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CONSENSUS STATEMENT

Diagnosis and management of vitamin D deficiency in the Gulf Cooperative Council (GCC) countries: an expert consensus summary statement from the GCC vitamin D advisory board

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Abstract

Objective
A summary of recommendations is given within the Gulf Cooperation Council (GCC) setting on the assessment and management of vitamin D deficiency in the region.

Methods
An assembly of 11 regional experts gathered to formulate an all-inclusive approach to vitamin D deficiency within GCC.

Results and Conclusion
Several gaps were identified before regional guidelines could be developed. These include adequacy and standardization of vitamin D testing, frequency of repeated testing and reference ranges, distinguishing prevention from the treatment of vitamin D

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deficiency, quality assurance of vitamin D products sold within GCC including contents and origins of products, and cut-points for vitamin D levels in local populations. A platform is created that can be further developed for overall regional implementation.

Keywords Vitamin D · Vitamin D status · Bone health · Osteoporosis · Osteomalacia · Vitamin D supplementation

Introduction

Management of vitamin D deficiency varies across healthcare sectors in the Gulf Cooperation Council (GCC) countries, depending on whether the hospital is private or government, supplements available in the market and whether vitamin D testing is covered by the individual's health insurance. Nevertheless, there is uniformity among GCC health practitioners that current international guidelines, at least for the general population, may not be applicable in the region. Aside from the known geographical and cultural differences that can contribute to the wide variations in serum 25(OH) D concentrations across ethnic groups, emerging evidence on the genetic components may also play a major factor in an individual's vitamin D status [1].

An assembly of 11 regional experts in vitamin D and endocrinology (6 from Saudi Arabia (SA), 3 from United Arab Emirates (UAE), and 2 from Bahrain) met in September 2018 in Dubai, UAE. One member from Kuwait, Oman, and Qatar joined the group later. They aimed to review vitamin D deficiency in populations within the Gulf Cooperation Council (GCC) countries with the view to the formulation of an all-inclusive approach to vitamin D deficiency management in the region. Further discussions, developments, and revisions were undertaken through several rounds of multilateral personal and electronic communications resulting in the final version of this manuscript.

Current international guidelines for vitamin D were highlighted in the meeting [2, 3], as well as the availability of country-specific vitamin D guidelines within the region including KSA [4] and UAE [5]. All experts agreed, based on current evidence, that the prevalence of vitamin D deficiency in the Middle East including GCC is relatively higher as compared with its Western and Eastern counterparts, and the adoption of regional guidelines is needed.

The present position paper discusses the issue of vitamin D deficiency in the region in terms of prevalence, its association to locally prevalent diseases such as osteoporosis, osteomalacia, and osteopenia. The position paper also addresses the applicability of European and Western guidelines in the Middle East, the necessity of standardizing laboratory tests in the region, the variability of vitamin D treatment regimens available, and the importance of promoting sunlight exposure and physical activity in local populations as a natural method for vitamin D level correction. The literature presented in this paper is non-protocol based and is a qualitative summary of evidence gathered based on existing literature available with emphasis on studies done in the region.

Vitamin D deficiency in GCC countries

There is already an abundance of epidemiologic evidence implicating that the Middle East and the North African region is home to a population with some of the lowest serum levels of 25-hydroxy (OH) D globally [6–8]. The most recent update as identified in 41 regional observational studies mentioned that the prevalence of people with serum 25(OH) D < 50 nmol/l in the region ranged between 12 and 96% in the pediatric population, 54–90% in pregnant women, and between 44 and 96% in the general adult population [9]. Within the region, GCC has registered some of the highest prevalence of vitamin D deficiency in the Arab population (25(OH) D < 50 nmol/l): 81% among Saudis (adults, children and adolescents, neonates and pregnant/lactating women) [10], 86% among adult Emiratis [11], 86.4% among healthy adult Bahrainis [12], 64% among adult Qataris [13], 100% among Omani women of reproductive age [14], and greater than 80% among adult Kuwaitis [15]. Predictors of vitamin D deficiency within the region include age, being female, multi-parity, clothing style, season, social status, and residing in urban areas [7].

Given the overwhelming evidence as described above, some GCC nations have already adopted their own guidelines such as KSA [4] and UAE [5]. Several more recent guideline statements have also been formulated for global [16] and regional [17] use, with full consideration of the statements made from the Institute of Medicine (IOM) and the Endocrine Society. Despite differences in management approach, there is near-universal agreement that serum 25(OH) D levels should be higher than 25–30 nmol/l regardless of the individual's age, especially in high-risk groups (children, pregnant and lactating women, and elderly), and that disease-specific vitamin D guidelines are almost applied globally. Regional and country-specific variations in vitamin D management are focused on the general population.

