Journal of Steroid Biochemistry & Molecular Biology 175 (2018) 102–107

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

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

Review

Vitamin D in Saudi Arabia: Prevalence,distribution and disease associations

Nasser M. Al-Daghri[a,b,*]

[a] Biomarkers Research Program, Biochemistry Department, College of Science, King Saud University,Riyadh 11451, Saudi Arabia
[b] Prince Mutaib Chair for Biomarkers of Osteoporosis, Biochemistry Department, College of Science, King Saud University, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:
Received 27 June 2016
Received in revised form 14 November 2016
Accepted 23 December 2016
Available online 24 December 2016

Keywords:
Vitamin D
Saudi Arabia
Vitamin D related-diseases
Prevalence

ABSTRACT

More than 33 years have passed since the first paper highlighting vitamin D deficiency as a public health concern in Saudi Arabia was published in 1983. Despite "early" detection,it wasn't until the year 2010 where the interest in vitamin D research grew exponentially worldwide and was finally visible in Saudi clinical and academic areas. Since then,many landmark studies have been generated with regards to the physiologic functions of vitamin D,both skeletal and extra-skeletal. This review is limited to the prevalence,distribution A systematic review on the prevalence studies done in KSA from 2011 to 2016 was done and revealed that the prevalence of vitamin D deficiency (<50 nmol/l) in Saudi Arabia among different populations (adults,children and adolescents,newborns and pregnant/lactating women) is 81.0% (Confidence Interval 95% 68.0–90.0),in line with most neighboring Gulf countries. Vitamin D deficiency in KSA has been mostly associated with bone and insulin-resistant diseases but limited data are available to prove causality. In conclusion,there is a need to develop local consensus guidelines that will identify candidates for screening,monitoring and treating those who are at most risk for vitamin D deficiency complications.

Contents

1. Background

During the last decade,no other micronutrient has gained and sustained massive interest in the fields of health and biomedical research community as much as vitamin D. Globally,vitamin D deficiency is widespread and is considered an epidemic [1]. The Middle East and North African (MENA) region in general has a very high prevalence of vitamin D deficiency [defined as 25(OH) D levels

* Corresponding author at: Prince Mutaib Bin Abdullah Chair on Osteoporosis, Biochemistry Department,College of Science,King Saud University,PO Box,2455, Riyadh,11451,Saudi Arabia.
E-mail address: aldaghri2011@gmail.com (N.M. Al-Daghri).

http://dx.doi.org/10.1016/j.jsbmb.2016.12.017
0960-0760/

Table 1
Overview of Studies in Different Saudi Populations Highlighting the Prevalence of Vitamin D Deficiency Published in 2011–2016.

Author	Setting/Location	Sample Size	Method Used	Serum 25(OH)D Cut-Off Definition Used	Central Measure	Prevalence (%)
Adults						
Tuffaha et al. [10]	Multi-Center (National), April-June 2013	806 Males 1434 Females	ECL (Roche)	<28 ng/ml	Not mentioned	40.6 in Males 62.7 in Females
Al-Daghri et al. [11]	Multi-Center (KSU), Riyadh Feb-Oct 2013	368 Males 462 Females	ECL (Roche)	<25 nmol/l	40.9 ± 1.1 in Males 39.8 ± 1.4 in Females	17.7 in Males 36.8 in Females
BinSaeed AA et al.[12]	Single Center (KSU), Riyadh	255	ECL	<30 nmol/l	Not mentioned	75.2
Alfawaz et al. [13]	Single Center (KAMC), Riyadh Sept 2009-Dec 2010	756 Males 2719 Females	HPLC	<25 nmol/l	35.5 ± 30.6	36.1 in Males 48.8 in Females
Kanan et al. [14]	Single Center (KAMC), Riyadh Jun-Aug 2009 (Summer) Jan-March 2009 (Winter)	659 Females 897 Females	HPLC	<50 nmol/l	33.3 ± 1.65 (SE) 28.5 ± 1.16 (SE)	80.0 85.0
Ardawi et al. [15]	Multi-Center (Jeddah) Jan 2008-Dec 2009	834 Males	ECL (Roche)	<50 nmol/l	≥50 years 31.2 ± 17.5 < 50 years 26.8 ± 15.0	87.8
Ardawi et al. [16]	Multi-Center (Jeddah) June 2008-June 2009	1172 Females	CLIA (Diasorin)	<50 nmol/l	Premenopausal 43.0 ± 30.5 Postmenopausal 33.3 ± 24.9	80.0
Children and adolescents						
Al-Daghri et al. [11]	Multi-Center (KSU), Riyadh February-October 2013	1187 Boys 1038 Girls	ECL (Roche)	<25 nmol/l	39.0 ± 0.6 in Boys 29.4 ± 0.6 in Girls	19.4 in Boys 47.0 in Girls
AlBuhairan et al. [17]	Multi-Center (National)	6444 Boys 6131 Girls	CMI (Abbott)	< 50 nmol/l	Not mentioned	95.6
Mansour and Alhadidi [18]	Single Center (Jeddah) Oct-December 2010	220 Boys 290 Girls	CLIA (Diasorin)	<20 ng/ml	13.1 ± 7.8	58.8
Newborns						
Al-Faleh et al. [19]	Single Center (KSU) November-March 2013	200	ECL (Roche)	<25 nmol/l	21 (13)	59.5
Aly et al. [20]	Single Center, 2011	92	EIA (IDS)	<30 nmol/l	33.4 ± 18.3	Not mentioned
Pregnant/Lactating						
Al-Faris (2016) [21]	Single Center (KFMC), Riyadh March-May 2010	160	ECL (Roche)	<50 nmol/l	49.9 (28.0)	50.0
Al-Ajlan et al. [22]	Multi-Center (KSU) Riyadh	515	ECL (Roche)	<25 nmol/l	19.1 ± 15.1	68.0

