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Vitamin D in the Persian Gulf: Integrative Physiology and Socioeconomic Factors

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Abstract Countries of the Persian Gulf region—Bahrain, Iran, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates—have become increasingly modernized, resulting in a transformation of lifestyle based on technology, sedentary activity, lack of sunlight, and unhealthy dietary patterns. These factors have led to a higher prevalence not only of vitamin D undernutrition, but also chronic obesity, insulin resistance, prediabetes, and type 2 diabetes. This review explores the integrative physiologic effects of vitamin D with socioeconomic factors and propose a hypothesis-driven model for their contributions to obesity and diabetes in the Persian Gulf. Further research into these interactions may ultimately lead to novel preventive strategies and therapies for metabolic disorders in this geographic region.

Keywords Vitamin D · Obesity · Osteoporosis · Diabetes · Metabolic syndrome · Persian Gulf region

Introduction

Global economic growth has produced industrialization and prosperity in previously impoverished regions. This phenomenon has witnessed parallel increases in technologic advancement and personal wealth [1]. Unfortunately, concomitant lifestyle and nutritional changes produced many metabolic derangements. A case in point is the Persian Gulf region: Bahrain, Iran, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates (UAE). These Arab states have been negatively impacted by urbanization, resulting in significant demographic and lifestyle shifts [2]. The Persian Gulf region has experienced dramatic changes in the prevalence rates of vitamin D undernutrition (insufficiency and deficiency; 25-hydroxyvitamin D [25(OH)D] levels<30 ng/mL) [3]. In addition, when an agricultural society transitions into an industrialized, service-oriented society, the prevalence of sedentary activity increases [4]. Coupled with a change in the supply and demand for calorically dense foods and unhealthy dietary patterns, these environmental factors lead to chronic obesity, dyslipidemia, insulin resistance, prediabetes, and frank type 2 diabetes (T2D) [5]. Moreover, it is also useful to consider metabolic syndrome (MeS) as a cluster of these metabolic disorders that ultimately lead to chronic inflammation and increased risk for cardiovascular disease (CVD) [6]. An integrative physiology role of vitamin D has been described elsewhere [7–9] and raises important epidemiologic and physiologic questions relevant to the Persian Gulf, which have prompted this review.

Herein, we explore vitamin D undernutrition in the Persian Gulf. We hypothesize that vitamin D nutriture not only plays an important role in bone and mineral homeostasis, but may also contribute to the conspicuously coincident obesity and diabetes epidemics. There is insufficient evidence at present to implicate causal relationships between vitamin D undernutrition and components of MeS. However, if causality can eventually be demonstrated in the Persian Gulf where these features are highly prevalent, then one could envision vitamin D–centric therapeutics to reduce overall CVD risk and improve health care.

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Epidemiology of Vitamin D Undernutrition in the Persian Gulf

Vitamin D Undernutrition

Vitamin D undernutrition is becoming a worldwide epidemic. A total of 20% to 25% of people in the United States, Canada, Mexico, Europe, Asia, and Australia have a vitamin D deficiency [10]. Current evidence-based clinical practice guidelines provide population-specific recommendations for daily vitamin D intake amounts and target 25(OH)D levels (Table 1). Scientific bodies evaluating appropriate vitamin D intakes disagree on the recommended daily values and target serum values, yet agree on the tolerable upper limit of 4000 IU/day. The National Academy of Sciences Institute of Medicine (IOM) advocates a target level of 20 to 50 ng/mL: 400 to 600 IU/day for adults 18 to 70 years old and 400 to 800 IU/day for those older than 70 years [11, 12]. The American Association of Clinical Endocrinologists recommends a higher intake of 1000 to 2000 IU/day to reach a target vitamin D serum concentration of 30 to 50 ng/mL [3].

Experts from around the world have argued that the latest IOM recommendations undervalue the benefits of vitamin D while overstating the dangers of higher doses [13]. Members of the Grassroots Health Call to Action Panel, comprised of vitamin D experts, state that daily intakes of 4000 to 8000 IU, necessary to reach a target range of 40 to 60 ng/mL, halve the risk of breast and colon cancers, multiple sclerosis, and type 1 diabetes [14•]. In addition, toxic serum levels of vitamin D (200 ng/mL) are not achieved with vitamin D intakes less than 10,000 IU/day [14•].

There is little consensus within the scientific community on how to differentiation vitamin D deficiency from vitamin D insufficiency based on serum 25(OH)D concentrations. Vitamin D insufficiency, which does not manifest overt signs or symptoms, has been associated with skeletal pathologies such as osteopenia and osteoporosis, an increased risk of falls, and an increased risk of fractures [15].

