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Invited Review

Paradoxical Vitamin D Deficiency in a Sunny Country: A Narrative Review of the Literature from the United Arab Emirates (1992–2018)

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Abstract

Deficiency of Vitamin D is a global problem related to lack of sunlight exposure and reduced dietary intake. Vitamin D deficiency (VDD) affects mainly skeletal structure and function but has a number of recognized nonskeletal effects that have wide ramifications. It sounds ironic that low serum Vitamin D levels are widely documented in a sunny country like the United Arab Emirates (UAE). The study objective was to review the literature on VDD in the UAE. This is a narrative nonsystematic review of the literature on the epidemiological and clinical aspects of Vitamin D status in the UAE based on PubMed search using two search terms "Vitamin D" and "Emirates." We discuss the various themes that emerged as follows: epidemiology and disease burden of VDD in the UAE population in general and in specific groups (adults, children, females, and pregnant and nursing mothers); awareness of dietary intake, climate, genetics, and metabolic factors affecting serum Vitamin D levels; and the overview of current clinical management guidelines, interventional trials, and clinical practices. VDD is a widely documented health problem in the UAE population as a whole and in several special groups. This may have serious skeletal and nonskeletal health implications.

Keywords: Adult population, diet, direct sun exposure, epidemiology, female health, genetic polymorphism, joint and bone weakness, Middle East, obesity, sunlight, United Arab Emirates, Vitamin D deficiency

Introduction

Vitamin D deficiency (VDD) is a global problem, which is related to lack of sunlight exposure, with a contribution from reduced dietary intake.[1,2] VDD affects mainly the skeletal structure and function. In addition, there are a number of recognized nonskeletal effects that have wide ramifications.[3]

Despite living in a sunny country all year round, paradoxically, hypovitaminosis D with clearly demonstrable low serum Vitamin D levels has been repeatedly recorded in the United Arab Emirates (UAE) and the surrounding Arabian Gulf countries. This problem has attracted increasing clinical and academic interests. However, the relevant publications are too widely scattered in different types of journals of different levels of access for the interested clinician and researcher to follow them and may be difficult to grasp them. Hence, in the present article, we aimed to present a narration of the international literature focusing on Vitamin D status and the clinical implications of its deficiency to make it available for practicing clinicians and researchers developing a new interest in the subject.

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Materials and Methods

This is a narrative nonsystematic review of the literature on the epidemiological and clinical aspects of Vitamin D status in the UAE, a country which is invariably sunny on a daily basis all the year round. PubMed search was conducted

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using the combination of two search terms "Vitamin D" and "Emirates" with no filters. Eighty-six records were identified. The abstracts were examined, and irrelevant records were excluded. The remaining references were retrieved and reviewed. A manuscript was drafted primarily by SAB and KH and further developed by the rest of the authors via several rounds of multilateral personal discussions and electronic communications using shared online documents (Google Docs). The authors developed their assigned sections and reviewed the rest of the manuscript for intellectual content, presentation, and scholarly standards. All authors approved the final version of the manuscript.

We considered the emergent themes as follows: (a) epidemiology in the whole of the UAE population and in specific groups (adults, children, and college students); (b) awareness on dietary intake, climate, genetics, and metabolic factors affecting serum Vitamin D levels; (c) Vitamin D status in pregnant women, neonates, and children; (d) clinical management, guidelines, and interventional trials and e) academic interests and notable cases reports. Significant findings are tabulated for descriptive comparisons.

Results

Disease burden

Numerous population studies in our region have confirmed the presence of VDD in various groups, namely, adults, pregnant women, adolescents, and children. Large studies from the UAE provide evidence that VDD could be a major public health burden among UAE residents.[4-12] Table 1 summarizes the salient studies on the epidemiology and disease burden.[4-10] Haq A *et al.* determined Vitamin D status in 60,979 patients seen in a large private health-care network in Abu Dhabi between 2012 and 2014.[5] The concentrations of total Vitamin D [25(OH)D] were all measured in a single laboratory. Females represented 57.5% of the study population. Serum 25(OH)D measurements showed that 82.5% have either VDD or Vitamin D insufficiency. Furthermore, an extreme deficiency was found in 26.4% of females and 18.4% of males, with higher variability in females than males. Serum 25(OH)D concentrations lower than 75 nmol/L were found in 86.1% of UAE nationals and 78.9% of expatriates. In addition, severe deficiency was evident in 28.4% of UAE nationals and 17.5% of expatriates. Furthermore, around half of those aged between 1 and 18 years (58.1% of females and 43.3% of males) had serum 25(OH)D levels <50 nmol/L.[6] Furthermore, serum 25(OH)D level <30 nmol/L was found in 31.4% of patients in the age group of 10–12 years, 50.4% in the age group of 13–15 years, and 52.9% in the age group of 16–18 years. Reference ranges used in this study are based on the recommendations of the Endocrine Society and the Institute of Medicine.[2] Similar findings were shown by Yammine *et al*. who measured serum Vitamin D levels in 7924 patients in a day surgery hospital in Dubai.[11] VDD was found in 85.4% and insufficiency in 12.5% of patients. In a multivariate model, Vitamin D levels correlated directly with male sex, native population, and age between 17 and 31 years.

Several smaller series addressed special groups.[4,7-10,12] Al Anouti *et al*. assessed serum 25(OH)D status and examined diet, obesity, and sun exposure in 138 females and 70 males.[12] In the summer, the mean serum 25(OH)D concentration was 20.9 nmol/L and 27.3 nmol/L in females and males, respectively. Females seem to avoid sun exposure to a greater extent than males, possibly explaining the lower Vitamin D levels. A significant negative correlation between

Table 1: Summary of population- and clinic-based epidemiological studies on Vitamin D status in the United Arab Emirates