Note: Central measures were presented as mean ± standard deviation, median (range) or mean ± standard error (SE).

lower than 50 nmol/l (20 ng/ml)] and is most prominent in women of varying ages [2]. The kingdom of Saudi Arabia (KSA), being part of the MENA region, therefore, is not spared from vitamin D deficiency, despite the year-round sunlight rich-environment. Even though local evidence is accumulating, the response at the national level remains is equally deficient. In this review, the local studies done on vitamin D deficiency are highlighted, with emphasis on epidemiology and associated diseases, with the hope that the evidence presented will compel the Saudi medical and scientific authorities to initiate tougher measures on early intervention and prevention of vitamin D deficiency in KSA.

2. Methods

A review of literature on the most recent epidemiology, clinical trials and reviews done in KSA with respect to vitamin D deficiency was conducted. The literature search was done in May 2016 using the MEDLINE/PubMed database. For epidemiology, the search was limited to studies conducted locally from 2011 to 2016 using the key words “Vitamin D deficiency”; “Saudi Arabia” and “observational study” which yielded 105 results. Reviews; case reports and studies with very small sample sizes; genetic studies; studies involving the prevalence of vitamin D deficiency in connection to other diseases (types 1 and 2 diabetes; osteoporosis; liver diseases; kidney diseases; autoimmune diseases and studies with vague diagnostic cut-offs used and technique); interventional studies and animal studies were excluded. Studies including non-Saudis or not done in KSA were also excluded. Studies that involved other populations with common diseases associated with vitamin D deficiency in KSA were used in Table 2. A flowchart of study inclusion is presented in Fig. 1.

2.1. Meta-analysis

Studies included were assessed using an adjusted CASP tool [9]. Forest plot was generated using the comprehensive meta-analysis (CMA) software version 3.0 (http://www.meta-analysis.com/index.php).

3. Results

A total of 13 studies (N = 24,399) were included and are summarized in Table 1 [10–22]. These studies include several apparently healthy subpopulations (adults, children and adolescents, newborns and pregnant/lactating women). A forest plot was generated and showed that the prevalence of vitamin D deficiency (<50 nmol/l) in Saudi Arabia among different populations (adults, children and adolescents, newborns and pregnant/lactating women) is 81.0% (Confidence Interval 95% 68.0–90.0) using the random-effect model (Fig. 2). Furthermore from the studies included it is apparent that there is no clear cut-off used for vitamin D deficiency as well as no uniformity in the methods for

Table 2
Major Diseases Associated with Vitamin D Deficiency in Saudi Arabia.