Counterintuitively, despite the hot desert climate and presumed increased access to sun exposure, the Persian Gulf has some of the highest vitamin D insufficiency rates in the world [16]. Shielding oneself from sunlight and decreased skin exposure due to covering one's body in clothing greatly reduces ultraviolet B (UVB) exposure and consequent vitamin D production in the skin [17]. For example, the very low levels of vitamin D found in Persian Gulf women have been associated with modest clothing, low intake of the vitamin, a high number of pregnancies, and obesity [18]. In both Iran and Saudi Arabia, women wear an “abaya” (a full black cloak) and may additionally shield other body parts such as their face with a “niqab,” as well as hands and feet [19]. Prevalence among youth indicates the severity of insufficiency with up to 70% of Iran's and 80% of Saudi Arabia's adolescent-aged girls presenting with vitamin D levels less than 10 ng/mL [20]. Average levels of serum vitamin D in women inhabiting these two areas remain at 10 ng/mL [20]. A study from the UAE reported that vitamin D levels were below 32 ng/mL in both 259 Emarati women and 7 Western women living in the UAE yet the Emarati women had much lower levels than the Western women with 10.4 versus 25.2 ng/mL, respectively [19]. Serum vitamin D values were also lower at the end of the summer versus winter indicating little outdoor sun exposure with the extremely high summer temperatures [19].

In a study of 321 premenopausal Saudi women with conservative dress style, the mean vitamin D level was markedly reduced at 11 ng/mL [21]. Of 360 Saudi Arabian patients with back pain, 83% had vitamin D levels below 9 ng/mL [22]. These results were corroborated by a study of 259 female Emirati with a mean vitamin D level of 10 ng/mL and a study of 245 postmenopausal Iranian women in which 5% had vitamin D levels less than 10 ng/mL and 37% between 10 and 20 ng/mL [23]. Furthermore, in healthy Saudi men, 10% were deficient with a mean vitamin D level of 16.6 ng/mL and 18% were insufficient with a mean vitamin D level of 25.4 ng/mL. In

Table 1 Recommendations on vitamin D nutriture

Organization	Recommended target serum 25(OH)D range (ng/mL)	Recommended daily vitamin D intake (IU/day)
National Academy of Science: Institute of Medicine [11]	20–50	400–600 (age 18–70 y)
		400–800 (age 70+ y)
American Association of Clinical Endocrinologists [3]	30–50	1000–2000
Garland et al. [14•]	40–60	4000–8000

25(OH)D 25-hydroxyvitamin D

(*Data from* American Association of Clinical Endocrinologists [3], National Academy of Sciences [11], Institute of Medicine of the National Academies [12], and Garland et al. [14•])

the 50+ age group, 25% had insufficient 25(OH)D levels (mean level of 25.3 ng/mL), and 12% were deficient with a mean value of 16.6 ng/mL [24]. In Iran, over two thirds of pregnant women do not take vitamin D supplementation while pregnant [19]. Glerup et al. [25] found that veiled Arab women had the lowest concentration of serum vitamin D at 2.85±0.44 ng/mL, compared with 6.82±0.92 ng/mL in ethnic Danish Muslim women, and 18.84±1.8 ng/mL in Danish controls.

Dairy products in the region lack vitamin D fortification. The Saudi Ministry of Health is trying to change this by fortifying cholecalciferol in milk. However, consumption of milk in Saudi Arabia is very low, in part due to the prevalence of lactose intolerance [19]. This problem is compounded by the dietary consumption of phytates in bread, which chelate and limit calcium absorption in the gut [19].

Whereas diet, clothing, and sun exposure may be modified, age and skin pigmentation cannot; specifically, skin pigmentation resulting in darker skin may be linked to reduced dermal vitamin D production [18]. More melanin results in decreased generation of cholecalciferol because of its competition with 7-dehydrochoelsterol and attraction of UVB photons away from 7-dehydrocholesterol [26]. A study by Lo et al. [27] demonstrated that there is similar capacity to produce vitamin D in people of varying skin pigments yet darker-skinned individuals need a longer exposure time.

Epidemiology of Metabolic Disorders in the Persian Gulf

Generally, the economic growth of a nation heralds a rise in the quality of life for its citizens. However, countries with a too rapid rate of increasing wealth (ie, transition economies) have faced critical health obstacles, such as the rising prevalence of obesity [28]. The Persian Gulf States including the Persian Gulf Cooperation Council (GCC) countries—Bahrain, Iran, Iraq, Kuwait, Oman, Qatar, Saudi Arabia, and UAE—are examples of transitional economy states, reflected by the exponential rise in both their real gross domestic product (GDP) and GDP per capita over the past two decades, as well as an average 5% GDP growth per year from 2006 to 2008 (Fig. 1). This pace of economic growth, primarily from the discovery of oil in the early 20th century, was followed by booming economic growth in the 1970s and 1980s, and then adoption of various western sociocultural changes [29].