Reference	First authors	Year	Population	Sample Size	Conclusions
[4]	Sadiya A *et al*.	2014	Obese T2DM individuals	309	There is an overwhelming prevalence of VDD in the sample of the Emirati population with obesity and T2DM
[5]	Haq A *et al*.	2016	Patients seen in a large private facility (Abu Dhabi)	60,979	82.5% of the studied patients were with VDD, particularly in females. As 78% of other nationalities mentioned in this study also have VDD, it can be said that deficiency is not related to culture but to modern lifestyle where every individual of different backgrounds has to be fully clothed to attend work/schools etc., and that essentially most of the time is spent indoors precluding adequate sun exposure
[6]	Haq A *et al*.	2018	Young patients (Abu Dhabi)	7883	High rates of VDD among the juvenile population were seen in a large private hospital, particularly in females
[7]	Muhairi SJ *et al*.	2013	Adolescents in schools (Al Ain)	315	VDD and Vitamin D insufficiency are highly prevalent in adolescents and more common in girls (28%) than boys (10%). Consumption of fast food per week and body mass index positively correlated with physical activity scores
[8]	Narchi H *et al*.	2015	Adolescent school girls (Al Ain)	293	A high prevalence of hypovitaminosis D in adolescent females (11-18 years) in the UAE was documented. No predictive risk factors could be identified
[9]	Sridhar B *et al*.	2016	Adult males and females	425	There was no substantial difference in 25(OH)D levels of different ethnic groups
[10]	Bani Issa W *et al*.	2017	Adult males and females	216	Emirati participants had higher odds of having VDD compared to non-Emiratis

T2DM: Type 2 diabetes mellitus, UAE: United Arab Emirates, 25(OH)D: 25-hydroxyvitamin D, VDD: Vitamin D deficiency

sun avoidance index and Vitamin D status was found, neither significant association was evident between Vitamin D status and body mass index (BMI) nor low dietary intake of Vitamin D-fortified foods. The mean serum Vitamin D concentration for females was higher in winter than in summer. The seasonal trend is different from Western populations. This seasonal variation suggests that sun exposure may play an important role in Vitamin D status in the UAE. Narchi H *et al*. examined the prevalence of hypovitaminosis D and its associated risk factors in female students aged 11–18 years attending public schools.[8] Socioeconomic status, diet, and amount of sun exposure were evaluated by interviews. Complete data were available for 293 girls. Of these, 19.8% were Vitamin D deficient (27.5–50 nmol/L) and 231 had severe vitamin deficiency (<27.5 nmol/L). Serum Vitamin D levels declined between the ages of 11 and 13 years before progressively rising until the age of 18 years. Vitamin D status was not related to age, BMI, accommodation type, family income, percentage of surface area unexposed to the sun in outdoors, consumption of oily fish, or total Vitamin D intake. Muhairi *et al*.[7] examined the prevalence of VDD and its correlates in healthy adolescents (n = 315) aged 15–18 years in schools. VDD (≤37.5 nmol/L) was detected in 19.7% and Vitamin D insufficiency (≤50 nmol/l) was evident in 45.4% of the participants. VDD was found in 28% of girls and 10% of boys. In a multivariate model, Vitamin D level concentrations correlated inversely with female gender, consumption of fast food, and BMI but correlated directly with physical activity scores after adjustment for age. Sadiya A *et al*.[4] examined the impact of Vitamin D on metabolic parameters in a cross-sectional study of 309 individuals with obesity and type 2 diabetes mellitus (T2DM). VDD (<50 nmol/L) was found in 83.2% of the participants. Serum 25(OH)D correlated inversely with BMI, fat mass, waist circumference, parathyroid hormone (PTH), alkaline phosphatase (ALP), triglycerides, low-density lipoprotein (LDL)-cholesterol (LDL-C), and apolipoprotein B and correlated directly with age and calcium concentration. Waist circumference was the main predictor of 25(OH)D status. No significant association was found between serum 25(OH)D and glycemic metrics. Furthermore, Sridhar SB *et al*.[9] examined ethnic and demographic variables associated with hypovitaminosis D in a retrospective electronic database analysis at a secondary care hospital. Records of all the patients who had had their Vitamin D levels measured between 2010 and 2012 were examined. Severe VDD, VDD, Vitamin D insufficiency, and Vitamin D sufficiency were defined as serum 25(OH)D levels of <10, 10–20, 21–30, and > 30 ng/mL, respectively. Out of the total 425 patients, VDD existed in 48.9%, followed by severe VDD and Vitamin D insufficiency in 33.2% and 14.8% of the patients, respectively. An inverse correlation was present between BMI and 25(OH)D levels. Female gender, age, and BMI were predictors of 25(OH)D levels, but no differences in 25(OH)D levels between different ethnic groups were detected. In addition, VDD and its associated factors were examined in 216 adults from community-based health-care settings over a 6-month period (Bani-Issa W *et al*., 2017).[10] Recent values of Vitamin D and glycated hemoglobin (HbA1c) were retrieved from medical records, and factors related to VDD and other covariates were retrieved to measure their heights and weights. VDD defined as Vitamin D level <30 nmol/L was evident in 74% of patients. Emirati participants had higher odds of having VDD compared to expatriates. Increased odds appeared in the older, less educated, and employed adults. T2DM, depression, and obesity were significantly associated with an increased likelihood of VDD after accounting for other covariates. These observations denote associations rather than having causative relationships. The improvement in levels after bariatric surgery in some studies may indicate the presence of Vitamin D but is stored in body fat and mobilized after such surgery. This study contradicts previous work where no such association was detected.

Impact of culture and lifestyle factors on Vitamin D status

The prevalence of hypovitaminosis D might be related to cultural factors around sun exposure or other factors affecting serum level in Vitamin D metabolism or yet undefined biological factors.[13-17] Salient studies from the UAE related to these issues are summarized in Table 2. Many of these studies looked into UAE women's cultural background and lifestyle, specifically clothing styles (*veils and hijabs*), as a determinant of limited sun exposure and hence VDD. Some of these studies include a comparison to Arabs of other nationalities and Westerners. Most of these studies showed that dressing style might contribute to the high prevalence of VDD in the UAE. Neither there are similar comparative data for men in the UAE nor similar comparative data for non-UAE men (Arabs vs. Westerners). Dawodu A *et al*.,[13] examined the effects of duration of sunshine exposure weighed against the magnitude of clothing (ultraviolet [UV] exposure score) and other sociobiological variables on serum 25-OHD and mineral status of 33 UAE female nationals. These data were compared to those of 25 non-Gulf Arabs and 17 Europeans. Serum concentrations of bone markers and intact PTH were not significantly different between the groups. The mean serum concentrations of 25-OHD were 8.6 and 12.6 ng/ml in UAE nationals and non-Gulf Arabs, respectively. Both these values were significantly lower than that in European participants. Compared with Europeans, Arabs in this study were younger and had statistically significantly lower clothing and UV exposure scores ($P < 0.0001$). There was a positive correlation between serum 25-OHD and UV score, but not with the length of exposure. Even after adjusting for other confounding variables such as nationality, clothing and UV scores remained the major determinants of serum 25-OHD ($P < 0.0001$). Saadi HF *et al*.[14] determined factors influencing serum 25OHD concentration and relationships between serum 25OHD concentration and bone-related factors in Emirati women. The mean serum 25OHD concentration in 259 female volunteers was 25.3 nmol/l, and all had VDD (25OHD <80 nmol/l). No significant difference in 25OHD concentration was noted among Emirati women with different dress styles, but

