low 25(OH)D	25(OH)D Level Mean ng/ml % below cut-off
Middle East								
Iran	Baradaran et al. 2012[39]	Hospital based Iran (32°N)	259 ♀♂ 20–64 y	Yes	EIA/IDS	NA 2010	High adiposity, high BMI	12 ± 6 Median: 10
	Kashi et al. 2011[40]	Telephone population based Sari (37°N)	232 ♀,118♂ 11–69 y	Yes	ELISA/DRG	End of summer and winter NA	High humidity climate, winter	Summer: 13.4 ± 13 Winter: 11.7 ± 11
	Hovsepian et al. 2011[41]	Outpatient clinic Isfahan (32°N)	243 ♂, 868 ♀ 20–80 y	Yes	RIA/Biosource	Autumn/Winter-Spring/Summer NA	Young age, women	Median Spring: 21 (2–300) Median Summer: 18 (3–208) Median Autumn: 19 (1.5–425) Median Winter: 17 (2–281) 27% < 10, 24% 10–20, 20% 20–30
	Kaykhaei et al. 2010[42]	Population based Zahedan (30°N)	431 ♂, 562♀ 20–88 y	No	CIA/DiaSorin	June -Aug 2008	Younger age	13.8 95% < 30 85% < 20 10% 20–30 5% 30–150
	Hosseinpanah et al. 2010[43]	Clustered sampling Tehran (35°N), Ghazvin (36°N)	200♀ 20–55 y	Yes	EIA/DRG	Sept 2007	Air pollution	Ghazvinian: ♀ 18 ± 11 Tehranian: ♀ 13 ± 7 Tehranian: 36% < 10 54% 10–20 Ghazvinian: 31% < 10 32% 10–20
	Maddah et al. 2009[44]	Clustered sampling Guilan (37°N)	427 ♀ Urban 219 ♀ Rural 51–92 y	No	Commercial kit/ BioSource	Oct 2004-Feb 2005	Low education, urban living	♀ Urban: 18.5 ± 13.5 ♀ Rural: 22.9 ± 13.8
	Masoompour et al. 2008[45]	Clustered sampling Shiraz (30°N)	520 ♂ 20–74 y	Yes	IRMA/IDS	Jan-Mar 2001	NA	14 ± 6.8 34% ≤ 10
	Hosseinpanah et al. 2008[46]	Population based study Tehran (35°N)	245 p.m.♀ 40–80 y	Yes	RIA/IDS	NA	NA	5% < 10 38% 10–20 43% < 20 25% > 32
	Hashemipour et al. 2006[47]	Clustered sampling Tehran (35°N)	1210 ♂♀ 20–69 y	Yes	RIA/IDS	NA	NA	12.9 ± 16.5 9% ≤ 5 56% 5–10
	Rassouli et al. 2001[48]	Densitometry center Tehran (35°N)	73 p.m.♀ 49–63 y	Yes	HPLC	Feb-June 2000	NA	Winter: 13.3 ± 5.0 Spring: 18.3 ± 12 36% < 12

Abbreviations in table listed here in alphabetical order: BMI: Body Mass Index; Ca: Calcium; CIA: Chemiluminescent Assay; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLIA: Electrochemiluminescent Immunoassay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; IRMA: Immunoradiometric Assay; LC-MS: Liquid Chromatography–Mass Spectrometry; NA: Not Available; PM: Post-Menopausal; Prem: Pre-Menopausal; PBM: Peak Bone Mass; RIA: Radioimmunoassay; SES: Socio-Economic Status; Vit: Vitamin; WHR: Waist Hip Ratio; Yrs: Years.

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Occupied Palestine/ Israel	Saliba et al. 2012[49]	Population Based CHF covers > 50% of Israeli population (31°N)	198,834♀♂ Median 60 y	Yes	CIA/Diasorin	Jan-Dec 2009	Female gender, winter, adults, Arabs > Jews	Summer-Autumn: 22.52 ± 9.8 Winter-Spring: 18.72 ± 9.4 14% < 10 31% < 15 50% < 20 16% > 30
	Saliba et al. 2012[50]	Population Based	2571♂, 6310♀ 56.1 ± 17.6 y (1st test) 57.6 ± 17.7 y (Last test)	Yes	CIA /Diasorin	Jan 2008-Sep 2011	Female gender	First test: 20.68 ± 9.6 50% < 20 Last test: 22.68 ± 9.88 41% < 20 *First and last test done in the same month
				Middle East				
	Saliba et al. 2012[51]	Population Based	182, 152 ♀♂ Vit D ≤ 13: 59.4 ± 17.4 yrs Vit D13–20: 61 ± 16.1 y Vit D20–26: 61.1 ± 16 y Vit D > 26: 59.9 ± 17.1 yrs	No	CIA/Diasorin	Jan 2008–Dec 2009	History of diabetes History of Cardiovascular disease	25% ≤ 13ng/ml, mean 9.3 ± 2.7 25% 13–20 ng/ml, mean 16.8 ± 1.8 25% 20–26 ng/ml, mean 22.8 ± 1.8 25% > 26 ng/ml, mean 32.6 ± 6.4
	Tsur et al. 2011[52]	Institution based Jerusalem (31.7°N)	74♂ students (A) Ultra-orthodox Indoors 20.1 ± 0.6 yrs (B) Ultra-Orthodox Outdoors 33.0 ± 4.2 yrs (C) Religious 19 ± 2.0 yrs	Yes	RIA /DLS	Mar-Apr NA	Low sun exposure, traditional cloth-ing	(A) 8.9 ± 3.6 100% < 20 65% < 10 (B) 10.2 ± 5.7 91% < 20 65% < 10 (C) 21.7 ± 10.4 51% < 20 12% < 10
	Saliba et al. 2011[53]	Population Based (31°N)	19,172 ♂♀ 63.7 ± 15.5 y Normal:19,172 Renal failure:5449	No	CIA/Diasorin	Jan-Dec 2009	Renal Failure	Renal Failure: 22.8 ± 11 Normal Function: 25.32 ± 10.64
	Steinvil et al. 2011[54]	Retrospective Population based (31°N)	26,699♀ 55 ± 15 y 8175♂ 55 ± 17 y	No	RIA /Diasorin	Jan-Dec 2001–2008	Low sun exposure	♂ 23.22 ± 10.1 79% < 30 ♀ 22.7 ± 9.9 78% < 30
	Oren et al. 2010[55]	NA (31°N)	100♀, 95♂ < 5y rs–> 50 yrs	No	CIA/Diasorin	Feb-Jan NA	Older Age, Ashkenazi > Sephardic > Arab	22.9 ± 10.1 78% < 30
Jordan	Nichols et al. 2012[56]	National micronutrient survey Jordan (31°N)	2032 ♂ 15–49 y	No	LC-MS/MS	Mar-Apr 2010	Urban living, veil-ing	Median: 11 96% < 20 60% < 12 No cover n = 98 40% < 12 Scarf/hijab n = 1842 62% < 12 Niqab (full) n = 73 68% < 12

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	Batieha et al. 2011[57]	National population based Jordan (31°N)	1128 ♂, 3462 ♀ > 18 y	No	RIA/Biosource	July–Oct-Nov 2009	Older age, middle and south region, winter season, low altitude, sunscreen use, indoor work, urban, veiling	♂ 73.3 ± 29.3 94% ≥ 30 4% 20–29.9 2% < 20 ♀ 39.8 ± 20.7 63% ≥ 30 23% 20–29.9 14% < 20
	Mallah et al. 2011[58]	NA Jordan (31°N)	201 ♀, 99 ♂ 29–32 y	No	ELISA/IDS	November 2010	Veiling	♂18 ± 4 ♀ 12 ± 5 Western Style: 16 ± 3 Hijab: 12.5 ± 2.5 Niqab: 11.4 ± 1.52
	Mishal 2001[59]	Hospital based Jordan (31°N)	131 ♀, 23 ♂ 18–45 y	Yes	RIA/Diasorin	Summer: July–Sep Winter: Jan–Mar NA	Winter, veiling	3% < 5 60% 5–12 Both seasons: 62% < 12 Summer: 50% < 12 Winter: 73% < 12
				Middle East				
Lebanon	Gannaje-Yared et al. 2009[60]	Hospital based Lebanon (33°N)	151 Christians, 100 Muslims ♀ 50–87 y	Yes	CIA/Nichols	July–Aug 2004 Feb-Mar 2005	Dress code covering the arms, high BMI, low education	19·5 ± 9·8
	Arabi et al. 2006[61]-2010[62]	Population based Beirut (34°N)	286 ♀, 157 ♂ 65–85 y Mean 73 y	Yes	RIA/IDS	Nov 2002-Mar2003	Female gender	11.4 ± 4.9 ♀ 55% < 10 ♂ 37% < 10
	Gannaje-Yared et al. 2000[63]	Community centers Bekaa, Beirut (34°N)	99 ♂, 217 Prem♀ 30–50 y	Yes	RIA/Incstar		Veiling, ♀ rural living, ♂urban living, low vit D intake	9.7 ± 7.1 31% (42% ♀, 7% ♂) < 5 73% (84%♀, 49% ♂) < 12 80% (89% ♀, 51% ♂) < 15
Saudi Arabia	Ardawi et al. 2012[64]	Population based Health Care Centers Jeddah (22°N)	834 ♂ 20–74 yrs 42.1 ± 13.9 y	Yes	CIA/Liaison	Jun 2008–Jun 2009	Heavy weight, summer, smoking, no education, sedentary lifestyle, low Vit D supplementation, low sun exposure	Total: 11.6 ± 6.45 < 50 y: 12.5 ± 7.01 ≥ 50 yrs: 10.7 ± 5.992 88% < 20 10% ≥ 20–30
	El Shafie et al. 2012[65]	Healthcare Center Riyadh (25°N)	50 married couples ♂40.1 ± 7.4 y ♀30.6 ± 6.8 yrs	Yes	ECLIA/Roche	Dec 2010–Jan 2011	Male gender, high physical activity, milk intake	♀ 8.5 ± 3.9 70% < 10 98% < 20 ♂ 12.2 ± 5.5 40% < 10 92% < 20

Abbreviations in table listed here in alphabetical order: BMI: Body Mass Index; Ca: Calcium; CIA: Chemiluminescent Assay; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLIA: Electrochemiluminescent Immunoassay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; IRMA: Immunoradiometric Assay; LC-MS: Liquid Chromatography–Mass Spectrometry; NA: Not Available; PM: Post-Menopausal; Prem: Pre-Menopausal; PBM: Peak Bone Mass; RIA: Radioimmunoassay; SES: Socio-Economic Status; Vit: Vitamin; WHR: Waist Hip Ratio; Yrs: Years.