There is a higher propensity for sedentary activity and consequent decline in caloric expenditure as the economy shifts from agriculture to a manufacturing/service orientation. As the labor-intensive infrastructural initiatives coordinated by the GCC in the 1970s waned, the rise in sedentary-style job opportunities rose, leading to a demand for expatriate professional workers [30]. The majority of the workforce emigrates from India and Pakistan, followed by other Southeast Asian countries, Arab countries, and Europe [31]. Approximately 70% of the growth in population of the UAE between 1980 and 1992 was due to expatriate inflow; it is expected that 80% of the UAE population consists of expatriates [32]. Similarly, Kuwait's population as of 2008 was composed of 31% natives and 69% expatriates. The Emirates National Diabetes and Coronary Artery Disease Risk Factor (ENDCAD) reports that the prevalence of T2D is 20%, with a larger prevalence among Emiratis (24%) compared with non-Emirati expatriates (17.4%) [33]. Consanguinity is common among native UAE residents. Traditional native UAE residents adhere to consanguineous marriage to keep family resources tightly controlled; a young man generally marries his father's brother's daughter or, if necessary, other first cousins [34]. These societal factors may also play a role in the increased prevalence of T2D among the native population.

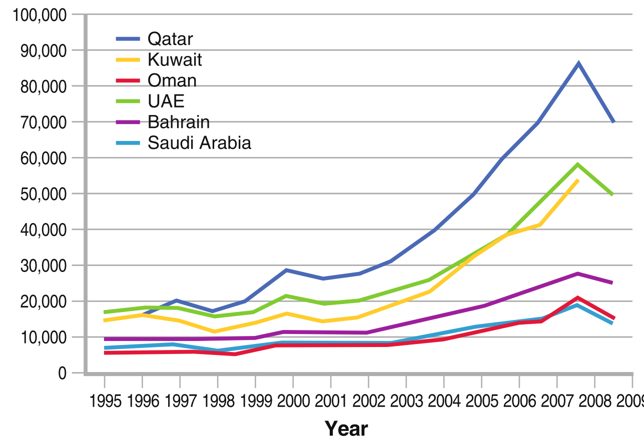

Fig. 1 Gross domestic product (GDP) per capita of the Gulf Cooperation Council from 1995 to 2009 in US Dollars [65]. UAE—United Arab Emirates

A Kuwait study on the incidence of MeS and its components illustrated differences in lifestyle and familial histories among native and non-native populations. Although there were no significant differences between the two populations in their exercise levels and smoking status, more expatriates dieted (53.5% of expatriate men [EM] and 72.1% of expatriate women [EW] compared with 39.3% of native men [NM] and 68.8% of native women [NW]), had less family history of T2D (42.1% of EM and 52.5% of EW, compared with 67.9% of NM and 81.1% of NW), and had less prevalence of obesity defined as body mass index greater than 30 kg/m^2 (27.2% of EM and 59% of EW, compared with 35.7% of EM and 71.2% of EW) [35]. Natives also faced higher rates of hyperlipidemia, hypertension, and ischemic heart disease compared with their expatriate counterparts [35]. Despite these differences, a larger percentage of expatriates had higher levels of hemoglobin A_{1c} (43.2% and 26.4% in EM and EW, respectively, compared with 12.2% and 18.2% in NM and NW, respectively), suggesting chronically elevated blood glucose levels. EM and EW had a higher prevalence of MeS (20% of expatriates compared with 13.5% of natives) [35].

The urbanization of the Persian Gulf has also generated a concomitant increase in access to technology and services that provide passive entertainment, reduce time spent on housework, or facilitate transportation. These changes have led to a temporal decrease in nonoccupational activity levels that have been compounded by existing cultural norms of the region. The total physical activity levels—both occupational and nonoccupational activities—among inhabitants of the Gulf region are lower than the nonoccupational physical activity alone of highly industrialized countries such as Australia, United States, and England. A total of 39.0% to 42.1% of Arab men and 26.3% to 28.4% of Arab women were able to accumulate at least 150 min of moderate physical activity per week. In comparison, 31% of adults in England, 60.0% and 49.7% of Australian men and women, respectively, and 54% and 46.7% of American men and women, respectively, were able to accumulate 150 min of moderate physical activity at work alone [5].

Adherence to social norms and traditions in Saudi Arabia, for example, translates into women spending most of their time in the home watching the children, with limited access to sports or other physical activities and socialization that usually involves food consumption or television, while domestic workers handle non-strenuous house work [36, 37]. Thirty-eight percent of Omani women report that they are able to engage in outdoor activity without the presence of an adult family member and few health clubs accommodate women [38–40]. As a rule, Saudi women do not exercise much [39]. Traditional Arab culture additionally praises the "plump" figures of women, making voluptuousness synonymous with ideals of a beautiful, healthy, and rich physique [36].