Table 2: Summary of the impact of culture and lifestyle on Vitamin D status in the United Arab Emirates in chronological order

Reference	First authors	Year	Population	Sample	Lifestyle studied	Conclusions
[13]	Dawodu A	1998	Females - childbearing age	33	Clothing/sun exposure	The limited exposure to sunlight predisposes to VDD
[14]	Saadi HF	2006	Females	259	Clothing	Local clothing style was associated with lower Vitamin D compared with Western clothing style
[15]	Laleye LC	2011	Female college students	146	Diet	Poor consumption of Vitamin D-rich food may predispose to VDD
[16]	Al Attia HM	2012	Females	255	Clothing	Dress style alone does not explain VDD
[17]	Nimri LF	2018	Female college students	480	Clothing/sun exposure	Dress style and sun avoidance behavior are potential causes of VDD

VDD: Vitamin D deficiency

the mean serum 25OHD was significantly lower in comparison with non-Arab Caucasian female volunteers who dressed in a Western style ($P < 0.001$). Nimri LF[17] in a cross-sectional study of Vitamin D status and risk factors in 480 female college students, aged 18–26 years, used thirty questions, covering demographic information, dietary intake, sun exposure, and autoimmune diseases. Overall, 47.9% of participants had suboptimal serum Vitamin D levels. It was suggested that wearing the hijab (by 37.5%) might have interfered with the penetration of UVB radiation into the skin. In addition, short time sun exposure, use of sunscreens, and limited intake of foods rich in Vitamin D were the potential causes for Vitamin D deficiency. This is at variance with the findings of Al Attia HM *et al*.[16] earlier who did not show significant differences in Vitamin D status among 255 women who used different dressing styles. They measured serum Vitamin D levels in women who are fully covered, covered but face and hands exposed, or dressed in Western style. Hypovitaminosis D occurred in 90.5%, 94%, and 83% of individuals with a mean value of 17.6, 16, and 18.6 ng/ml in the three groups, respectively (significant differences were observed between the first vs. second groups and the second vs. third groups). Another contributing factor to VDD may be inadequate dietary intake, as shown by Laleye LC *et al*.[15] who studied female university students using a self-reported survey. Nearly 37% of them were considered Vitamin D insufficient. Over 70% of them did not consume enough milk and other Vitamin D-rich foods. Almost 40% of the students residing in the hostels also had Vitamin D insufficiency (<5 μg/day) based on self-reported dietary food consumption.

The relationship of Vitamin D status and other bone and nonskeletal factors

The relationship of serum 25OHD concentration with bone turnover markers, bone mineral density (BMD), and Vitamin D receptor gene polymorphisms in patients examined by a few UAE research groups is highlighted.[14,18-22] Saadi HF *et al*. investigated the factors influencing serum 25OHD concentration and relationships between serum 25OHD concentration, bone turnover markers, BMD, and VDR genotype in 259 Emirati female volunteers who were participating in a study aiming at establishing a reference database for BMD.[14] All had VDD defined as serum 25OHD <80 nmol/l; mean was 25.3 nmol/l. The level was highest in April, marking the end of the short and cooler winter season, and lowest at the end of summer, i.e., August. No significant difference in 25OHD concentration was noted among Emirati women with different dress styles, but the mean serum 25OHD was significantly lower in comparison with non-Arab Caucasian female volunteers who dressed in a Western style ($P < 0.001$). Vitamin D level correlated directly with age, number of pregnancies, dietary Vitamin D intake, serum calcium, phosphorus, Vitamin D-binding protein (VDBP), and urinary calcium/creatinine and inversely with PTH, osteocalcin, and urinary deoxypyridinoline/creatinine; $P < 0.05$ for all correlations, thus confirming that VDD is associated with increased bone turnover. Multiple linear regression analysis showed that age, dietary Vitamin D intake, multivitamin intake, and cooler season were independent positive predictors of serum 25OHD concentration. The frequencies of VDR genotypes were 36% GG, 44.1% AG, and 19.9% AA. Four VDR genotypes were identified. However, there was no statistically significant influence of VDR genotype on bone turnover or BMD.

It was argued that studies on the determinants of Vitamin D status have tended to concentrate on input exposure to UVB radiation and the limited sources in food. However, Vitamin D status, determined by circulating concentrations of 25(OH)D, can vary quite remarkably in groups of people with apparently similar intake of Vitamin D.[18] It was suggested that small effects of polymorphisms in the genes for key proteins involved in Vitamin D production and metabolism have a highly variable half-life in blood. In addition, there is evidence that the half-life of 25(OH)D is affected by calcium intake and some therapeutic agents. Fat tissue may serve as a sink for the parent Vitamin D, which is released mainly when there are reductions in adiposity. It was also proposed that skeletal muscle is an important site of sequestration of 25(OH)D, protecting this metabolite from degradation by the liver cells. This may help explain why exercise, not necessarily outdoors, is usually associated with better Vitamin D status.

Given the high prevalence of T2DM and VDD in the Emirati population, an association between them has been postulated. Safar HA *et al*. investigated the association between VDR

polymorphisms and T2DM among 264 patients with T2DM and 91 controls.[19] The study population was genotyped for three VDR gene mutations, an association between single-nucleotide polymorphisms (SNPs) in the VDR gene (except for Taq 1) and T2DM *per se* was demonstrated. In addition, Osman E *et al*. determined the frequency of Taq1 and Fok1 variants in healthy Emirati individuals and compared their genotype and allele distribution with those of other populations.[20] Two hundred and eighty-two unrelated healthy UAE nationals were involved. DNA samples were collected to genotype Taq1 and Fok1 VDR SNPs. Their results indicated that the distribution of the alleles and genotypes of Taq1 and Fok1 varies considerably in different populations. In the Emirati population, the distribution of Taq1 and Fok1 was AA 38%, AG 42%, and GG 20% and AA 27%, AG 42%, and GG 31%, respectively. The Emirati population genotype and allele distribution of Taq1 and Fok1 had no difference with Caucasians from the USA and France. However, there was a significant difference between Asian populations.