The present consensus is tailored to the geographical location and while recommendations from several GCC countries already exist, other GCC nations are still reliant on international guidelines which are inapplicable to the GCC setting, given its unique risk factors. An assembly was thus created to address the vitamin D deficiency management scheme within the GCC with the hope of producing a unified and customized approach to combat vitamin D deficiency for the general GCC population.

Table 1 Vitamin D status by definition

Status	Deficiency	Sufficiency
Serum total 25(OH) D	< 20 ng/ml	≥ 20 ng/ml
	< 50 nmol/L	≥ 50 nmol/L

Cut-off based on impact on bone health [18–23]

Vitamin D status definition

The consensus of regional experts is to adapt the following cut-offs presented in Table 1 on the basis of impact on bone health [18–23].

Although the majority of international guidelines have a target of ≥ 50 nmol/l, the minimum consensus within the global scientific community is that serum 25(OH) D < 25–30 nmol/l must be treated and prevented [18]. The global consensus on the minimum target is also well within the new proposed cut-off of 50 nmol/l for 25(OH) D for optimal bone health in the Saudi population, which was conducted among 2131 adult Saudis and was based on the gold standard parathyroid hormone (PTH) cut-off > 6.9 pmol/l threshold [19]. Vitamin D deficiency has already been clearly established as a major cause of nutritional rickets and osteomalacia [20, 21]. Harder outcomes, however, such as fracture remains controversial, as new studies implicate that even genetic predisposition to low vitamin D is not associated with fracture risk [22] and that vitamin D supplementation as a monotherapy or in combination with calcium was not linked with reduced fracture incidence among community-dwelling adults without history of fracture, osteoporosis, or known vitamin D deficiency [23]. European experts, however, acknowledge that although calcium and vitamin D supplementation may not be the best strategy at a population level intervention, it is still recommended at least for those at high risk for calcium and vitamin D insufficiency, as well as those who are on anti-osteoporosis medications [24]. Regional experts also agree that while seeing patients presenting with bone pathologies due to vitamin D deficiency were not frequently seen, the aim of treating vitamin D deficiency was the prevention of diseases by reducing the risk of developing them.

Vitamin D status assessment

At present, the most appropriate instrument for the assessment of total 25(OH) D and other analogues is the liquid chromatography-tandem mass spectrometry (LC-MS/MS) [25]. Reference methods that are considered as gold standards from the Vitamin D Standardization Program (VDSP) include those taken from the Centers for Disease and Control (CDC), National Institutes of Standards and Technology (NIST), and University of Ghent [26]. In the GCC setting of major hospitals, however, automated immunometric assays are widely used, and significant variations in vitamin D status have been documented [27, 28]. All regional experts agreed that all major hospitals and clinical laboratories that measure vitamin D metabolites within the GCC should be standardized by participating in major quality assurance schemes such as the Vitamin D External Quality Assessment Scheme (DEQAS) or the College of American Pathologists Accuracy-Based Vitamin D program (ABVD). Experts also agreed with the use of total serum 25(OH) D for the assessment of nutritional vitamin D status and that general practitioners within the region should be aware of the common units used for vitamin D and its conversion to prevent misdiagnosis and management. Among the GCC countries, only UAE, courtesy of the Dubai Health Authority has no restriction on vitamin D testing. Other GCC countries, however, have restricted vitamin D testing and is not covered by many medical insurance companies. Hence, standardized testing may prove unnecessary due to the variability in vitamin D treatment practice as well as vitamin D test priority in different health systems. Given that the majority of residents within the GCC are already vitamin D deficient, universal screening for vitamin D deficiency, therefore, is not recommended. Asymptomatic patients with a high risk of vitamin D deficiency should be treated empirically without testing, and those at high risk and with high clinical suspicion should be tested to determine the appropriate dose. The group also agreed that conducting more than 3 tests per year was irresponsible, which stipulates a minimum interval of 3–6 months between repeated tests.