Table 1. Overview of Studies on 25(OH) D Values in Adults in Middle East and North Africa

Kanan et al. 2012[66]	Retrospective out-patient clinics Riyadh (25°N)	1556 ♀ Summer 44.4 ± 16.1 y Winter 46.1 ± 15.9 y	Yes	HPLC	Jan–Dec 2009	Low latitude, veiling, sun avoidance	13.3 ± 0.7 Prem Summer 80% < 20 11.4 ± 0.5 Prem Winter 85% < 20 17.7 ± 0.9 p.m. Summer 68% < 20 14.5 ± 0.6 p.m. Winter 76% < 20
Ardawi et al. 2011[67]	Population based Health Care centers Jeddah (22°N)	1,172 healthy ♀ 50.9 ± 12.6 y	Yes	CIA/Liaison	Jun 2008–Jun 2009	Older age, high BMI, low sun exposure, poor dietary, low vit D supplementation, high WHR	17.18 ± 12.19 (Prem) 13.32 ± 9.94 (PM) 11% (6% Prem 14% PM) < 5 46% (38% Prem 51% PM) < 10 34% (34% Prem 34% PM) 10–20 9% (11% Prem 7% PM) 20–30 12% (16% Prem 8% PM) ≥ 30
Alissa et al. 2011[68]	Hospital based Jeddah (22°N)	122 p.m.♀ 46–70 y	Yes	RIA/Diasorin	NA	High SES, heavy weight, low activity	9.6 ± 0.47 (Controls) 100% < 20 12.7 ± 1.06 (Osteopenic) 97% < 20
				Middle East			
Sadat-Ali et al. 2011[69]	Hospital based Al-Khobar (26°N)	400 Peak Bone Mass age group and ≥ 50 yrs	Yes	RIA/Wallac	Feb–May 2008	Older age	PBM age group 11% ♀ 10% ♂ < 20 19% ♀ 19% ♂ 20–30 70% ♀ 71% ♂ > 30 ≥ 50 y 19% ♀ 12% ♂ < 20 36% ♀ 25% ♂ 20–30 45% ♀ 63% ♂ > 30
El Sammak et al. 2011[70]	Hospital based Al-Khobar (26°N)	87 ♂, 52 ♀ blood donors	Yes	CIA/Liaison	Dec 2008–Mar2009	Veiling	♂ 10.1 ± 4.5 ♀ 9.9 ± 4.5
El Sammak et al. 2010[71]	Hospital based Al-Khobar (26°N)	87 ♂ 30.0 ± 8.5 yrs 52 ♀ 31.0 ± 7.2 yrs	Yes	CIA/Liaison	Dec 2008–Mar 2009	NA	♂ 10.1 ± 4.7 ♀ 9.9 ± 4.5
Al-Elq et al. 2009[72]	Hospital based Al-Khobar (26°N)	200 ♂ 46.5 ± 14.6 yrs 200 ♀ 42.6 ± 15.9 yrs	Yes	RIA/Wallac	Feb–May 2008	Older age, life Style, higher BMI ♂, lower BMI♀	♂ 31.1 ± 10.7 ♀ 28.9 ± 10.7

Abbreviations in table listed here in alphabetical order: BMI: Body Mass Index; Ca: Calcium; CIA: Chemiluminescent Assay; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLIA: Electrochemiluminescent Immunoassay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; IRMA: Immunoradiometric Assay; LC-MS: Liquid Chromatography–Mass Spectrometry; NA: Not Available; PM: Post-Menopausal; Prem: Pre-Menopausal; PBM: Peak Bone Mass; RIA: Radioimmunoassay; SES: Socio-Economic Status; Vit: Vitamin; WHR: Waist Hip Ratio; Yrs: Years.

Table 1. Overview of Studies on 25(OH) D Values in Adults in Middle East and North Africa

	Sadat-Ali et al. 2009[73]	Hospital based Al-Khobar (26°N)	100 ♂ 28.2 ± 4.5yrs 100 ♂ 59.4 ± 15.6yrs	Yes	RIA/Wallac	Feb-May 2008	Low sun exposure	Younger: Mean 16.6 ± 3.4 in those ≤ 20 Mean 25.4 ± 2.7 in those > 20- < 30 Older: Mean 16.7 ± 3.4 in those ≤ 20 Mean 25.3 ± 3.3 in those > 20–30
	Al-Turki et al. 2008[74]	Hospital based Al-Khobar (26°N)	200 ♀ 25–35 y (Group 1) ≥ 50 y (Group 2)	Yes	RIA/Wallac	Feb -May 2008	Low sun exposure, low vit D diet	Group 1: 11% < 20 19% 21–29 70% > 30 Group 2: 19% < 20 36% 21–29 45% > 30
UAE	Al Anouti et al. 2011[75]	University based Al-Ain (24°N)	208 ♀ 20.8 ± 4.0 y 70 ♂ 21.0 ± 4.6 y	No	HPLC	Oct 2009 138♀70 ♂ Apr 2010 70 ♀	Low sun exposure, female gender	Summer ♀ 8.3 ± 5.9 ♂10.9 ± 6.2 Winter ♀ 12.5 ± 4.9
	Dawodu et al. 2011[76]	Pilot Study Al-Ain (24°N)	8 Healthy Arab ♀ 20–30 y.	Yes	HPLC	Sep –Nov 2001	Decreased surface area of the skin exposed, sun exposure low vit D intake	Expose face, arms and hands 15 min/d twice a week for 4 weeks pre-intervention 7.04 post intervention 9.2
	Saadi et al. 2006[77]	Local clubs, primary care clinics, local hospitals Al-Ain (24°N)	175Prem 84PM♀ Prem: 37.5 ± 9.5 y PM: 58.3 ± 8.9 y	Yes	RIA/Diasorin	Jan 2003-Jun 2005	Younger age, low vit D intake, summer	10.1 ± 4.3 Prem: 9.7 ± 4.2 PM: 10.9 ± 4.5 All ♀ vit D < 32 Apr 11.6 ± 5.2 Aug 7.2 ± 2.3
				North Africa				
Morocco								
	El Maghraoui et al. 2012[78]	Hospital based Rabat (34°N)	178 p.m. ♀ ≥ 50 y	Yes	ECLIA/Roche	Summer 2010	NA	15.8 ± 11.6 85% < 30 66% < 20 52% < 10
	Allali et al. 2009[79]	Hospital based Rabat (34°N)	415 ♀ 24–77 y	Yes	CIA/Diasorin	Summer NA	Older age, lack of sun exposure, veiling, Ca intake < 700 mg	91% < 30 43% < 15 4% < 5
Tunisia	Bahlous et al. 2009[80]	NA Manouba (37°N)	134 p.m. ♀ [illegible]	Yes	HPLC	March–April 2004	Osteoporosis	Fracture pts: 27.5 ± 15.1 51% < 20 Non fracture pts: 21.3 ± 13 25% < 20
	Meddeb et al. 2005[81]	NA Ariana (37°N)	261♀ 128♂ 20–60 y	Yes	RIA/Incstar	Jan-March 2002	Older age, veiling, high parity, post-menopausal	47% < 15, 16% 5–10 36% 20–28 y 60% 50–59 y

Abbreviations in table listed here in alphabetical order: BMI: Body Mass Index; Ca: Calcium; CIA: Chemiluminescent Assay; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLIA: Electrochemiluminescent Immunoassay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; IRMA: Immunoradiometric Assay; LC-MS: Liquid Chromatography–Mass Spectrometry; NA: Not Available; PM: Post-Menopausal; Prem: Pre-Menopausal; PBM: Peak Bone Mass; RIA: Radioimmunoassay; SES: Socio-Economic Status; Vit: Vitamin; WHR: Waist Hip Ratio; Yrs: Years.