However, the desired Vitamin D status, measured by the serum concentration of the most stable Vitamin D3 metabolite (25-hydroxyvitamin D3), may not be the main determinant for the respective recommended daily supplementation. Calberg and Haque proposed that a personal *Vitamin D response index* exists that reflects the efficiency of the molecular response to supplementation with Vitamin D.[21] This concept was based on the fact that Vitamin D3 activates via its metabolite (1α,25-dihydroxy vitamin D3) the transcription factor Vitamin D receptor and thus has a direct effect on the epigenome and transcriptome of many human tissue and cell types. It was suggested that, individuals can be identified as high, mid, and low responders to Vitamin D. Therefore, the dose needed for Vitamin D depends on the Vitamin D status in relation to the personal Vitamin D response index of an individual rather than solely on the Vitamin D status itself.

Assessment of Vitamin D deficiency

Having established that VDD constitutes an epidemic in our region, we ought to examine how we assess the status of this sunshine vitamin and whether the different assays and methods of detection have a significant bearing on the results.[22-24]

Within a clinical context, the qualitative and quantitative analysis of Vitamin D is vital. The main metabolic markers for assessing Vitamin D status in humans are the hydroxylated forms of Vitamin D, 25(OH)D3, and 25(OH)D2 on account of their long half-lives within the body and an excellent stability. An adequate level for healthy individuals of these hydroxylated forms is estimated to be around 20–40 ng/ml of blood. There are three main analytical techniques for determining the levels of 25OHD3 and 25OHD2.[22] The first technique is immunoassay based and can be performed in a rapid, high-throughput, automated manner, allowing as many as 240 tests per hour, with the duration of each assay as little as 18 min. Furthermore, it offers excellent sensitivity with a detection range of 3.4–156 ng/ml. A major downside of immunoassays is that they are unable to distinguish between the various forms of Vitamin D. While high-performance liquid chromatography is a high-throughput, low-cost instrument, it is not a very sensitive technique and cannot quantify the downstream metabolites of Vitamin D. The third technique, namely liquid chromatography tandem-mass spectrometry (LC/MS/MS), provides excellent sensitivity with a wide dynamic range from 0.068 pg/ml to 100 ng/ml. In addition, it offers a high level of separation and permits the identification of Vitamin D-related metabolites. However, a huge limitation with LC/MS/MS is their poor throughput for sample analyses. As yet, there is no analytical technique which combines the fine detection capabilities of mass spectrometry and the rapid, automated format of immunoassay, for Vitamin D analyses. Future attention, therefore, needs to be given to this area if the current clinical diagnostic tools for Vitamin D analysis are to be further improved.[22] It was further emphasized that there are significant differences in the 25(OH)D determination between various assays.[23] Therefore, standardization and harmonization of 25(OH)D measurements are, therefore, urgently needed. The widespread introduction of well-standardized assays in clinical laboratories is the challenge in the years to come. Differences between various assays may not allow direct comparisons of various epidemiological studies and responses to treatment.

Immunoassay techniques may not be the best choice for the estimation of Vitamin D in humans. Some immunoassays cannot distinguish between 25-OHD3 and 25-OHD2 Vitamin D metabolites. To this end, Shah I *et al*. developed and validated an improved LC-MS/MS method that could accurately detect and quantitate up to ten different metabolites of Vitamin D, as well as differentiate the epimers and isobars with a view to accurately measure blood Vitamin D levels in the Emirati population.[24] However, this is not yet widely available.

Prevention and intervention

Public awareness

Like most of the noncommunicable diseases, it is essential that besides early identification and treatment, there should be great emphasis on how to prevent it. Salmanpour VA *et al*. evaluated the knowledge and the practices related to VDD among 503 adults aged 20–40 years (mean age: 30 years) selected from public places using convenience sampling employed by a self-administered questionnaire.[25] They had a relatively homogenous gender distribution. The mean knowledge score on VDD was 39%. Less than half of the respondents knew that sunlight is the main source of Vitamin D. The mean score for participants' practice was 39%; 77% of them reported avoiding sun exposure and 97% never had Vitamin D levels measured before.

Management and interventions

Replenishing Vitamin D levels involves a multitude of established strategies which include adequate sunlight exposure, exercise, and dietary supplementation.[1,2] We highlight below some of the studies involving such interventions in UAE populations and their impact on improvement in associated metabolic conditions.

Sunlight exposure and Vitamin D status

Sunlight exposure appears to be a natural and physiological means, but over the years, the period or frequency of sun exposure has been debated. Vitamin D is made when UVB rays react with a compound 7-dehydrocholesterol in the skin. The best UVB rays wavelengths are between 270 and 300 nm. These wavelengths are present when the UV index is greater than 3. The angle of the sun above the horizon (at sea level) also affects the production of Vitamin D as the atmosphere is thicker at lower angles and absorbs more UVB. At angles >45° above the horizon, Vitamin D production will be occurring, although some recent research suggests that Vitamin D production may occur at angles as low as 30°. Most people would have adequate Vitamin D levels just from incidental exposure even outside the peak UV times of 11 am and 4 pm. As little as 5 minutes per day of incidental sun exposure may be adequate for someone who burns easily, and up to 20 min is enough for a person with darker skin. Therefore, it is generally accepted that the amount of time a person needs to produce enough Vitamin D for good health depends on the person's distance from the equator, the season of the year, and the amount of melanin in their skin. Dawodu A *et al*. investigated the effect of sun exposure at recommended levels on Vitamin D status in eight healthy Arab women.[26] They exposed their face, arms, and hands for 15 min per day twice a week for 4 weeks within the privacy of their courtyard to avoid changes in dietary Vitamin D intake. The median serum 25(OH)D levels were significantly higher post intervention (23 nmol/L) than pre intervention (17.6 nmol/L); however, the Vitamin D levels remained suboptimal perhaps due to the short duration of the study.