Non-pharmacologic treatment for the GCC general population

Vitamin D deficiency is usually a reflection of inadequate sunlight exposure. Safe sunlight exposure, therefore, is the clear primary option for vitamin D correction and not exogenous sources [29]. Adequate sun exposure is advised for the GCC general population. Vitamin D recommendations from Saudi Arabia included the most appropriate times for sunlight exposure and are as follows: summertime from 9:00 a.m. until before 10:30 a.m. as well as 2:00 p.m. until 3:00 p.m. and winter time from 10 a.m. to 2 p.m., 3–4 times a week [4, 30]. Some experts also noted that despite year-long sunlight and long summer seasons in the GCC and Saudi Arabia in particular, the prevalence of skin cancer is low as compared with the West [31]. While limited studies are available in the GCC as to the length of sunlight exposure relative to skin color, one study in Saudi Arabia demonstrated the lack of effect of sunlight exposure and skin color on vitamin D status in both children and adults [32].

Increased dietary vitamin D intake is also advised, especially among postmenopausal women, in combination with increased protein intake in maintaining musculoskeletal health

Table 2 Selected dietary sources of vitamin D

Food	IUs/ serving	% Daily value
Cod liver oil, 1 tablespoon	1360	340
Swordfish, cooked, 3 oz	566	142
Salmon, cooked, 3 oz	447	112
Tuna fish, canned in water, drained, 3 oz	154	39
Orange juice fortified with vitamin D, 1 cup	137	34
Milk, no-fat, reduced fat, and whole, vitamin D-fortified, 1 cup	115–124	29–31
Yogurt fortified with 20% of the DV for vitamin D, 6 oz (more heavily fortified yogurts provide more of the DV)	80	20
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 oz	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Cheese, Swiss, 1 oz	6	2

DV, daily value; adapted with permission from Al-Daghri et al. 2017 [4]

in this demographics [33]. A summary of vitamin D-rich foods are presented in Table 2 [4]. All regional experts agree that food fortification is necessary to combat vitamin D deficiency. A recent meta-analysis done in Middle Eastern countries highlighted several micronutrient deficiencies common in the region including folate, iron, and vitamin D and that food fortification within the region is ineffective and insufficient despite a wealth of data indicating high prevalence of micronutrient deficiencies in the region [34].

Vitamin D supplements

Available literature derived from Western countries using doses above 2000 IU daily has not provided compelling evidence of additional benefits to warrant recommendation [35]. Unfortunately, there is also a lack of randomized clinical trials in GCC supporting the use of higher doses of vitamin D supplementation in the region. Almost all regional experts agree, however, that doses of 1000–2000 IU daily, or higher, has been the common practice within the larger Middle East area, given the high prevalence of vitamin D deficiency and the failure of patients to achieve desired levels as set by international recommendations. Meta-analysis studies done by Chaktoura and colleagues within the Middle East and North Africa (MENA) region identified that individuals given high dose (> 2000 IU/day) had at least 71% chances of achieving the target of > 50 nmol/l in adults [36]. The same group recommended an intermediate dose (1000–2000 IU/day) among children and pregnant women as it had 74% and 73% chance of achieving the target of > 50 nmol/l, respectively [37]. Higher maintenance doses are needed for the obese, patients with malabsorption, and some post-bariatric surgery patients.

Cholecalciferol was the recommended type of vitamin D to be prescribed and adoption of 50,000 IU initial loading dose weekly for 6 weeks was preferred for severely deficient cases and those at high risk for osteoporosis (except for pregnant women and those with renal impairment). The regional experts recommended that product origins and descriptions should be explicitly provided in the labels, as most GCC patients are cautious on how the medications were prepared and if it is in accordance with Islamic traditions since some may contain gelatin of pork origin. Toxicity to vitamin D is a rare phenomenon and has been echoed by most regional experts. Nevertheless, mega-doses of vitamin D is still practiced with caution in the region, especially if the aim of therapy is for non-skeletal outcomes. The recent negative results of ViDA and VITAL trials support the theory that vitamin D supplementation is not effective with respect to

Table 3 List of Available (at this time) Vitamin D3 (Cholecalciferol) Supplements in Saudi Arabia (Multivitamins excluded)[a]