Diseases	References
Asthma	Aldubi et al. [40]
Cancer	Abulkhair et al. [41]
	Nabi et al. [42]
	Yousef et al. [43]
Cardiac Disease	Fanari et al. [44]
Chronic Kidney Disease	Kari et al. [45]
Fibromyalgia and Chronic Low back pain	Matthana [46]
	Abokrysha [47]
	Al-Eisa et al. [48]
Fractures	Rouzi et al. [37]
	Al-Daghri et al. [38]
Hyperparathyroidism	Abdek-Gayoum et al. [39]
Obesity And The Metabolic Syndrome	Al-Daghri et al. [11]
	Abdelkareem et al. [57]
Osteoporosis/Osteopenia	Alissa et al. [35]
	Sadat-Ali et al. [36]
	Rouzi et al. [37]
Rickets/Osteomalacia	Al Jurayyan et al. [33]
	Sulimani et al. [29]
	Mosalli et al. [34]
Rheumatoid Arthritis	Azzeh and Kensara. [50]
Sickle Cell Disease	Sadat-Ali et al. [51]
	Shams et al. [52]
Systemic Lupus Erythematosus	AlSaleem et al. [53]
Subfertility	Al-Jaroudi et al. [49]
Type 1 Diabetes Mellitus	Bin Abbas et al.[55]
	Al Shaikh and Zahrani. [56]
Type 2 Diabetes Mellitus	Al-Daghri et al. [58]
	Alkharfy et al. [59]
	Al-Shahwan et al. [60]
Vitiligo	Khurrum and AlGhamdi [53]

quantifying serum 25(OH)D. Electrochemiluminescence (ECL) immunoassay was the most common method used for serum 25 (OH)D quantification. Table 2 shows the most common diseases associated with vitamin D deficiency among Saudis based on the most recent local publications and the most common diseases studied so far involved skeletal and metabolic diseases.

4. Discussion

4.1. Vitamin D deficiency in KSA and in the middle east

The extremely high prevalence of vitamin D deficiency in KSA based in the present meta-analysis confirms the report of Bassil and colleagues for the entire Middle East and North Africa (MENA) region [23]. Sedrani and colleagues in 1983 [3] were the first to document vitamin D deficiency in KSA, and this was observed among apparently healthy student males of King Saud University (KSU), Riyadh, KSA. Since then, other studies using different healthy sub-populations have emerged, mostly women of child bearing age [4–6]. Consequently at this time, rapid industrialization was taking place at KSA. Environmental risk factors in lifestyle such as daytime sleep and night time activities, work environments which are sedentary and extreme weather conditions may have been contributory [7]. Certain groups such as the elderly, dark-skinned and/or veiled women and their children are at particular risk for vitamin D deficiency [2]. But more importantly, urbanization and tremendous socioeconomic growth has resulted in profound changes in the way of life during the last three decades, resulting to increased and sustained incidence of obesity and type 2 diabetes mellitus [8], diseases known to elicit depressed circulating levels of vitamin D.

The widespread vitamin D deficiency in KSA has also been similarly documented in neighboring Gulf countries such as expatriates and locals from the United Arab Emirates where the prevalence was noted to be at 82.5% [24]. In Kuwait, the prevalence was 83.0% based on a recent national survey [25]. In a cohort of 500 apparently healthy Bahrainis the prevalence of those whose serum 25(OH)D falls below 50 nmol/l was 86.4% [26] and among a cohort of 523 middle-aged Arab women from Qatar the prevalence was observed to be 84.7% [27]. These similar findings can be attributed mostly to the shared geographical location of these countries (the Arabian Peninsula) where the desert climate of extreme high temperatures during summer season dominates preventing people from the much needed sun exposure as well as the shared culture of Islamic type of dressing where most women are covered from head to toe. The former also explains why the prevalence of vitamin D deficiency is much lower during the winter season than the summer season, a unique counterintuitive seasonal effect not shared in other regions in the world [28,29].

4.2. Vitamin D deficiency has been associated with a wide range of diseases in the saudi community

Vitamin D deficiency has been consistently associated with hypertension, diabetes mellitus, cardiovascular disease, stroke, multiple sclerosis, inflammatory bowel disease, osteoporosis, periodontal disease, macular degeneration, mental illness, propensity to fall and chronic pain and various cancers [30]. Most tissues have not only vitamin D receptors, but also hydroxylase enzyme that is required to convert 25(OH)D to the active form, 1α,25-dihydroxyvitamin D3 [31]. Therefore, vitamin D can affect tissues that are not involved in calcium homeostasis and bone metabolism. Almost all tissues in the body possess vitamin D receptors including brain, heart skeletal muscle, smooth muscle cells, pancreas, activated T and B lymphocytes, and monocytes [32].