The Consensus Statement, on Vitamin D and sun exposure in New Zealand, recommended for sufficient exposure to UVB from sunlight.[27] It is assumed that healthy people should be able to synthesize all of their Vitamin D requirements in their skin. However, there is no scientifically validated, safe threshold level of UVD exposure that allows for maximal Vitamin D synthesis without increasing skin cancer risk. Between September and April, sun protection is recommended especially between 10 am and 4 pm. Daily walks or some other form of outdoor physical activity in the early morning or late afternoon is recommended. Direct sun exposure should be a lifelong habit/practice in order to maintain the gains obtained.

What foods are good sources of Vitamin D?

Vitamin D3 exists in small quantities in a few foods such as fatty fish. Furthermore, liver, eggs, and fortified foods such as margarine and some low-fat dairy products contain very small amounts of Vitamin D. Adequate intakes of Vitamin D are hard to achieve through diet alone.

Does the type of supplement and delivery mode matter?

Saadi HF *et al*. determined the efficacy of daily and monthly supplementation with Vitamin D2, the only high-dose calciferol available in the UAE at the time of the study, in lactating and nulliparous women.[28] Ninety healthy lactating and 88 nulliparous women were randomly assigned to consume 2000 IU Vitamin D2/day or 60,000 IU Vitamin D2/month for 3 months. Most women had VDD (<50 nmol/L) at entry. Serum 25(OH)D levels were significantly higher at 3 months than baseline in both groups. In total, Vitamin D supplementation was effective in achieving serum 25(OH)D concentrations of >50 nmol/L in 30% of women at the end point. Oral Vitamin D2 supplementation with 2000 IU/day or 60,000 IU/months for 3 months was safe, and it increased serum 25(OH)D concentrations significantly; however, only a small proportion of the women studied achieved concentrations of >50 nmol/L. In addition, the effect of Vitamin D3 supplementation on metabolic control was evaluated in 87 obese T2DM Emiratis.[29] A randomized, double-blind clinical trial was conducted for 6 months, followed by another 6 months of unblinded follow-up. Serum 25(OH)D level, anthropometric data, and lifestyle factors were recorded. The study was executed in three phases in two arms. At baseline (n = 87), there was an inverse relationship between serum 25(OH)D and fasting blood glucose, HbA1c, total cholesterol, and triglycerides. At the baseline, a statistically significant ($P < 0.01$) positive association between body fat mass and body weight, muscle mass, water mass, waist circumference, and serum PTH was observed. Following supplementation, serum 25(OH)D peaked in phase 1, followed by a decrease in phase 2 paralleled by a decrease in PTH in phase 2 compared to baseline in the Vitamin D group.

Independent meta-analytic reviews suggest a relationship between VDD and depressive symptoms.[30] Theoretically, behavioral withdrawal is likely to exacerbate VDD. The efficacy of a modified form of behavioral therapy designed to simultaneously screen for the symptoms of Vitamin D deficiency and depressive symptoms was assessed in 114 female UAE college students who were screened for depressive symptoms and VDD).[30] Severely Vitamin D-deficient participants who are experiencing clinically significant depressive symptoms were randomly allocated to either a 12-week program of behavioral activation, emphasizing safe sun exposure, or a waiting list control group. The sun exposure and behavioral activation group showed normalization of Vitamin D levels and deterioration in the control group. Similarly, positive results were observed for depressive symptoms. Thus, sun exposure and behavioral activation may be an effective approach to improving Vitamin D status and alleviating depressive symptoms.

It has been previously documented that alfacalcidol is inefficient in healing rickets. Rajah J *et al*. examined the biochemical response to alfacalcidol and subsequently the change in response to ergocalciferol.[31] They included all patients referred with active rickets after a failed course of alfacalcidol. After 3 months of treatment with ergocalciferol, the concentrations changed markedly with biochemical healing. The results confirm the biochemical and physiological basis for using ergocalciferol (or cholecalciferol) in nutritional rickets. However, if these preparations are not available, stoss therapy or drops for 3 months may be used. The former

ensures compliance and is associated with higher 25(OH)D and 1,25$(OH)_2$D concentrations.

Sadiya A *et al*. have demonstrated doses of 6000–10,000 IU of Vitamin D3 for treatment for 3 months and later 3000–6000 IU for maintenance are sufficient.[29] These could be used for recommending doses in UAE as they were based on the Endocrine Society Guidelines.[1] Although in their small study 6000 IU/day was able to achieve optimal levels in phase 1, later, 3000 IU/day was not able to maintain that level in phase 2 and was probably low to optimize all Vitamin D-dependent functions.

From the guidelines and above data, it appears that a daily dose of 5000 IU could be optimal for most patients to treat and then maintain the levels if they are overweight and 3000 IU/day for those who are not overweight/obese. Experiences elsewhere support the notion that large oral dosing would be ideal where rapid correction is needed as in patients with rickets or osteomalacia, and intramuscular dosing is preferred when malabsorption is suspected. Based on the available international and regional data, it appears that a dose of 300,000 IU given as a single dose or divided dose (50,000/week or 10,000/day) should be able to treat and maintain levels for 3 months and thereafter 5000 IU/day given as daily or weekly doses would be an optimal maintenance dose.[32]

Vitamin D in mothers and children

The frequency, causes, and implications of VDD on mothers, infants, and children have been addressed by several groups.[33-41] The main results of these studies are highlighted in Table 3. Low serum 25(OH)D <25 nmol/L was identified by Dawodu A *et al*. in 92% of rachitic Arab children and 97% of their mothers compared with 22% of nonrachitic children and 52% of their mothers.[33] There was a direct correlation between maternal and child Vitamin D levels. They proposed that mothers of rachitic children should be investigated and treated for VDD. Also, Narchi H *et al*. examined Vitamin D status and risk factors in 75 pregnant women from early pregnancy until 6 months postpartum, by serial measurement of serum 25(OH) Vitamin D levels.[34] The serum levels at booking were not significantly different between nationalities, parity, education levels, dress code, consumption of Vitamin D-fortified milk or fatty fish, sun-exposed body surface area, weekly time exposed to the sun, or the sun exposure index. Vitamin D levels progressively declined as the proportion with adequate serum levels fell from 31% at the antenatal visit, to 23% after birth, and to 17% 6 months later. While 80% of mothers who were exclusively breastfeeding had low Vitamin D levels 6 months after delivery, this occurred in 67% of those breastfeeding partially. Furthermore, an investigation the Vitamin D status of Arab mothers and 34 preterm infants measured Vitamin D levels and other markers in maternal serum and cord blood at delivery.[35] The median serum 25(OH)D levels were low at 17 nmol/L in 28 mothers and 14.5 nmol/L in 34 cord blood samples. The median maternal and cord blood calcium (Ca), phosphate (P), and ALP levels were within the normal range. Fifteen infants had moderately severe VDD. The median serum 25(OH)D levels of mothers who had reportedly taken prenatal Vitamin D supplementation and those who had not been were similar. Amirlak I *et al*. investigated the association between micronutrients and birth weight in 84 singleton term infants born to healthy Arab and South Asian women at the City of Al-Ain.[36] The median serum 25-hydroxyvitamin D (25-OHD) concentrations were low in mothers and infants. In a multivariate analysis, maternal serum 25-OHD correlated positively with birth weight, while serum ferritin showed a negative correlation. Dawodu A *et al*.,[37] determined the prevalence of hypovitaminosis D in exclusively breastfeeding infants and their mothers in a community where maternal sunshine exposure is low. Serum levels of Ca, P,