Tradename	Formulations	Dosage Form	Company
VI-DE-3	4500 /IU/ml	Oral drops	Novartis Pharma Ag
VIDROP	2800 /IU/ml	Oral drops	Medical Union Pharmaceuticals Co
BIODAL	50000 IU	Tablet	Hayat Pharmaceutical Industries
ESSENTIAL D-3	50000 IU, 5000 IU, 10000IU	Capsule	Arnet Pharmaceutical Corp
VITA D 50000	50000 IU	Tablet	Synergy Pharma
VI-DAL	5000 IU,10000 IU, 50000IU	Capsule	Jazeera Pharmaceutical Industries (JPI)
VEGGIE VITAMIN D3	50000 IU. 5000 IU	Capsule, soft	Saudi Dox For Pharmaceutical Industries
PRIMA D3	2000 IU, 5000 IU, 10000 IU,50000 IU	Capsule, soft	Jamjoom Pharmaceuticals Company
DIVAD 10000 I.U	10000 /IU	Capsule	Dar Aldawa
DIBASA 10000 I.U	10000/IU	Oral drops	NewBridge Pharmaceuticals
DIBASA 100000 I.U	100000/IU	Ampoule, oral	
DIBASA 300000 I.U	300000/IU	Ampoule, oral	

Note: Taken from the Saudi Food and Drug Authority Drug List (available at www.sfda.gov.sa/en).

Table 4 List of Available Vitamin D3 (Cholecalciferol) Supplements in United Arab Emirates, Oman, Kuwait and Bahrain (Multivitamins excluded)

Tradename	Formulations	Dosage Form	Manufacturer
1. United Arab Emirates[a]			
VITA D	50,000/IU 10,000/IU 1,000/IU	Tablets	Synergy Pharma, UAE
SunTabs	400/IU	Tablet	
Sundrops	400/IU/ml	Oral Drops	
ULTRA D	5000/IU	Tablets	
VITAMIN D3	50,000/IU	Capsules	Ameri-Vite, Inc., USA
VITAMIN D3	300,000/IU	Injection	Streuli, Switzerland
EURO D	10,000/IU	Capsules	Euro-Pharma Int'l, Canada
MINISUN	400/IU; 800/IU	Tablet	Oy Verman Ab, Finland
D-CAL	5mcg, 600mg	Film coated tablets	Pharmalab, Canada
PROVITA D3	1000/IU	Tablets	Factors Group of Nutritional Companies, Canada
2. Oman[b]			
HI-DEE	10,000/IU, 50,000/IU, 5,000/IU 2000/IU 2000/IU	Capsule Drops Capsules	United Pharmaceutical Manufacturing Co. Ltd., Jordan
3. Kuwait[c]			
Sundrops VITA D	400/IU/ml 50,000/IU	Drops Tablets	Synergy Pharma, UAE
ULTRA-D3	1000/IU	Tablets	Vitabiotics Ltd
Vitamin D_3	10,000 IU	Capsule	Future Way Nutrition
Vitamin D_3	50,000 IU	Capsule	Natro Health
Vitamin D_3	5,000 IU/ml	Liquid	Solgar
Vitamin D_3	2,800 IU	Drops	Mup
Vitamin D_3	600,000 IU	IM injection	Multiple
Dibase 10000 Dibase 25000	10000 IU 25000 IU	Oral drops Oral solution	NewBridge Pharmaceuticals
Dibase 50000	50000IU	Oral Solution	
4. Bahrain[d]			
HI-DEE	2000 IU/5 ML	Drops	United Pharmaceutical Manufacturing Co. LTD, Jordan.
	2000 IU, 5000 IU, 10,000 IU, 50, 000 IU	Capsule	
Ultra D3	1000 IU	Tablet	Thompson & Capper Limited for Vitabiotics, UK
D-Trol	1000 IU	Capsule	Vitane Pharma USA
Vita D3	5000 IU,10,000 IU	Capsule	Tishcon Corp, USA
Vidrop	2,800 IU/ml	Drops	Medical Union Pharmaceuticals (MUP), Egypt.
Solgar Vit D3	400 IU	Capsule	SOLGAR INC., USA
Health Aid Vit D3	1000 IU	Tablet	Thompson & Capper Limited For Health Aid, UK
Nb Vitamin D3	400 IU, 1000 IU	Tablet	Nature's Bounty Inc., USA
Sun-D	1000 IU	Tablet	Vitex Pharmaceuticals PTY. Ltd, Australia
D-Lux	400 IU/SPRAY	Oral spray	Cultech Limited For Betteryou, UK
5. Qatar[5]			
Tera-D3	300,000 IU/	Ampoule IM injection	Terra Pharmaceuticals, Istanbul, Turkey
D-VIT3	4,000IU/Ml	Oral drops	Istanbul ILacKoz, Turkey

[a] Health Authority Abu Dhabi, UAE (Available at https://www.haad.ae/haad)

[b] Ministry of Health, Oman (Available at https://www.moh.gov.om/en/web/dgpadc)

[c] Ministry of Health, Kuwait (Available at https://www.moh.gov.kw)