Table 2. Overview of studies on 25(OH) D values in Children in Middle East

Country	Author/Yr	Sampling Method City (Latitude)	N Gender/Age	Exclusion criteria specified	Assay type/ Manufacturer	Season Yr	Predictors for low 25(OH)D	25(OH)D Level Mean ng/ml % below cut-off
Iran	Ghergherechi et al. 2012[93]	Children hospital Tabriz (38°N)	52 Obese children 4–16 y 57 Control	Yes	CIA/Nichols	NA 2009–2011	Obesity, high BMI	Case: 32.7 ± 29.6 Control: 44.2 ± 11.2
	Neysestani et al. 2012[86]	Random systematic districts schools Tehran (35°N)	573 Boys, 538 Girls 9–12 y	Yes	Competitive protein-binding assay/IDS	Fall-winter 2007–2008	Female gender	Boys: 11 Girls: 8
	Olang et al. 2011[87]	Vaccination heath centers Tehran (35°N)	7112 infants 15–23 mo	Yes	HPLC	May–June2001	Female gender	24.5 3% < 10 33% < 20 44% 20–30 20% > 30
	Ardestani et al. 2010[91]	School random sampling Isfahan (32°N)	271 Boys, 242 Girls 6–7 y	Yes	RIA/Incstar	Summer 2006	Low intake of vitamin D, low sun exposure, dress style	46 ± 17 3% < 20
	Razzaghy Azar 2010[89]	Clinic university hospital Tehran (35°N)	192 Girls, 121 Boys 8–18 y	Yes	EIA/IDS	Apr 2006-Apr 2007	High BMI, puberty stage, female gender	25% (Boys 8% Girls 92%) < 5 27% (Boys 34% Girls 66%) 5–10 26% (Boys 58% Girls 42%) 10–20
	Dahifar et al. 2007[30]	One middle school Tehran (35°N)	414 Girls 11–15 y	Yes	Gamma counter/Genesys	Dec 2002–Mar 2003	NA	30 ± 15.8
	Moussavi et al. 2005[84]	High school Sampling Isfahan (32°N)	153 Boys, 165 Girls 14–18 y	Yes	RIA/Biosource	NA 2004	Female gender	Total: 46.2% < 20 Boys: 37.3 ± 18.8 18% < 20 1% < 8 Girls: 16.8 ± 8.4 72% < 20 14% < 8
Jordan	Abdul Razzak et al. 2011[88]	Hospital based Amman (32°N)	136 Infants, 139 Toddlers 6–36 mo	Yes	EIA/IDS	Oct 2008–Jan 2009	Sun exposure < 30 min, female gender, exclusive breast feeding	17% < 15 11% < 20 28% < 30 44% > 30
	Jazar et al. 2011[97]	Pediatrics Clinic Jordan (31°N)	100 Boys 1–3 y 100 Girls 3–6 y	Yes	ECLIA/Roche	May–June 2009	Older age, high BMI, low outdoor activity indoor physical activity, nutrition	Toddler: 26.2 ± 1.2 Preschool children: 21.5 ± 1.2 17% ≤ 15 16% 15- 20

Abbreviations in table listed here in alphabetical order. BMI: Body Mass Index; CIA: Chemiluminescent Assay; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLIA: Electrochemiluminescent Immunoassay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; NA: Not Available; RIA: Radioimmunoassay; Supp: Supplemented; Unsupp: Unsupplemented; Vit: Vitamin; Yrs: Years.

Table 2. Overview of studies on 25(OH) D values in Children in Middle East

	Gharaibeh et al. 2009[98]	Local community center Jordan (31°N)	93 Mothers 30 yrs Children 60.7 mo	Yes	ELISA/IDS	June -July 2007	Low milk intake, high income > 212$/month	Mother: 10.2 2% < 5 49% < 10 98% < 20 Children: 22.3 82% < 20 15% > 30
Lebanon	El Hajj-Fuleihan et al. 2007[99]	School based Beirut (33.5°N)	180 Boys 13.1 ± 2 y	Yes	RIA/Diasorin	Winter- Spring 2001–2002	NA	17 ± 7
	El Hajj-Fuleihan et al. 2006[100]	School based Beirut (33.5°N)	179 Girls 13.1 ± 2 y	Yes	RIA/Diasorin	Winter–Spring 2001–2002	NA	14 ± 8
	El Hajj-Fuleihan et al. 2001[83]	School based Beirut (33.5°N)	Spring: 81 Boys, 88 Girls 13.3 ± 1.6 yrs Fall: 83 Boys, 94 Girls 13.3 ± 1.7 yrs	Yes	RIA/Diasorin	Spring–Fall 1999	Spring season, female gender, age, Tanner staging, low sun exposure, calcium intake, vitamin D intake, BMI	Spring: Total: 17 ± 8 21% < 10 44% 10–20 Boys: 19 ± 7 9% < 10 46% 10–20 Girls: 15 ± 8 32% < 10 42% 10–20 Fall: Total: 22 ± 7 4% < 10 36% 10–20 Boys: 24 ± 6.2 25% 10–20 Girls: 19 ± 7 7% < 10 46% 10–20
Qatar	Bener et al. 2009[103]	Primary Health Care Centers Doha (25.3°N)	458 Mean 10.9 ± 3.54 y in those < 20 ng/ml Mean 9.54 ± 3.98 y in those 20–80 ng/ml	No	RIA/Diasorin	Aug 2007–Mar 2008.	Older Age, non White low sunlight expos, low physical activity, low dietary vit D, family history of vit D deficiency	69% < 20 ng/ml, mean 13.4 ± 8.9 31% < 20 ng/ml, mean 27.5 ± 8.3
Saudi Arabia	Al-Ghamdi et al. 2012[85]	School-based Jeddah (22°N)	150 ♂ 7–16 y 150 ♀ 6–18 y	Yes	ECLIA/Roche	May NA	Female gender	16.5 ± 3.7 (6–9 y ♀) 24.5 ± 5.2 (6–9 y ♂) 22 ± 4.5 (10–12 y ♂) 12.6 ± 3.7 (10–12 y ♀) 19.6 ± 5.2 (13–14 y ♂) 11.6 ± 3.6 (13–14 y ♀) 8.8 ± 3.8 (15–18 y ♀) 15.7 ± 5.6 (15–18 y ♂)
	Al Othman et al. 2012[82]	Primary Health Care Centers Riyadh (25°N)	331 (153♂178 ♀) Physically inactive: 13.4 ± 3.2 y Moderate Activity: 12.6 ± 3.3 y Active: 12.1 ± 3.6 y	Yes	ELISA /IDS	Mar–Dec 2010	Low physical activity, low sun exposure	7.1 ± 0.6 (Physically In Active) 8.5 ± 0.6 (Moderate Activity) 9.1 ± 0.6 (Active) 11% < 5 72% 5–10 17% 10–20

Abbreviations in table listed here in alphabetical order. BMI: Body Mass Index; CIA: Chemiluminescent Assay; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLIA: Electrochemiluminescent Immunoassay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; NA: Not Available; RIA: Radioimmunoassay; Supp: Supplemented; Unsupp: Unsupplemented; Vit: Vitamin; Yrs: Years.

Table 2. Overview of studies on 25(OH) D values in Children in Middle East

	Kensarah et al. 2012[102]	School-based Makkah (21°N)	87 ♂ 61♀ ♂10.4 yrs, ♀9.6 yrs	Yes	ECLIA /Roche	NA	Female gender	97% ♀ < 20 78% ♂ < 20
UAE	Rajah et al. 2012[101]	Pediatric outpatient clinics Abu Dhabi (24°N)	183 (52% ♂) 5.32 ± 3.76 y	Yes	RIA /Diasorin	All year 2005–2008	Sedentary lifestyle, veiling, Ca deficient diet.	Total: 21.4 18% > 10 27.5 (0–0.9 yrs) 31 (1–2 yrs) 21.2 (2–8 yrs) 14.1(8–12 yrs)
	Dawodu et al. 2003[90]	Maternal and child health clinics Al-Ain (24°N)	90 unsupp breast feeding Infants and Mothers	Yes	HPLC	Apr–Oct 1999	Low dietary vit D intake, low sun exposure	Mothers 8.6 (61% < 10) Infants 4.6 (82% < 10)
	Dawodu et al. 2001[104]	Hospital based Al-Ain (24°N)	51 15.4 mo UAE nationals (26) non-Gulf Arabs (25)	Yes	HPLC	Feb–Sep NA	Low Vit D supplementation	Infants 22% < 10 25 ± 11.9 (dietary Vit D supp) 15.4 ± 10.9 (unsupp) Mothers 50% < 10 11.36 ± 5.6

Abbreviations in table listed here in alphabetical order. BMI: Body Mass Index; CIA: Chemiluminescent Assay; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLIA: Electrochemiluminescent Immunoassay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; NA: Not Available; RIA: Radioimmunoassay; Supp: Supplemented; Unsupp: Unsupplemented; Vit: Vitamin; Yrs: Years.

Loss of CYP2R1 was also shown to be associated with 25(OH)D deficiency in several families in Nigeria[116-118] and associations between VDR polymorphisms and rickets in subjects from the Middle East has also been previously raised.[31,119] In a retrospective study of 34 Saudi children above age 10 y, who presented with rickets to a major hospital in Riyadh between 1994–2000, 59% had vitamin D deficiency, 11% calcium deficiency, 3% renal failure and 27% genetic causes. Of the total, 12% were reported by authors to have hypophosphatemic rickets, 9% to have 25-hydroxylase deficiency and 6% to suffer from vitamin D dependent rickets type I.[119] In addition, a recent report of 2 adolescent siblings from a Saudi family presenting with short stature and rickets, revealed 2 new mutations in CYP2R1.[120] The classical biochemical profile of very low 25(OH)D levels (below 4 ng/ml), within normal range calcitriol levels, the very high doses needed to normalize serum 25(OH)D levels, and an autosomal recessive inheritance pattern, had raised the author's suspicion for 25 hydroxylase deficiency. Residual hydroxylase function in the mutant allele or the presence of other hydroxylase enzymes that became more functional, in the presence of high levels of substrate, were proposed as possible mechanisms for the correction with supra-physiologic doses of vitamin D.[120]

In conclusion, there is a growing body of substantial evidence supporting a genetic basis for low 25(OH)D levels in several populations and some data for it in cases of rickets in the MENA, the latter is however based on small series and case reports. Thus the need for large scale population based genome wide association studies to adequately address this question in a definitive manner.