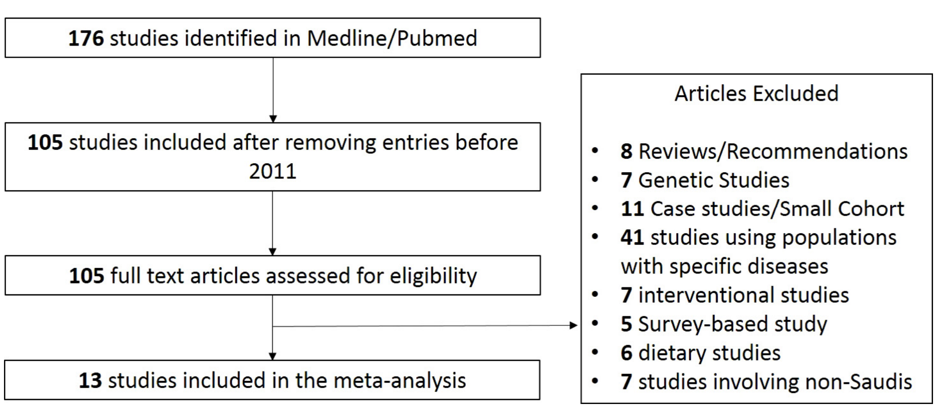

Fig. 1. Workflow of review.

Vitamin D Deficiency in KSA (2011 - 2016)

Model	Study name	Statistics for each study: Event rate	Lower limit	Upper limit	p-Value
	Al-Daghri et al., 2015	0.51	0.50	0.53	0.143
	BinSaeed et al., 2015	0.92	0.88	0.95	0.000
	Al-Fawaz et al, 2014	0.77	0.75	0.78	0.000
	Kanan et al., 2013	0.83	0.81	0.85	0.000
	Ardawi et al., 2012	0.88	0.85	0.90	0.000
	Ardawi et al., 2011	0.80	0.78	0.82	0.000
	Al-Buhairan et al., 2015	0.96	0.95	0.96	0.000
	Mansour & Alhadidi, 2012	0.59	0.54	0.63	0.000
	Al-Faleh et al., 2014	0.88	0.82	0.91	0.000
	Aly et al., 2013	0.66	0.56	0.75	0.002
	Al-Faris, 2016	0.50	0.42	0.58	1.000
	Al-Ajlan et al., 2015	0.94	0.92	0.96	0.000
Fixed		0.78	0.78	0.79	0.000
Random		0.81	0.68	0.90	0.000

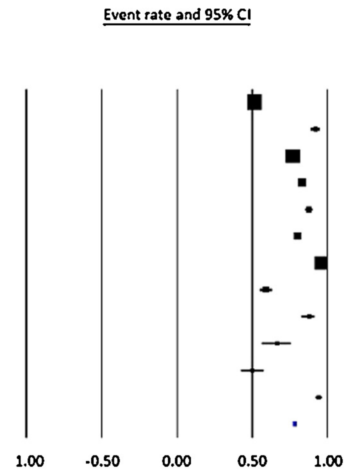

Fig. 2. Forest Plot on the prevalence of Vitamin D Insufficiency in Saudi Arabia 2011–2016.

The major diseases associated with vitamin D deficiency in KSA are listed in Table 2. Among these, the most widely documented include rickets and osteomalacia among Saudi children [29,33,34] as well as osteopenia and osteoporosis in adults [35,36]. Other local studies done covering the skeletal effects of vitamin D include fractures [37,38] and hyperparathyroidism [39]. Furthermore, it is expected that with the increasing elderly Saudi population, the prevalence of chronic non-communicable diseases including osteoporosis in KSA will increase if not remain steady, and uncorrected vitamin D deficiency being a risk factor to these diseases will play a major role in the progression of these diseases. Among the non-skeletal diseases observed to be related in the Saudi population in the recent times include asthma [40], cancer [41–43], cardiac disease [44] as well as chronic kidney disease [45]. Worthy to note among these diseases is the emergence of increasing incidence of fibromyalgia or chronic muscle pain mostly experienced by Saudi women that showed significant improvement after treatment of high-dose vitamin D [46–48], the link between vitamin D deficiency and subfertility [49] as well as autoimmune diseases such as rheumatoid arthritis [50], sickle cell disease [51,52], systemic lupus erythematosus [53], vitiligo [54] and type 1 diabetes mellitus [55,56]. Lastly, the associations of vitamin D status in obesity, components of the metabolic syndrome, insulin resistance and type 2 diabetes mellitus is well documented in the Saudi population, including several intervention trials highlighting the beneficial effects of vitamin D correction [57–60].