Table 3: Vitamin D deficiency status and consequences in mothers, infants, and children (including adolescents) from the United Arab Emirates

Ref	Authors, year	Findings and conclusions
33	Dawodu A *et al*., 2005	VDD was found in 92% of mothers of rachitic children. Mothers should be investigated and treated for VDD
34	Narchi *et al*., 2010	The transfer of Vitamin D through breast milk has a negative effect on the maternal Vitamin D status. 80% of mothers who were exclusively breastfeeding had low levels 6 months after delivery
35	Dawodu A *et al*., 2011	There was a high prevalence of moderately severe vitamin D deficiency (i.e., serum 25(OH)D <12.5 nmol/L) in preterm Arab infants
36	Amirlak I *et al*., 2009	Median serum ascorbic acid and 25(OH)D levels were low in 84 singleton infants and their mothers. Mothers' serum 25(OH)D correlated with birth weight while serum ferritin showed a negative correlation
37	Dawodu *et al*., 2003	Hypovitaminosis (serum Vitamin D <10 ng/ml) is common in summer in exclusively breastfeeding infants and their mothers in the UAE
38	Saadi HF *et al*., 2009	Combined maternal and infant Vitamin D supplementation (2000 U daily or 60,000 U monthly) over 3 months was associated with a threefold increase in infants' serum 25(OH)D concentration
39	Narchi *et al*., 2011	Serum Vitamin D levels were measured after birth and 6 months later. Serum levels improved at 6 months despite the lack of pharmacological interventions. The mechanism for normalization was not clearly understood
40	Rajah *et al*., 2012	In an ambulatory setting, the highest prevalence of VDD (<25 nmol/L) occurred in the 8-14-year-old age group (31.2%)
41	Rajah *et al*., 2008	Vitamin D supplementation alone was efficient in resolving radiological and biochemical disturbances as well improving the z-score for height in a cohort of children with nutritional rickets

25(OH)D: 25-hydroxyvitamin D, VDD: Vitamin D deficiency

ALP, 25-hydroxyvitamin D (25-OHD), and intact PTH were measured in ninety supplemented healthy breastfed Arab/South Asian infants and their mothers in the summer. The maternal dietary Vitamin D intake was also estimated. The median age of the infants was 6 weeks. The median serum 25-OHD concentrations in mothers and infants were low, and 61% of the mothers and 82% of the 78 infants tested had hypovitaminosis D (serum 25-OHD <10 ng/mL). The infants with hypovitaminosis D had elevated serum ALP and a tendency to higher serum intact PTH levels. The average daily maternal Vitamin D intake from commercial milk was 88 IU. Thus, hypovitaminosis D is common in exclusively breastfed infants and their mothers. The results provide justification for Vitamin D supplementation of breastfeeding infants and mothers in the UAE. Low Vitamin D intake probably contributed to low maternal Vitamin D status. Further work from the same community investigated the effect of combined maternal and infant Vitamin D supplementation on Vitamin D status of the breastfed infant.[38] They examined the effects of supplementation on Vitamin D antirachitic activity of breast milk in a subset of mothers. Ninety healthy breastfeeding mothers were randomly assigned to 2000 IU daily or 60,000 IU monthly supplementation of Vitamin D2, and all their infants (n = 92) received 400 IU daily supplementation of Vitamin D2 for 3 months. Most infants had VDD at the study entry. Serum 25(OH)D concentrations at 3 months increased significantly from baseline in infants of mothers in the first group and second group. Maternal and infant serum 25(OH)D concentrations correlated positively at baseline and 3 months. Milk antirachitic activity increased from undetectable level to a median of 50.9 IU/L. Thus, combined maternal and infant Vitamin D supplementation was associated with a threefold increase in infants' serum 25(OH)D concentrations and a 64% reduction in the prevalence of VDD. Narchi H *et al*. estimated the prevalence of VDD and examined the longitudinal changes and risk factors in infants between birth and 6 months of age.[39] Serum 25-OH-vitamin-D levels were measured after birth and 6 months later in 27 infants. At delivery, mean maternal serum 25-OH-vitamin-D level was 35.5 nmol/L; 22% of mothers had adequate serum levels, 48% had insufficient levels, and 30% had deficient levels. In the infants, serum 25-OH-vitamin-D levels were adequate in 30%, insufficient in 48%, and deficient in 22%. None had received any Vitamin D supplementation since birth. Despite the high prevalence of hypovitaminosis D at birth and the lack of pharmacological supplementation, the number of infants with adequate levels at 6 months of age rose to 87%. No infant had a deficiency, and 13% had Vitamin D insufficiency. Adequate levels were detected in four infants who were partially breastfed and in 84% of the 19 exclusively breastfed infants, but the difference was not statistically significant. Although serum levels improved at 6 months, it occurred more slowly in exclusively breastfed infants. Rajah J *et al*. evaluated the Vitamin D and calcium status of children in an urban ambulatory pediatric clinic in Abu Dhabi.[40] A total of 183 patients were recruited prospectively from the pediatric outpatient clinic visits if their blood was taken for laboratory investigations other than those related to the analysis of Vitamin D and calcium status. The Vitamin D status was compared between four age groups. The percentage of females and males in the deficient range was 21% and 16%, respectively, whereas 32% and 46% of females and males, respectively, were Vitamin D sufficient. The highest prevalence of VDD occurred in the 8–14-year-old age group, with 31.2% being deficient. The study highlights that in an ambulatory pediatric clinic population, peripubescent children are most at risk of VDD. This age group is often not considered in the discussion for the need for Vitamin D supplementation. The same group followed up the patients to document changes in z-scores for height after treatment and determined the proportion of affected children who had VDD or calcium deficiency and were compared in patients before and after treatment.[41] The z-score significantly improved after treatment. Half of the children were diagnosed with severe VDD. The variables 25D and age were moderately and positively correlated, indicating that younger infants had the lowest 25D levels. Vitamin D treatment alone was efficient in resolving radiological and biochemical disturbances as well as improving z-scores for height in a cohort of children with nutritional rickets, which included patients with VDD as well as calcium deficiency. These results support the hypothesis of the interplay and continuum of VDD and calcium deficiency in the pathogenesis of rickets.