Impact of Vitamin D on Surrogate Markers or Major Health Outcomes in MENA

The evidence for a beneficial effect of vitamin D on musculoskeletal health and a potential effect on non-classical outcomes, such as cardiovascular diseases, diabetes, inflammatory, infectious, immune disorders and cancers, as well as mortality has been extensively reviewed,[1,3,5,121,122] and is beyond the scope of this paper. Cardiovascular diseases, maternal-neonatal health and infections are on the top of the health agenda of the World Health Organization and health authorities in countries worldwide, including the MENA region. Association and intervention studies evaluating the relationship between vitamin D and health outcomes, available to-date in the MENA region, will be examined here-in **Table 4**,[61,94,123-140] and **Table 5**.[100,141-149]

Associations studies. *Musculoskeletal health.* Significant negative associations between 25(OH)D and PTH levels were reported in young and old Lebanese subjects,[62] adults and elderly subjects from Iran,[134,150] and patients with hyperparathyroidism from Israel.[135] Positive associations between 25(OH)D levels and bone mass were also reported at several skeletal sites, in adolescent Lebanese girls[100] and elderly subjects.[61] In the elderly Lebanese, 25(OH)D levels also correlated with lean mass in men but not women and the correlations with BMD disappeared for all skeletal sites except for trochanter after adjusting for lean mass and PTH.[61] In the same study, subjects were followed prospectively and25(OH)D levels significantly correlated with bone loss over a mean follow-up of 4.4 y. This relation disappeared after adjusting for PTH levels.[94] In the adolescent study, there were no significant relationships between VDR genotype and baseline bone mass BMD, but in the elderly study, elderly women with the heterozygous VDR genotype had the highest bone mass at the lumbar spine and forearm.[151]

Non-classical outcomes. Lower mean 25(OH)D levels were reported in patients with type I DM in Saudi Arabia and Qatar[137,138] and it has been suggested that low levels may also contribute to metabolic syndrome and type II DM.[152] This is particularly pertinent, considering that the Middle East registers some of the highest rates for obesity, exceeding the rising tide in western countries, reaching 40–50%,[153] and has the greatest relative increase in diabetes prevalence, with rates reaching 20% in Bahrain, Saudi Arabia and the United Arab Emirates.[153,154] In patients with type II diabetes, negative correlations with BMI and several lipid parameters, were reported in studies from Iran and Saudi Arabia.[133,139] Mean 25(OH)D levels were also low in subjects with metabolic syndrome and also negatively correlated with BMI, lipid parameters, blood pressure and indices of insulin sensitivity.[127,145] The relationship between vitamin D and cardiovascular diseases and mortality has been intensely scrutinized in western populations,[122] and examined in three studies from MENA (**Table 4**). In the Tehran Lipid Glucose study, subjects with 25(OH)D levels below 10 ng/ml, had an almost 3-fold higher risk of developing cardiovascular outcomes than those above 15 ng/ml.[129] In a small longitudinal study of 139 Iranian women admitted with acute myocardial infarction, 25(OH)D levels correlated with overall survival.[128] These findings were validated in large HMO population-based database from Israel, that demonstrated that patients with heart failure and 25(OH)D levels below 10 ng/ml, had an increased risk of mortality, HR 1.52 (95% CI 1.21–1.92) and that patients who took vitamin D, at doses of 800–1000 IU/day reduced mortality, HR = 0.68 (95% CI 0.54–0.85), at a median follow-up of 518 d.[143]

Lower 25(OH)D levels have also been described in subjects with Systemic Lupus Erythematosis (SLE) and negative correlations reported with several indices of SLE disease activity in patients from Iran, Egypt and Israel.[126,130,136] Associations with other rheumatologic conditions, musculoskeletal pain and fibromyalgia have also been described in patients from Egypt and Iran.[123,131] Mean 25(OH)D level was significantly lower in Egyptian patients with Hepatitis C Virus

Table 3. Overview of Studies on 25(OH) D Values in Pregnant Women/Neonates in Middle East

Country	Authors/Yr	Sampling Method City (Latitude)	N/Age	Exclusion criteria specified	Assay type/ Manufacturer	Season /Yr	Predictors for low 25(OH)D	25(OH)D Level Mean ng/ml % below cut-off
Iran	Asemi et al. 2010[109]	Maternity clinic Kashan (34°N)	147 pregnant ♀ 18–35 y	Yes	HPLC	NA/2008–2009	NA	15 ± 8
	Kazemi et al. 2009[108]	Maternity clinics general hospital Zanjan (37°N)	67 full-term pregnant mothers 28.5 ± 5 y and 61 neonates	Yes	ELISA	Mar–Sep 2005	Winter for maternal and cord blood	Mother 8 ± 1.5 Summer 13 Winter 3 Cord 7 ± 1 Summer 8.7 Winter 5
	Bassir et al. 2001[110]	Maternity Hospital Shohalda Tehran (25–35°N)	50 mothers 16–40 y and their neonates	Yes	Radioligand assay	Jan–Sep 1997	NA	Mother 5 ± 2 80% < 10 Cord 2
Israel	Mukamel et al. 2001[111]		156 Orthodox and 185 non-Orthodox Jewish mothers at delivery	Yes	Competitive Protein Binding Assay	All year 1998–1999	Sect	Orthodox 13.5 ± 7.5 5% < 5 32% < 10 Non-Orthodox 18.6 ± 9.6 3% < 5 13% < 10
Kuwait	Molla et al. 2005[112]	Hospital based n = 2 Kuwait city (29 °N)	214 pregnant mothers 27.7 yrs and their neonates	Yes	RIA/Incstar	All year 1999–2000	NA	Mothers 13–17 Neonates 8 40% mothers, 60% neonates < 15
UAE	Narchi et al. 2010[92]	Maternal and Child Health Al Ain (24°N)	75 pregnant from early pregnancy to 6 mo post-partum 18–40 y	Yes	RIA/IDS	Sep-Nov 2007	Dietary habits, voluntary avoidance of sun exposure, veiling	First antenatal visit 17.3 ± 10.5 After delivery 14.4 ± 9.8 At 6 mo 11.9 ± 11.2

Abbreviations listed in alphabetical order: ELISA: Enzyme-linked immunosorbent Assay; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; NA: Not Available; RIA: Radioimmunoassay; Yrs: Years.