[d] Courtesy of Dr Wiam Clinic for Diabetes and Endocrine Disorders, Riffa, Bahrain

[e] Compiled by Dr Tarik Elhadd, Doha, Qatar.

cancer and cardiovascular diseases, specifically if the patient's baseline vitamin D status is high [38, 39]. The findings of the above 2 studies may not apply for the GCC countries since baseline Vitamin D levels are quite low. High bolus of vitamin D (100,000 IU) monthly has also been observed as non-beneficial in the prevention of falls and fractures among adults [40]. Injectable vitamin D therapy is not recommended as routine treatment of vitamin D deficiency except in very rare situations such as severe malabsorption, non-compliance, and non-response to oral therapy. Genetic factors such as vitamin D binding gene polymorphisms should be taken into consideration as it has been shown to affect response to vitamin D therapy among Arab adults, but more research needs to be done before this can be translated in actual clinical practice [41]. Details of commonly marketed vitamin D products are provided in Tables 3 and 4.

Future steps

The present consensus statement is the first among regional advisory board meetings that culminated in the formulation of vitamin D guidelines within the GCC region. The regional experts identified several gaps that need to be addressed fully within the region, including the necessity for quality assurance of products, adequate laboratory testing, standardization of units and tests, frequency of repeated testing and reference ranges, examining relevance of vitamin D in full life course, including pregnancy and deriving adequate cut-off points for vitamin D levels in local populations. More observational, interventional, and clinical trial studies are encouraged to be done within the region to determine the efficacy of current available medications to other markers (e.g., irisin) and in the presence of other diseases for both skeletal and non-skeletal outcomes [42–44] as well as the impact of PTH and vitamin D in fracture incidence within GCC [45]. The regional experts also welcome experts from other regions to share knowledge in similarities and differences in treatment of vitamin D comparable with the ones previously done between Europe and China [46]. The regional experts are also on stand by for the results of the ongoing mega-trials on the non-skeletal effects of vitamin D supplementation [47, 48] as well as on falls and non-vertebral fracture [40]. The present consensus statement has been endorsed by the Gulf Chapter of the American Association of Clinical Endocrinologists (AACE), the Saudi Society of Endocrinology and Metabolism and the different osteoporosis societies in GCC. All endorsing societies will mention the present consensus in their newsletters, local publications, and national/regional assemblies. All society members will be notified via email about the present consensus and will be encouraged to utilize it in their clinical practice. However, as with all consensus reports, it is just a tool and by no means a substitute for good clinical judgment.

Summary of recommendations

Optimum 25 hydroxyvitamin (OH) D level and testing

- The operational definition for severe vitamin D deficiency is < 25 nanomoles per liter (nmol/l) or 10 nanograms per millilitre (ng/ml).
- The operational definition of vitamin D deficiency is based on serum levels of 25(OH) D < 50 nmol/l. Optimum levels should be above 50 nmol/l or 20 ng/ml.
- The higher limit for optimum levels is 125 nmol/l or 50 ng/ml.

Vitamin D deficiency testing

- Although the most appropriate instrument for 25 (OH) D testing is mass spectrophotometry, this is not widely available in GCC laboratories.
- Serum or plasma 25(OH) D is recommended to determine nutritional vitamin D status.
- Standardization of vitamin D tests and its metabolites by clinical laboratories in all GCC from internationally recognized agencies is recommended.
- Universal screening for vitamin D deficiency is not recommended. The current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. The panel recommend targeted screening of at-risk population.
- Vitamin D testing should not exceed 3 times per year.

Recommendations for the general population

- Increased sunlight exposure
- Increased vitamin D intake through fortification of foods

Vitamin D supplements

- Product origins and descriptions should be explicitly provided for GCC physicians and patients
- Vitamin D3, not D2, is recommended. D2, however, can be used if no D3 is available.
- Adoption of 50000 IU loading dose weekly for 6 weeks is preferred for severely deficient cases and those at high risk for osteoporosis (except for pregnant women and those with renal impairment).

- Daily treatment dose of 800 to 2000 IU was the most appropriate for adults and children over 12 years of age. Daily dose should not exceed 4000 IU.

Endorsements

This consensus report is endorsed by the following societies:
American Association of Clinical Endocrinologists, Gulf Chapter
Saudi Osteoporosis Society
Saudi Society of Endocrinology and Metabolism
Kuwait Osteoporosis Society
Emirates Diabetes Society

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Compliance with ethical standards

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