The extra-skeletal benefits of vitamin D supplementation, specifically insulin resistance, is of particular interest in the Saudi population since the prevalence of diabetes mellitus type 2 is quite high in the country and the region in particular. It is well known that the β-cells of pancreas contain VDRs and that 1,25(OH)2D stimulates insulin release [61]. Confirming these theories are local intervention studies that highlight significant improvements in HOMA-IR after vitamin D correction [59,60]. Furthermore, the same vitamin D interventional studies highlight the significant lipid lowering effects of vitamin D correction, confirming long stand theories on the direct suppression of apolipoprotein A1 (ApoA1) by VDRs that enhance fat absorption in the gut, as well as reduction of circulating triglycerides through inhibition of hepatic triglyceride formation secondary to increased hepatic calcium intake induced by vitamin D [61,62]. Lastly, the significant inverse association of vitamin D to obesity may have been well established in cross-sectional studies but failed to translate in vitamin D supplementation clinical trials and interventional programs, confirming that this association maybe reverse causation, or the increased adiposity and vitamin D storage in adipose tissues leading to decreased circulating vitamin D levels [63,64]. It is interesting to note that several VDR single nucleotide polymorphisms (SNPs) studied in the local population plays a role in obesity, inflammation and several components of the metabolic syndrome [65,66].

Despite the abundance of diseases linked to vitamin D in the local population, several intervention studies are further required for the rest of the non-skeletal diseases to determine whether vitamin D status correction will provide major improvements and beneficial effects. Worthy to note is that most of these local studies are observational in nature and are at most, suggestive.

4.3. How do we move forward from vitamin d deficiency?

Considering the evidences presented, a lot has already been done by the Saudi scientific community in increasing awareness of vitamin D deficiency. Several sectors need to be involved with media playing an important role for the message to reach grassroots level. Correction of vitamin D status through increased sun exposure and vitamin D supplementation has been the mainstay advice of the medical community worldwide which makes a lot of common sense yet seemingly unachievable for some populations. There is an imperative need to utilize all the information gathered at a local level to implement a more potent strategy in the fight against vitamin D deficiency. Current international guidelines for vitamin D may not all apply to the local population. One possible caveat from the widely used guidelines is that they were tailored mostly for the European and North American populations whose geographical location, climate conditions, culture of outdoor social activities, not to mention the ethnicity itself, varies widely from other populations. The differences in the factors mentioned, which are considered major determinants of vitamin D status, therefore cast doubt on the suitability of some international recommendations to populations coming from other regions in the world. Perhaps, a customized approach might prove more effective than following international guidelines. Al-Saleh and colleagues' updated recommendations on osteoporosis emphasized vitamin D correction [67], but fell short on limiting vitamin D correction on patients suspected and at increased risk of osteoporosis. Since vitamin D deficiency complications extend beyond the bone, vitamin D status should be made a routine clinical test and correction encouraged to the subpopulations most susceptible in harboring vitamin D deficiency (e.g. elderly, women). Vitamin D fortification of food products is arguably the best possible alternative to increased sunlight exposure for vitamin D deficiency prevention in the Saudi population. Although there is still scarcity of information with regards to vitamin D status and the Saudi diet, fortification should nevertheless be initiated, considering the overwhelming evidence pointing to increased prevalence of vitamin D deficiency in KSA, and the roster of diseases that go along with it. Finally, the message of vitamin D correction is clear to the scientific and medical community, who already made a significant advancement in the battle against vitamin D deficiency. The public health policy makers and the Ministries in charge of health, education and media should now take charge in a more aggressive and unified campaign against vitamin D deficiency that will reach the lay Saudi community at a national level. It is only through their involvement, that the spread of vitamin D deficiency and the diseases hidden under its shadow can be effectively controlled and reversed.

5. Conclusion

In summary, vitamin D deficiency is highly prevalent in KSA across all demographics and is associated with several extra-skeletal, chronic metabolic diseases in the local population, particularly insulin resistance and its related comorbidities. The lack of a unified cut-off for vitamin D deficiency and discrepancies in methods of measurement highlight the need to assemble and create local guidelines as to who to screen and treat among those deemed to be clinically at risk for chronic vitamin D deficiency complications. Furthermore, interventional and clinical trials studies are highly encouraged as there is a clear shortage of these types of studies that are necessary to determine appropriate doses and concomitant effects of vitamin D supplementation.

Competing interest

None.

Acknowledgments

The study was supported by King Saud University, Deanship of Scientific Research, Prince Mutaib Bin Abdullah Chair for Biomarkers of Osteoporosis (PMCO).

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