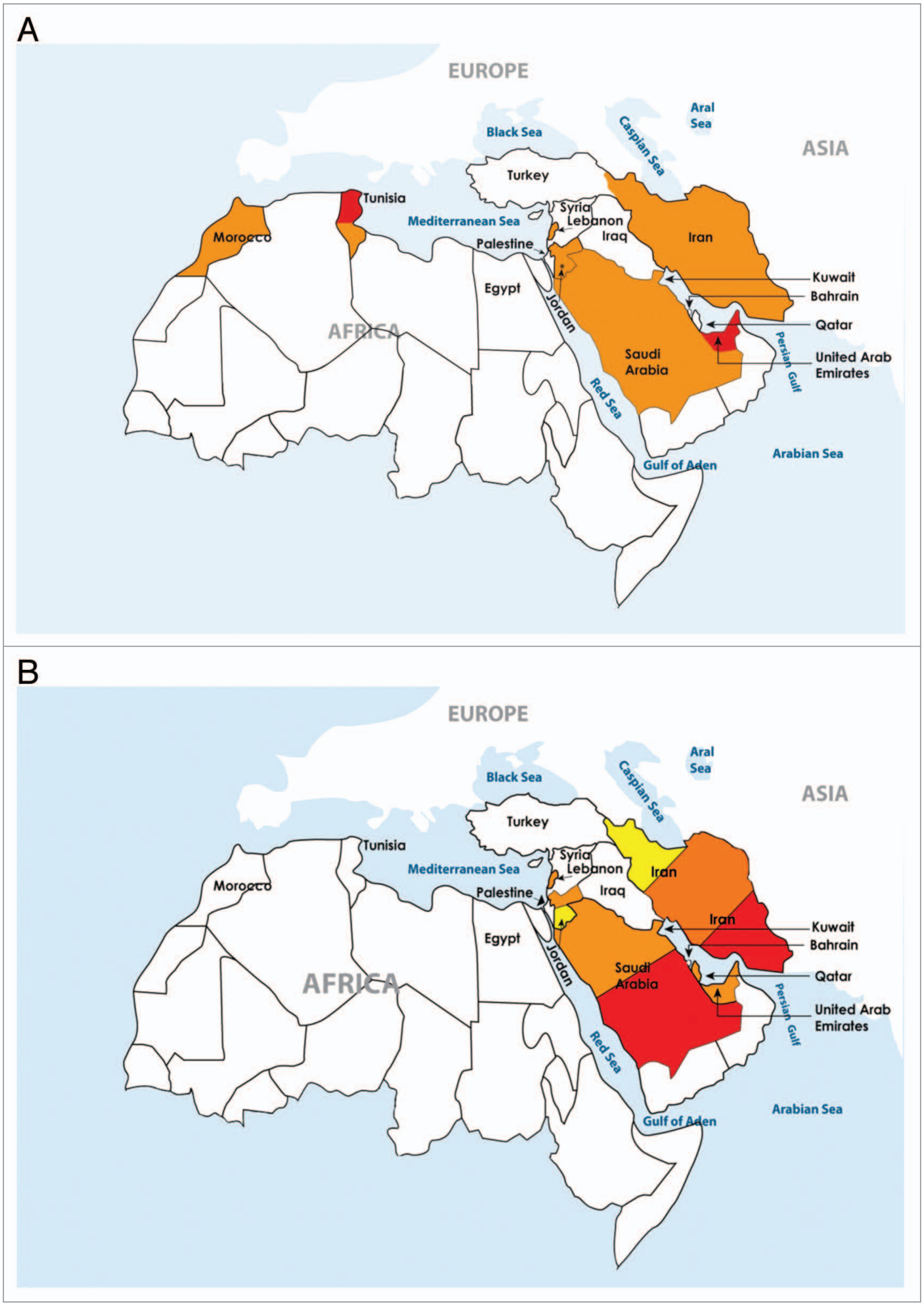

Figure 1. Serum 25(OH)D Levels in Adults (**A**) and Children (**B**) Based on Color Codes. The color codes are: green > 30 ng/ml, yellow 20–29 ng/ml, orange 10–19 ng/ml, and red < 10 ng/ml. To convert from ng/ml to nmol multiply by 2.5. The color codes were selected based on mean or median results from population based studies available or as obtained from most representative studies for each country. For countries with varying results, the color code was chosen as valid for ≥ 50% of reported values; or more than one color code was used (for, e.g., children in Iran).

(HCV) infection than controls, measured at 10 ng/ml and negatively correlated with viral load and circulating levels of several interleukins.[124] Calcitriol also negatively correlated with interleukin levels in the same study subjects.[125] Lower 25(OH)D levels have also been noted in adults Iranian patients with multiple sclerosis,[155] and children suffering from Celiac Disease in Israel.[156] Only few are the studies that performed the necessary adjustments to identify the independent impact of vitamin D on health outcomes. Furthermore, association studies cannot control for all potential confounders and thus the lack of good evidence for a cause-effect relationship. For example obese subjects have low vitamin D and are also more likely to display the profile of metabolic syndrome, but that does not prove that low vitamin D is the cause for metabolic syndrome. Similarly, illnesses in general and cirrhosis in particular are conditions more likely to be associated with low vitamin D, but there is no good evidence for a causative effect for vitamin D in the illness. Thus there exists the need to rely on intervention studies, which are however scarce.

Intervention Studies

Rickets. A Cochrane review of four interventions trials enrolling around 1700 term infants, lasting between 9 mo and 2 y, showed that vitamin D at doses of 300–400 IU/day was sufficient to prevent rickets.[157]

Various regimens to treat rickets in the region have been described and were mostly conducted in non-randomized, non-blinded interventional studies. Treatment with a single intramuscular injection of vitamin D at doses of 150,000–600,000 IU, single oral doses between 50,000 IU and 600,000 IU, daily injections or oral doses of 5,000 to 20,000 IU for 1–3 mo followed by 400 IU daily maintenance, all revealed substantial improvement in biochemical, clinical and radiological features of rickets.[11]

In a dose ranging study of 52 Turkish infants with nutritional rickets and a mean age of 10 mo, subjects were randomized to receive one oral dose of vitamin D of 50,000 IU, 300,000 IU or 600,000 IU, and all received oral calcium for one week. On the 30th day there was no difference in the improvement between the three groups, and all patients had improved by the 60th day post-therapy, however, eight infants developed hypercalcemia, six of which were allocated to the high dose group.[158] The two most recent intervention studies conducted in ME are detailed in **Table 5** and confirm findings from previous studies as summarized above. Children with rickets from some countries in ME such as Egypt, Saudi Arabia and the United Arab Emirates have low calcium intake. Therefore, careful assessment of calcium nutrition and concomitant therapy with calcium, in cases from the region is indicated and would expedite clinical recovery.

Skeletal health in adults. The relationship between 25(OH) D levels and indices of bone and mineral metabolism, based on randomized controlled trials, are well established and extensively studied in western populations and to a lesser extent in other ethnic groups.[106] There are no such studies on subjects in the MENA region.

Skeletal health in children and adolescents. The IOM report states that the Recommended Dietary Allowance (RDA) is the dose of vitamin D that would result in desirable 25(OH)D levels, above 20 ng/ml, in 97.5% of the population. In children, the RDA is 600 IU/d.[16] **Table 5** summarizes mean pre- and post-intervention 25(OH) D levels from recent studies in the region. The administration of doses of vitamin D, several folds above 600 IU, fail to bring most subjects above the 20 ng/ml cut-off, presuming the same desirable level is needed across ethnic groups.

A recent meta-analysis of 6 randomized placebo controlled trials studies, concluded that it is unlikely that vitamin D supplements are beneficial to bone mass in subjects with normal 25 (OH)D levels.[159] However, planned subgroup analyses by baseline 25(OH)D level suggest that vitamin D supplementation of deficient children and adolescents could result in clinically useful improvements.[159] The latter was in large part driven by results from a randomized placebo controlled trial in 179 Lebanese girls, mean age 13 y, that showed a positive impact of vitamin D, administered weekly, at the equivalent daily doses of 200 IU and 2000 IU/day on musculoskeletal parameters in girls, including bone mineral content, density, area and lean mass, especially during the pre-menarcheal period.[100] A significant relationship between VDR genotypes and changes in bone mass at one year emerged and remained significant after adjustment for puberty, changes in lean mass, height and bone area.[160]

Maternal and neonatal health. There are very few studies evaluating effect of vitamin D on musculoskeletal outcomes in mothers or neonates. In a randomized controlled vitamin D trial, conducted in 2000 neonates in India, vitamin D administration at 35 μg/day (1400 IU/day), significantly increased standard deviation (Z) scores for weight, length and arm circumference and decreased the proportion of children with stunted growth at 6 mo, but had no effect on death, hospitalization, in or out-patient visits.[161] Two on-going large multicenter trials, one conducted in US and the other in England, are evaluating the safety and efficacy of vitamin D administration, in pregnant mothers after the first term. The first uses doses of 400, 2000 to 4000 IU D/d until delivery,[162] and the second 1000 IU cholecalciferol/d or Placebo from 14 weeks gestation until delivery.[163] Considering the severe vitamin D deficiency in pregnant and lactating women in MENA, the gap in this field is substantial.

Metabolic syndrome. A close examination of individual randomized controlled trials investigating the effect of vitamin D supplementation (± calcium) on components of the MetS reveals negative findings for most trials, with the exception of the few that used high doses of vitamin D in high-risk individuals with obesity and insulin resistance at entry, but none was conducted in MENA.[152] In a study of 59 adult non diabetic, overweight and obese Saudis, advised to regularly expose themselves to sunlight and increase intake of vitamin D–rich foods, mean 25(OH)D levels increased from 7.6 to 11.2 ng/ml and the overall prevalence of MetS decreased from 25% to 13%, after one year.[145]

Infections. Chronic infections are still prevalent in the MENA region. Strong associations between hypovitaminosis D and tuberculosis (TB) infection and acute lower respiratory tract infections have been reported in Indian, Turkish and Sub-Saharan African populations.[10] Although 25(OH)D levels below 20 ng/ml were associated with increased susceptibility to active TB in HIV-uninfected (n = 196) and HIV-infected (n = 174) black Africans in Cape Town, South Africa,[164] vitamin D supplementation failed to improve clinical outcome or mortality in a randomized placebo controlled trial of 126 subjects recruited

Table 4. Overview on Association Studies Between 25(OH) D Levels and Health Outcomes in the Middle East and North Africa