Notable Clinical Case Reports

Isolated, family, or small case reports of rare nature continue to provide useful information to understand the presentation and management of certain conditions in specific populations and/or localities. In the context of VDD, several interesting cases were reported from the UAE. The outlines of these case reports are listed in Table 4.

Two unrelated patients were found to have hereditary Vitamin D-resistant rickets (HVDRR) had severe growth and motor developmental retardation, rickets with chest deformities, pulmonary abnormalities, hypocalcemia, secondary hyperparathyroidism, and susceptibility to pulmonary infections.[42] In both cases, good response with normalization of abnormal biochemistries and healing of rickets was achieved with intravenous (IV) calcium infusion. Subsequently, the improvement was maintained with oral calcium. Both the children harbored the same unique missense mutation in the VDR gene that substituted arginine with histidine at amino acid 274 (R274H) in the VDR ligand-binding domain. R274 is a contact point for the one alpha-hydroxyl group of $1,25(OH)_2D3$, the active ligand for the VDR. Functional analyses of the R274H mutation revealed a 100-fold decrease in activity compared to wild-type VDR. They described a novel missense mutation at R274H in the VDR gene that resulted in the HVDRR syndrome in two unrelated children. Vigorous treatment using IV calcium to normalize their hypocalcemia achieved dramatic improvement in these complex and severely ill patients.

Table 4: Notable clinical case reports related to Vitamin D deficiency in the United Arab Emirates

Reference	First author, year	*n*	Type	Theme
42	Aljubeh JM, 2011	2	Genetic, child	HVDRR due to the same novel mutation in the Vitamin D receptor
43	Bharwani SS, 2011	1	Clinical, child	A failing-to-thrive, 18-month-old child with VDD rickets and *Helicobacter pylori* gastritis
44	Mufaddel A, 2014	1	Genetic, adult	A case of Gorlin-Goltz syndrome presented with psychiatric features
45	Saadah M, 2014	5	Genetic	Autosomal recessive progressive myoclonic EPM1
46	Amirlak I, 2008	2	Infants	Dilated cardiomyopathy secondary to nutritional rickets

EPM1: Epilepsy Type 1, VDD: Vitamin D deficiency, HVDRR: Hereditary Vitamin D-resistant rickets

A 14-month-old girl presented with recurring bouts of vomiting and diarrhea and failure to thrive was found at 7 months of age to be exclusively breastfed, and her blood tests revealed low calcium, low phosphorous, and markedly elevated ALP.[43] She was started on Vitamin D and calcium supplements. Five months later, she presented with lower-limb bowing, irritability, vomiting, and loose stools. Laboratory studies revealed very low serum OH Vitamin D and high serum $(OH)_2D$, so the Vitamin D dose was doubled. Ten weeks later, her growth velocity had fallen, and she continued to have intermittent loose stools. Endoscopic biopsies showed *Helicobacter pylori* gastritis and mild duodenitis. After the eradication of *H. pylori*, there was a dramatic improvement in her growth and activity and at 6-month follow-up, there was no clinical or radiologic evidence of rickets.

A 34-year-old male presented with an acute onset of pleomorphic psychiatric features. He was later diagnosed with Gorlin–Goltz syndrome based on clinical and radiological findings that are characteristic of this rare autosomal dominant syndrome.[44] His Vitamin D level was low (20 ng/L) and serum PTH level was high. The patient improved on antipsychotic medications and Vitamin D supplementations for symptomatic management. This case highlights the importance of considering rare organic etiologies in the differential diagnosis of patients presenting with psychiatric symptoms. This is of vital importance for early intervention to prevent complications and for better outcomes of the coexistent diseases.

Progressive myoclonic epilepsy type 1 (PME1) is a neurodegenerative disorder characterized by action- and stimulus-sensitive myoclonus, tonic-clonic seizures, progressive cerebellar ataxia, preserved cognition, and poor outcome. The clinical, neurophysiological, radiological, and genetic findings were reported in an Emirati family with five affected siblings.[45] Genetic testing confirmed the diagnosis of autosomal recessive PME1 for the first time in two males and three females. The median age at onset was 3 years. Action- or stimulus-sensitive myoclonus and generalized seizures were recorded in 100% of their patients, at a median age at onset of 3 and 4 years, respectively. Multisegmental myoclonus and generalized status myoclonicus were observed in 80% of their patients. Dysarthria and ataxia developed in 100% of their patients. VDD and recurrent viral infections were noticed in 100% of their cohort. Cognitive, learning, and motor dysfunctions were involved in 100% of their patients. The sphincters were affected in 60% of their patients. Abnormal electroencephalogram was recorded in 100% of their cohort. Generalized brain atrophy progressively occurred in 60% of their patients. Phenytoin and carbamazepine were used in 60% of their patients with worsening effect. Valproate and levetiracetam were used in 100% of their patients with improving effect.

Finally, dilated cardiomyopathy secondary to nutritional rickets was described in two 9-month-old breastfed infants who presented with congestive heart failure secondary to dilated cardiomyopathy.[46] No underlying etiology was found, except for the presence of advanced rickets. Treatment with Vitamin D and calcium supplements induced quick normalization of myocardial function in both infants. These case reports may not indicate any unique findings in UAE patients but help stimulate interest in the subject and may help focus diagnostic skills and better clinical management.