Country	Author/Yr	Sampling Method City Cases/Controls N Gender/Age	Assay type / Manufacturer	Exclusion criteria specified	Disease condition /Health Outcomes	25(OH)D Level Mean ng/ml	Association between 25(OH)D and outcome (Correlation)
Egypt	Olama et al. 2012[123]	Clinic based Cases: 50 ♀ 32.3 ± 9.4 y Controls: 50 healthy ♀ 33.1 ± 9.7 y	ELISA/IDS	Yes	Fibromyalgia	Cases: 15.1 ± 6.1 Controls: 18.8 ± 5.4	Lumbar spine: r = −0.352 VAS of pain: r = −0.338 Beck score for depression: r = −0.328
	El Husseiny et al. 2012[124]	Clinic based Cairo Cases: 36♂, 14 ♀ 30–65 y Controls:: 25 age- and gender-matched healthy subjects	RIA/Incstar	Yes	HCV infection	Cases: 15 ± 5.2 Controls: 39.7 ± 10.8	Cases: Viral load: r = −0.84 IL-23: r = −0.776 IL-17: r = −0.665 MCP-1: r = −0.94
	Schaalan et al. 2012[125]	Clinic based Cairo Cases: 36♂, 14 ♀ Controls:: 25 age- and gender matched healthy subjects	RIA/Incstar	Yes	HCV infection	Cases: ♂10.30 ± 2.12 ♀10.00 ± 2.60 Controls: 39.70 ± 10.80	Cases: 25(OH)D and IL-17: r = −0.679 1.25(OH)D and IL-17: r = −0.679 1.25(OH)D and IL-23: r = −0.801
	Hamza et al. 2011[126]	Clinic, Hospital and university based Cairo Cases: 52 ♀ and 8 ♂/6–19 y Controls: 50 ♀, 10 ♂/7.2–18.5 y	ELISA/VDBP	Yes	SLE	Cases: 26.33 ± 12.05 13% < 10 60% < 30 27% > 30 Controls: 42.66 ± 9.20	SLEDAI: r = −0.91
	Al Sayed 2007[127]	Clinic based Cairo Cases:93♂♀ 45.2 ± 2.6 y Controls:70 healthy 47.1 ± 3.1 y	RIA/IDS	Yes	Metabolic syndrome	Cases: 16.2 ± 4.52 Control: 25 ± 4.48	Cases: BMI: r = -0.684 HOMA: r = −0.395 HDL: r = 0.277 PTH: r = −0.235 S. Insulin:r = −0.396
Iran	Khalili et al. 2012[128]	Hospital based Tehran 139 ♀ > 55 y, ♂ > 45 y	RIA/Abcam pic	Yes	Acute Myocardial infarction	10.92 ± 7.2	Hypertension: OR = 2.92 Use of cardiovascular drugs: OR = 2.36 Survival: OR = 0.216
	Hosseinpanah et al. 2011[129]	Population based Tehran Cases: 251♂♀ 56.0 ± 10.6 y Controls: 251 healthy subjects 56.7 ± 11.7 y	EIA/DRG	Yes	Cardiovascular	Median Cases: 12.5 (8.4–24.4) Controls: 18.1 (11–31)	Vit D < 10 had an almost 3-fold higher risk of developing cardiovascular outcomes r^a = 2.90 than those between 10–15 ng/ml r = 1.46

*Only significantly different 25(OH)D levels between cases and controls, and correlations. Details on studies that presented adjusted correlations are as follows: Hosseinpahanh et al. 2011, r^a adjusted for BMI, FPG, SBP, DBP, CT, TG, HDL-C, Smoking Status, degree of physical activity, premature CVD familial history. Bonakdar et al. 2011, r^b adjusted for age, BMI, sun exposure, use of sunscreen, physical activity. Heidari et al. 2011, OR^c adjusted for sex. Arabi et al. 2012, r^c adjusted for age, calcium intake, serum Creatinine and PTH in multivariate models, mean 25OHD was no more a predictor of bone loss. Arabi et al. 2006, r^d adjusted for age, height, lean mass and PTH levels, 25OHD level did not have residual significant contribution to BMD at any skeletal site except the trochanter in men. Abbreviations in table listed here in alphabetical order: ALKPhos: Alkaline Phosphatase; BILAG: British Isles Lupus Assessment Group; BMD: Bone Mineral Density; BMI: Body Mass Index; CIA: Chemiluminescent Assay; CRP: C- Reactive Protein; DsDNA: Double Stranded DNA; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLAM: European Consensus Lupus Activity Measurement; FN: Femoral Neck; HCV: Hepatitis C virus; HDL: High Density Lipoprotein; HOMA: Homeostasis Model Assessment; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; IL-17: Interleukin-17; IL-23: Interleukin-23; IRMA: Immunoradiometric Assay; LDL-C: Low Density Lipoprotein- Cholesterol; MCP-1: Macrophage chemoattractant protein-1; NA: Not Available; OR: Odds Ratio; r: Correlation; RIA: Radioimmunoassay; SBP: Systolic Blood Pressure; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; TC: Total Cholesterol; TG: Triglycerides; Troch: Trochanter; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; Vit: Vitamin; VAS: Visual Analogue Scale; VSP: Very Severe Pneumonia; VDBP: Vitamin Tracer, for the Binding Pocket of Vitamin D Protein; WHR: Waist Hip Ratio; Yrs: Years.

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	Bonakdar et al. 2011[130]	Clinic based Isfahan 40 ♀ 25.46 ± 4.16 y	RIA/DIAsource	Yes	SLE	9.68 ± 0.84	BILAG: r = −0.486 BILAG after Adjustment: r^b = −0.292 Low vit D higher titers of anti-dsDNA
	Heidari et al. 2010[131]	Clinic based Babol Cases: 276 ♂♀ 44.3 ± 15 y Controls: 202♂♀ 46.4 ± 14.2 y	ELISA/DRG	Yes	Musculoskeletal pain	Cases: 33.1 ± 28.4 Controls: 23.8 ± 29.1	Vit D < 20 vs. ≥ 20 with: Musculoskeletal pain: OR^c = 2.95 Leg pain: OR^c = 7.4 Widespread pain: OR^c = 2.8 Arthralgia: OR^c = 3.9
	Garakyaraghi et al. 2010[132]	Hospital based Isfahan 28 ♀, 67 ♂ 62 ± 11 y	CIA/Diasorin	Yes	Heart failure	56.78 ± 51.33	Diastolic volume: r = -0.24 Adjusted for age, Creatinine: r = -0.261
	Bonakkdaran et al. 2009[133]	Hospital based Mashhad 119 ♂♀ 55.3 ± 11.2 y	RIA/Biosource	Yes	T2DM	32.4 ± 21.6	Age: r = −0.21, BMI: r = -0.25, CRP: r = −0.06
	Omrani et al. 2006[134]	Cluster sampling Shiraz 676 healthy women aged 20–74 y	IRMA/IDS	Yes	Mineral Metabolism	28.9 ± 23.0	PTH r = −0.10 Independent of age
Occupied Palestine/ Israel	Saliba et al. 2012[135]	Population Based Clalit Health Services Cases: 1180 ♂♀ 65.30 ± 13.52 y Controls:184,479 ♂♀ 57.67 ± 18.25 y	CIA/DiaSorin	Yes	Primary Hyperparathyroidism	Cases: 19 ± 9 Controls: 20.8 ± 9.8	Cases: PTH: r = −0.238 ALKPhos: r = −0.180 Calcium: r = -0.054
	Amital et al. 2010[136]	278 with systemic lupus erythematosus activity (SLEDAI) 100 with European Lupus activity measurement (ECLAM) 40.2 ± 14.2 y	CIA/Diasorin	No	SLE	SLEDAI: 23.9 ± 14.0 ECLAM: 27.6 ± 13.9	Standardized values z-scores r = −0.12 The more active the disease, the lower the vitamin D concentration
Lebanon	Arabi et al. 2012[94]	Population based Beirut 65 ♂ and 130 ♀ 72.5 ± 5.1 y	RIA/IDS	Yes	BMD Mineral Metabolism	♂ 14.7 ± 4.0 ♀ 14.6 ± 7.4	Overall: % Change Trochanter BMD: r^d = 0.19 ♂:% Change Total hip BMD: r^d = 0.31 % Change F. Neck BMD: r^d = 0.36 % Change Trochanter BMD r^d = 0.26
	Arabi et al. 2006[61]	Population based Beirut 286♀ 73.4 ± 5.2 y 157♂ 74.1 ± 5.08 y	RIA/IDS	Yes	BMD Mineral Metabolism		♀BMD Total hip, FN, Troch: r^e = 0.10–0.18 ♂ BMD Total hip, spine, FN, Troch: r^e = 0.16−0.27

*Only significantly different 25(OH)D levels between cases and controls, and correlations. Details on studies that presented adjusted correlations are as follows: Hosseinpahanh et al. 2011, r^a adjusted for BMI, FPG, SBP, DBP, CT, TG, HDL-C, Smoking Status, degree of physical activity, premature CVD familial history. Bonakdar et al. 2011, r^b adjusted for age, BMI, sun exposure, use of sunscreen, physical activity. Heidari et al. 2011, OR^c adjusted for sex. Arabi et al. 2012, r^c adjusted for age, calcium intake, serum Creatinine and PTH in multivariate models, mean 25OHD was no more a predictor of bone loss. Arabi et al. 2006, r^d adjusted for age, height, lean mass and PTH levels, 25OHD level did not have residual significant contribution to BMD at any skeletal site except the trochanter in men. Abbreviations in table listed here in alphabetical order: ALKPhos: Alkaline Phosphatase; BILAG: British Isles Lupus Assessment Group; BMD: Bone Mineral Density; BMI: Body Mass Index; CIA: Chemiluminescent Assay; CRP: C- Reactive Protein; DsDNA: Double Stranded DNA; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLAM: European Consensus Lupus Activity Measurement; FN: Femoral Neck; HCV: Hepatitis C virus; HDL: High Density Lipoprotein; HOMA: Homeostasis Model Assessment; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; IL-17: Interleukin-17; IL-23: Interleukin-23; IRMA: Immunoradiometric Assay; LDL-C: Low Density Lipoprotein- Cholesterol; MCP-1: Macrophage chemoattractant protein-1; NA: Not Available; OR: Odds Ratio; r: Correlation; RIA: Radioimmunoassay; SBP: Systolic Blood Pressure; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; TC: Total Cholesterol; TG: Triglycerides; Troch: Trochanter; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; Vit: Vitamin; VAS: Visual Analogue Scale; VSP: Very Severe Pneumonia; VDBP: Vitamin Tracer, for the Binding Pocket of Vitamin D Protein; WHR: Waist Hip Ratio; Yrs: Years.

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Qatar	Bener et al. 2009[137]	Clinics /Face to face Interviews Doha Cases: 170 ♂♀ 10.5 ± 3.8 y Controls: 170 ♂♀ 9.9 ± 4.2. yrs	RIA/DiaSorin	No	T1DM	Cases: 15.8 ± 9.2 Controls:18.5 ± 9.6	NA
Saudi Arabia	Bin –Abbas et al. 2011[138]	Pediatric and Endo Clinics Riyadh Cases:59 ♀ 41 ♂ Controls: 52♀ 48 ♂	HPLC	Yes	T1DM	Cases: 14.7 ± 5.7 Controls:17.9 ± 5.6	No Correlation between glycemic control and 25 OHD level.
	Al Daghri et al. 2010[139]	Primary Health Care Centers Riyadh Cases: 76 ♀, 88 ♂ 50.6 ± 10.1 y Controls: 106 ♀, 71 ♂ non-diabetic 37.5 ± 15.3 y	ELISA/IDS	Yes	T2DM	Cases: 10.8 ± 4.7 Controls: 7.2 ± 2.9	Cases: TC: r = -0.20 LDL-C: r = -0.17 TG: r = -0.17 BMI: r = -0.22 Controls: SBP: r = 0.22 WHR: r = 0.16 Non-Adjusted values
Yemen	Salem et al. 2009[140]	Hospital based Sana'a 152 children with VSP 2–59 mo	ELISA/IDS	yes	Very severe pneumonia, some with rickets	Deficient n = 50:37.2 ± 17.3 Sufficient n = 9: 47.3 ± 17.6	Failure to respond to antibiotic therapy in rachitic compared with non rachitic OR = 1.38

*Only significantly different 25(OH)D levels between cases and controls, and correlations. Details on studies that presented adjusted correlations are as follows: Hosseinpahanh et al. 2011, r[a] adjusted for BMI, FPG, SBP, DBP, CT, TG, HDL-C, Smoking Status, degree of physical activity, premature CVD familial history. Bonakdar et al. 2011, r[b] adjusted for age, BMI, sun exposure, use of sunscreen, physical activity. Heidari et al. 2011, OR[c] adjusted for sex. Arabi et al. 2012, r[c] adjusted for age, calcium intake, serum Creatinine and PTH in multivariate models, mean 25OHD was no more a predictor of bone loss. Arabi et al. 2006, r[d] adjusted for age, height, lean mass and PTH levels, 25OHD level did not have residual significant contribution to BMD at any skeletal site except the trochanter in men. Abbreviations in table listed here in alphabetical order: ALKPhos: Alkaline Phosphatase; BILAG: British Isles Lupus Assessment Group; BMD: Bone Mineral Density; BMI: Body Mass Index; CIA: Chemiluminescent Assay; CRP: C- Reactive Protein; DsDNA: Double Stranded DNA; EIA: Enzyme immunoassay; ELISA: Enzyme-linked immunosorbent Assay; ECLAM: European Consensus Lupus Activity Measurement; FN: Femoral Neck; HCV: Hepatitis C virus; HDL: High Density Lipoprotein; HOMA: Homeostasis Model Assessment; HPLC: High-performance liquid chromatography; IDS: Immunodiagnostic Systems; IL-17: Interleukin-17; IL-23: Interleukin-23; IRMA: Immunoradiometric Assay; LDL-C: Low Density Lipoprotein- Cholesterol; MCP-1: Macrophage chemoattractant protein-1; NA: Not Available; OR: Odds Ratio; r: Correlation; RIA: Radioimmunoassay; SBP: Systolic Blood Pressure; SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; TC: Total Cholesterol; TG: Triglycerides; Troch: Trochanter; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; Vit: Vitamin; VAS: Visual Analogue Scale; VSP: Very Severe Pneumonia; VDBP: Vitamin Tracer, for the Binding Pocket of Vitamin D Protein; WHR: Waist Hip Ratio; Yrs: Years.

from National Health Service in United Kingdom with active TB.[165] Vitamin D did not significantly affect time to sputum culture conversion in the whole study population, but it did significantly hasten sputum culture conversion in participants with the *tt* genotype of the TaqI vitamin D receptor polymorphism.[165] However, vitamin D supplementation contributed to accelerating resolution of inflammatory responses and sputum smear conversion during tuberculosis treatment.[166]

Methods

Definition of middle east north africa region. According to the UNICEF, the MENA is composed of 20 countries: Algeria, Bahrain, Lebanon, Egypt, Djibouti, Syria, Occupied Palestinian Territory, Iran, Iraq, Yemen, Tunisia, Sudan, UAE, Saudi Arabia, Jordan, Oman, Libya, Kuwait, Morocco and Qatar.[17] According to the World Bank, countries in the Middle East include United Arab Emirates (UAE), Syria, Qatar, Lebanon, Kuwait, Saudi Arabia, Jordan, Iraq, Iran, Yemen, Oman and Bahrain; and in North Africa Algeria, Egypt, Libya, Morocco, Tunisia and Sudan.[18]

Literature search methodology. A systematic review of the literature was implemented targeting the following keywords: vitamin D, vitamin D deficiency or rickets, osteomalacia, conducted separately for each of the individual countries listed above for the Middle East North Africa region (MENA). Each of these keywords were searched on OVID Medline as MeSH terms and also as synonyms or related terms to achieve a comprehensive literature review. The OVID Medline interface was utilized as it allows searching for related MeSH-terms, explode functions, keyword searching in title, abstract and subject headings, adjacency and publication types, in addition to Boolean operators (and, or) and truncation, to identify as many relevant articles as possible. OVID Medline search was conducted from year 1946 until the third week of September, 2012, then tailored to years 2000-Dec 2012 (see **Appendix S1**). The exact procedure used for every country of the MENA region is detailed in **Appendix S1**. A PubMed search was also done using the key terms for each of the countries of interest to capture the most recent publications entered into PubMed, not yet indexed in OVID Medline. The following search was entered for each of the countries of the MENA region, the example for Lebanon was: (vitamin D OR rickets OR osteomalacia) AND (Lebanon OR Lebanese). The Embase database was also used to capture a more comprehensive view on studies done in the Middle Eastern

Table 5. Overview on Interventional Studies between 25(OH)D Levels and Health Outcomes in the Middle East

Country	Author Yr	Sampling Method City (Latitude) N Gender/Age	Protocol Design	Intervention Type/Dose/Duration	Assay type/ Manufacturer	Exclusion criteria specified	25(OH)D Level Mean ng/ml	Effect on Health Outcome
Iran	Shakinba et al. 2011[141]	School Based Yazd (32°N) 120 girls 12–15 y Group 1: 28 with Vit D Deficiency Group 2: 23 with Vit D Deficiency Group 3: 30 Group 4: 30	RCT	Group 1: 300,000 IU D3 once, randomized to 50,000 IU D3/ month Group 2: 300,000 IU D3 once, randomized to 100,000 IU D3/ 3 mo Group 3: 50,000 IU D3/3 mo Group 4: 100,000 IU D3/3 mo	CIA/DiaSorin	No	Baseline One year Group 1 29.7 ± 4.6 47% 20–30 53% 30–100 Group 2 30 ± 5.6 57% 20–30 43% 30–100 Group 3 15.2 ± 6 13% < 10 73% 10–20 11% 20–30 3% 30–100 Group 4 23 ± 6.8 45% 10–20 35% 20–30 19% 30–100	NA
	Ghazi et al. 2010[142]	School Based Tehran (35.7°N) 105 ♂, 105 ♀14–20 y 16 ± 1.5 y Group A:35♂,35♀ Group B:34♂,35♀ Group C:34♂,35♀	Double-blinded RCT	Group A:50,000 IU D3/monthly Group B: 50,000 IU D3/2 mo+ placebo every alternative month Group C:Placebo	ELISA/IDS		Baseline 6 mo Group A: 12.8 ± 8.8 ♀19.2 ± 9.4 ♂29 ± 10.5 Group B: 11.3 ± 5.8 ♀13.5 ± 9.2 ♂23.1 ± 7.6 Group C: 11.6 ± 7.2 ♀8 ± 5.6 ♂15.6 ± 6.4	NA
Israel	Gotsman et al. 2012[143]	Population based Clalit Health Services A- 3009 ♂♀ with Heart Failure 75.9 ± 10.7 y 46,825♀♂ controls 64.7 ± 11.3 y B- 791 ♂♀ with Heart Failure 458 ♂♀ with supplementation 333 ♀♂ without supplementation	A-Case-Control B-Interventional	B. 800 IU/d and 1000 IU/d for median follow up of 518 d.	RIA/DiaSorin	No	A- Cases Median:14.8 Controls Median:16.3 B- Survival Rate HF patients < 10 ng/ml with supplementation:85.6 ± 1.7% HF patients < 10 ng/ml without supplementation:81.6 ± 1.7%	Reduced Mortality in Heart Failure patients HR = 1.52 and controls HR = 1.91

Abbreviations in table listed here in alphabetical order: BMD: Bone Mineral Density; Ca: Calcium; CIA: Chemiluminescent Assay; ELISA: Enzyme-linked immunosorbent Assay; HPLC: High-performance liquid chromatography; HR: Hazard Ratio; IDS: Immunodiagnostic Systems; NA: Not Available; RIA: Radioimmunoassay.