Academic Interests and Research

With the increased clinical and academic interest in VDD and its implications, some basic and clinical research work were undertaken at UAE academic centers. Some of these studies are listed in Table 5.[47-54]

Saadi *et al*.[47] correlated the quantitative ultrasound (QUS) parameters of the calcaneus with bone density (BMD) in the hip and spine in Arabian women with different degrees of vitamin D deficiency. The correlations of QUS parameters with spine and hip BMD were modest for the spine and hip, respectively, for all comparisons, but stronger in postmenopausal women. All postmenopausal women with low estimated calcaneal BMD (T-score pound-1) had a T-score pound-1 by DXA of the spine or hip. Of the 21 premenopausal women with spine or hip T-score pound-1 who had 25(OH)D measurements, 95.2% had levels below 50 nmol/L and 57% had levels below 30 nmol/L. The subgroup with 25(OH)D <30 nmol/L had significantly lower spine and hip BMD than the subgroup with 25(OH)D >30 nmol/L. QUS parameters were not significantly different between the two subgroups. The QUS and DXA correlated modestly well in women with prevalent hypovitaminosis D. The authors concluded that QUS could be used in postmenopausal women with hypovitaminosis D to identify those at risk for osteoporotic fracture and in a separate report they also examined the relation of QUS parameters to anthropometric and lifestyle factors.[48]

The same group[49] investigated the relationships between 25(OH)D and N-terminal pro-B-type natriuretic peptide

Table 5: Basic research activities on Vitamin D in the United Arab Emirates

Reference	First authors	Year	Population	Sample size	Conclusions
47,48	Saadi, HF	2004, 2003	Females	56, 412	Correlation of QUS parameters of the calcaneus with bone density in women with hypovitaminosis D and with anthropometric and lifestyle variables.
49	Saadi, HF	2009	NA	NA	Vitamin D status and cardiac function and response to supplementation.
51	Hasan HA	2017		198	Association of Vitamin D receptor gene polymorphisms with metabolic syndrome and its components
14	Saadi HF	2006	Women	259	VDD is associated with increased bone turnover; VDR genotype is not related to markers of bone turnover or BMD
52	Abboud M	2017	-	-	Skeletal muscle provides a substantial site of sequestration of 25(OH)D, protecting its degradation by the liver. Exercise, not just outdoors, is usually associated with better Vitamin D status
50	Al-Jebawi AF	2017	T2DM + VDD	124	PTH responsiveness to VDD in T2DM patients
53	Obineche EN	2008	Dialysis patients		Study of the interrelationships between B-type natriuretic peptides and Vitamin D in patients on maintenance peritoneal dialysis.
54	Laleye LC	2009	Milk and edible oils	-	A study on vitamin D and vitamin A in milk and edible oils available in the UAE
19	Safar H	2018	T2DM and controls	355	Association between SNPs in the VDR gene (except for Taq 1) and T2DM *per se*
20	Osman E	2015	Males and females	282	The Emirati population genotype and allele distribution of Taq1 and Fok1; Similar to USA and France, but different from Asians

NA: Not applicable, BMD: Bone mineral density, 25(OH)D: 25-hydroxyvitamin D, T2DM: Type 2 diabetes mellitus, PTH: Parathyroid hormone, SNPs: Single-nucleotide polymorphisms, QUS: Quantitative ultrasound, VDD: Vitamin D deficiency

(NT-proBNP) and plasma renin activity (PRA) levels and also documented the effect of Vitamin D administration on NT-proBNP and PRA levels in Vitamin D-deficient individuals. Serum 25(OH)D, PTH, plasma or serum NT-proBNP, and PRA levels were measured at baseline in nulliparous and lactating women and after 2 months of oral Vitamin D2 supplementation to lactating women. The baseline levels of 25(OH)D were low in most women, whereas PRA and NT-proBNP levels were within the normal range. Baseline 25(OH)D and PTH did not correlate with NT-proBNP and PRA. Vitamin D supplementation over a 2-month period in lactating women was associated with a significant decline in NT-proBNP and PRA. However, there were no significant correlations between the changes from baseline in 25(OH)D and either NT-proBNP or PRA.

The relationship between hyperglycemia and PTH level in 124 adults with T2DM and VDD was examined. They were considered in four groups based on their glycemic control markers. Chronic hyperglycemia was associated with a significantly attenuated PTH responsiveness to VDD without a significant change in calcium level. On the other hand, there was no significant association between FPG and PTH level. The relationships of VDR polymorphisms to the components of metabolic syndrome among 198 Arab adults were investigated in a cross-sectional study of 198 Arab adults aged 21 years with a BMI of 26.8 kg/m^2.[51] Nearly 15% had metabolic syndrome with serum Vitamin D levels of 25.5 nmol/L. VDR genotyping yielded FokI, FF, Ff, BsmI, bb, and Bb, whereas TaqI showed TT and Tt. The ff carriers had higher total cholesterol than FF and Ff genotypes. Bb carriers showed higher BMI and LDL-C levels than BB and bb genotypes. FokI VDR polymorphism in females showed significant association with systolic blood pressure, and F allele carriers were at higher risk of developing it. VDR gene polymorphisms were not associated with metabolic syndrome, yet it may affect the severity of some of the components of metabolic syndrome. Interesting work has demonstrated that skeletal muscle provides a substantial site of sequestration of 25(OH)D, protecting its degradation by the liver suggesting that exercise, not just outdoors, is usually associated with better Vitamin D status.[52] Some more work addressed changes in dialysis patients and vitamin D content of milk and edible oils [Table 5].

Conclusions

Based on epidemiological data, it is evident that VDD and Vitamin D insufficiency are highly prevalent across different population subtypes in the UAE. These are not limited to the Emirati population but extends to the expatriate community as well and has been observed in both healthy controls and in other disease conditions. A gender difference has been identified in some studies.

We acknowledge the significant methodological differences between many of the studies. Nonetheless, all the studies have generated considerable information that can be useful to the practicing clinician to help build an evidence-based practice to some extent. Despite a plethora of publications on Vitamin D in our region, numerous gaps still exist. Small sample sizes, heterogeneous populations, differences in disease definitions and cut off points are only some of the limitations of the reviewed studies. Some of the study designs may have suffered from preconceived ideas on the extent of different factors. The differences in the magnitude and paradoxical nature of the problem in this country (UAE) and the surrounding region from the international scene call for further research and regionally adopted guidelines based on strong evidence and/or well-informed consensus.

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Authors' contributions

SAB conceived the idea of the review. SAB and KH drafted the outlines of the original manuscript. All authors provided their designated sections and critically revised the rest of the manuscript for intellectual content, language, and presentation. All authors approved the final version of the article.

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Compliance with ethical principles

Not required; No human or animal studies by the authors were reported.

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