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Lebanon	El-Hajj Fuleihan et al. 2006[100]	School Based Beirut (33°N) 179 ♀ Group A: 13 ± 2.1 y Group B: 13.1 ± 2.2 y Group C: 13.6 ± 2.1 y	Double-blinded RCT	Group A:Placebo Group B: Low dose 200 IU D3/d Group C: High dose 2000 IU D3/d	RIA/DiaSorin	Yes	Baseline One year Group A: 14 ± 7 16 ± 8 Group B: 14 ± 9 17 ± 6 Group C: 14 ± 8 38 ± 31	Low dose and High dose: increase in BMD, Lean Mass High dose:increase in Total BMD, Bone Area Premenarcheal girls had the highest increment
Country	**Author** **Yr**	**Sampling Method** **City (Latitude)** **N Gender/Age**	**Protocol Design**	**Intervention** **Type/Dose/Duration**	**Assay type/ Manufacturer**	**Exclusion criteria specified**	**25(OH)D Level Mean ng/ml**	**Effect on Health Outcome**
Qatar	Soliman et al. 2011[144]	General Practitioner Clinic Doha (25.3°N) 40 Adolescents with Vit D Deficiency	Prospective Open-Label Non-Randomized	600,000 IU D3 every 2–3 mo	RIA	No	Pre-Interv Post Interv 9.3 ± 4.6 27.7 ± 9.2	Healing of Rickets in all patients at one year.
Saudi Arabia	Al-Daghri et al. 2012[145]	Primary Health Care Centers Riyadh (24.6°N) 31♂28♀ 18–65 y 38 ± 14.1 y	Interventional	Advice for 5–30 min sun exposure twice/week and vitamin-D rich foods	ELISA/IDS	Yes	Baseline 6 mo 12 mo 7.6 ± 0.6 10.7 ± 0.6 11.4 ± 0.6	Decrease of Metabolic Syndrome from 25% to 13%
UAE	Rajah et al. 2010[146]	Hospital Based Abu Dhabi (24°N) 10 Children with Rickets: Group 1: 7 children Group 2: 3 children 21.2 ± 8.4 mo	Retrospective Audit	Group 1:2000 IU D2/d for 3 mo +400 IU D2/d subsequently+ Ca 40 mg/Kg/d for 3 mo Group 2: stosstherapy 600,000 IU D2 single dose + Ca 40 mg/Kg/d for 3 mo	HPLC	Yes	Baseline 3 mo 15.1 ± 10.3 NA Median: 11.6 Median: 57.4	NA
	Saadi et al. 2009[147]	Maternal-Child Health Clinic Al-Ain (24°N) Group 1: 22 mothers 28.1 ± 4.7 y Group 2: 22 mothers 27.6 ± 6.5 y Group 1: 22 infants 19.1 ± 25.4 d Group 2: 24 infants 20.6 ± 22.9 d	RCT	Mothers: Group 1:2000 IU D2/d for 3 mo Group 2:60,000 IU D2/m for 3months Infants:400 IU D2/d for 3 mo	RIA /DiaSorin	No	Mothers Pre-Interv Post Interv Group 1: 11 ± 4 16.9 ± 5.6 Group 2: 8.9 ± 4 15 ± 4 Infants 30% < 20 ng/ml at 3 mo Group 1: 5.6 ± 3.4 19.8 ± 7.4 Group 2: 5.5 ± 4.8 17.8 ± 6	NA

Abbreviations in table listed here in alphabetical order: BMD: Bone Mineral Density; Ca: Calcium; CIA: Chemiluminescent Assay; ELISA: Enzyme-linked immunosorbent Assay; HPLC: High-performance liquid chromatography; HR: Hazard Ratio; IDS: Immunodiagnostic Systems; NA: Not Available; RIA: Radioimmunoassay.

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Rajah et al. 2008[148]	Hospital Based Abu Dhabi (24°N) 31 Children with Rickets: 8 Vit D deficient 14.8 ± 3.2 mo 8 Ca deficient 19.8 ± 2.3 mo	Quasi-Experimental Non-Randomized	2000–5000 IU D2/d for 3 mo + 400 IU D2/d for a variable period	CIA/Nichols	No	Baseline: 8 Vit D deficient: 6.9 ± 1.3 8 Ca deficient: 17.7 ± 7.1	Height z-score Entry: −1.74 Termination: −0.88
Saadi et al. 2007[149]	Maternal-Child Health Clinic Al-Ain (24°N) Group 1:45 lactating♀ 29.2 ± 5.5 yrs Group 2:45 lactating♀ 29.9 ± 6.7 yrs Group1:43nulliparous♀ 23 ± 5.2 yrs Group2:45nulliparous♀ 24.6 ± 5.1 yrs	Open-Label RCT	Group 1:2000 IU D2/d for 3 mo Group 2:60,000 IU D2/m for 3months	RIA /DiaSorin	Yes	Lactating Pre-Interv Post-Interv Group 1: 10.9 ± 4.2 17 ± 5.6 Group 2: 9.3 ± 4.3 15 ± 4.2 Nulliparous Group 1: 7.8 ± 5 16.7 ± 10.6 Group 2: 7.6 ± 4.9 15.7 ± 8.6	1/3 ♀ achieved 25(OH)D ≥ 20 ng/ml

Abbreviations in table listed here in alphabetical order: BMD: Bone Mineral Density; Ca: Calcium; CIA: Chemiluminescent Assay; ELISA: Enzyme-linked immunosorbent Assay; HPLC: High-performance liquid chromatography; HR: Hazard Ratio; IDS: Immunodiagnostic Systems; NA: Not Available; RIA: Radioimmunoassay.

region. We also used data compiled in the 2011 International Osteoporosis Foundation (IOF) Middle East Africa Osteoporosis Audit,[19] and additional studies and reviews detailed in the papers retrieved and available in authors' libraries.

Search yield and manuscripts reviewed. A total of 2323 hits were identified from Embase, PubMed and OVID Medline for all the countries, with the exception of Djibouti and Libya, that had no hits. Three screening phases were implemented for identifying relevant articles. The first phase involved screening the titles and abstracts and resulted in 362 manuscripts between 1946 and 2012. The second phase involved deleting studies published before year 2000, thus resulting in 295 papers. The third phase involved retrieving and reviewing the full-text for all 295 papers, of which only 176 where retrievable and these were scored for quality measures based on specific criteria: type of the study (population based yes or no), sample size (n > 100 yes or no), whether the vitamin D assay was specified (yes or no), whether predictors were specified (yes or no) and exclusion criteria were specified (yes/no). Each criterion received a score of 1 if answered positively and articles were sorted into four quality categories: very good for score ≥ 4/5, good for score 3/5, fair for score 2/5 or poor if score 1/5. The large majority of the 295 retrieved papers were from Iran (n = 86), Saudi Arabia (n = 47), UAE (n = 21), Egypt (n = 20), followed by Lebanon, Kuwait, Jordan, Qatar and Morocco Jordan (n = 11–16 each) and Yemen, Tunisia, Iraq, Bahrain, Oman (n = 1–5 each). Out of the total of 176 studies, 109 studies characterized as of very good or good quality are detailed in this review.

For association and intervention studies, as well as reports on rickets or osteomalacia, rating score was not applied and all relevant studies were examined. Titles and abstracts for reviews on osteomalacia retrieved prior to 2000 (n = 338) were screened and all relevant reviews in the MENA, in addition to those on hypovitaminosis D[9-11] were used to summarize information for the period preceding year 2000.

Interpretation of results from papers on vitamin D and cut-offs used to determine desirable levels. Serum 25 hydroxyvitamin D [25(OH)D] 25(OH)D level is the best indicator of vitamin D nutritional status. The importance of variations in serum 25(OH)D assays and the lack of their standardization has been recently recognized.[20,21] Furthermore, there is no universal agreement on what constitutes a desirable level to optimize musculoskeletal health in elderly Caucasians,[15,16] let alone optimal levels across the lifecycle, for other ethnic groups or targeting other major chronic diseases outcomes. Findings from any paper on vitamin D, have to therefore be interpreted in this context. Results for serum 25(OH)D are reported in ng/ml, to convert to from ng/ml to nmol/L multiply the value by 2.5.

Conclusion

Reports of nutritional rickets and osteomalacia occur in the MENA region, despite its plentiful sunshine and at much higher rates than in western countries. Hypovitaminosis, defined as a serum 25(OH)D below 20 ng/ml, is also prevalent across populations throughout the lifecycle, with proportions varying for the most part between 30–90%, depending on gender, season and lifestyle pattern. Population based studies are scarce, but results available from such studies validate the above observations. Genetic polymorphisms along the vitamin D pathway have been described mostly in western populations. The extent to which they account for low 25 (OH)D levels in the region awaits population-based genome wide association studies. There are large information gaps on what may constitute a desirable level for various health outcomes for subjects from this region. Furthermore, the recommended vitamin D doses by the IOM and even ES are sub-optimal to bring 25(OH)D to the putative "desirable" level in various age groups. Thus the pressing need to address such knowledge gaps, in order to facilitate the development of evidence-based region specific guidelines and to impact this subclinical condition that may be at the root of several chronic diseases.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest was disclosed.

Acknowledgments

The authors would like to thank Ms Aida Farha, Medical Information Specialist, Saab Medical Library, American University of Beirut, for her advice and assistance in designing comprehensive and complex searches of the various medical literature resources and for the provision of select articles and Mr. Samir Hanoun for the art work. This review was in part supported by an educational grant from the Medical Practice Plan at the American University of Beirut and the Lebanese National Council for Scientific Research.

Supplemental Materials

Supplemental material may be found here: www.landesbioscience.com/journals/dermatoendocrinology/article/25111

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