The economic prosperity of the Arab Gulf has also fueled a "nutrition shift" toward an obesogenic, westernized diet. The diet of the Persian Gulf is changing from one reliant on dates, milk, fresh vegetables and fruit, whole wheat and fish, to energy-dense foods rich in fat and exceeding an average of 3000 kcal per capita [32]. Persian Gulf states were dominated by agricultural, grazing, and fish societies prior to industrialization whereas now, foods including fast food, fried chicken, and beef burgers are very common [4]. This "nutrition shift" in the Arabian Gulf countries began as early as the 1970s, when government food subsidies rose significantly to meet population growth rates and increases in world food prices. The rise in consumption of meat, rice, wheat flour, sugar, fat, and oil from 1987 to 1993 is attributed to lower subsidized pricing of foods and increased income from oil revenue [32].

The Gulf also relies on importing most of its food to meet demand; while seafood is abundant; its export exceeds domestic consumption [41]. Ng et al. [42•] hypothesize that this trade balance encourages a food system that favors prepackaging and processing with a high sodium and fat content. Socially, individuals spend large amounts of time sitting and eating food together, leading to excess caloric intake. Many families have a cook and eat at home, or, for example in Kuwait, regularly dine out in restaurants or opt for fast food [4]. Table 2 outlines the most recent prevalence of obesity, T2D, MeS, and CVD in the Persian Gulf region.

Integrative Physiology of Vitamin D and Metabolic Disorders

Vitamin D has had other functions that preceded skeletal calcium homeostasis; scientists have discovered the vitamin D molecule in krill and phytoplankton, which have remained largely unchanged for over 750 million years, as well as the lamprey—a vertebrate that lacks a calcified skeleton [43]. Provitamin D and its photoproducts have overlapping absorption spectra with DNA, RNA, and proteins, and may have served as a molecular sunscreen [43].

Vitamin D also coordinates with toll-like receptor (TLR) pathways, which are also phylogenetically ancient. Activation of human macrophage TLR upregulates the vitamin D receptor (VDR) and vitamin D 1α-hydroxylase gene expression to produce the antimicrobial peptide cathelicidin critical for killing intracellular *Mycobacterium tuberculosis* (TB) [44]. This may explain why African-American individuals, who have lower vitamin D serum levels due to skin pigmentation, are also more susceptible to TB [44].

Using molecular modeling, Lou et al. [45•] demonstrated how the prohormone 25(OH)D directly influences gene expression, proliferation, and differentiation as an agonist of the VDR. There are two conformational states of the VDR; a low-affinity conformational state for 25(OH)D that is considered evolutionarily older and a high-affinity conformational state for 1,25 dihydroxyvitamin D, further suggesting that vitamin D had ancestral roles before skeletal calcium homeostasis [45•]. In fact, 25(OH)D was shown to elicit a greater cell response in the form of megalin production than its metabolite 1α,25(OH)2D in the absence

Table 2 Recent obesity, diabetes mellitus, MeS, and CVD prevalences in the Persian Gulf

Country	Gender	Obesity (BMI≥30 kg/m^2)	Diabetes mellitus	MeS	CVD
Bahrain	M	23% (2002) [60]	24.4% (1996) [60]	–	–
	F	34% (2002) [60]	37.4% (1996) [60]	–	–
Qatar	M	34.6% (2003) [42•]	32.6% (2003) [42•]	27.7% (2008) [62]	–
	F	45.3% (2003) [42•]	31.7% (2003) [42•]	32.6% (2008) [62]	–
Oman	M	16.7% (2000) [38]	35.3% (2000) [37•]	19.5% (2001) [38]	–
	F	23.8% (2000) [38]	31.1% (2000) [37•]	23.0% (2001) [38]	–
UAE	M	25.6% (2000) [42•]	47.0% (2000) [42•]	35.1% (2000) [37]	3% (2000) [37]
	F	39.9% (2000) [42•]	32.4% (2000) [42•]	42.7% (2000) [37]	1.7% (2000) [37]
Saudi Arabia	M	28.3% (2005) [42•]	42.2% (2000) [42•]	37.2% (2005) [63]	3.2% (2004) [64]
	F	43.8% (2005) [42]	33.5% (2000) [42•]	42.0% (2005) [63]	1.7% (2004) [64]
Kuwait	M	39.2% (2006) [61]	–	36.2% (2006) [61]	–
	F	53.0% (2006) [61]	–	36.1% (2006) [61]	–

Results are presented as prevalence (year published) [reference]

BMI body mass index, *CVD* cardiovascular disease, *F* female, *M* male, *MeS* metabolic syndrome, *UAE* United Arab Emirates

of 25(OH)D-1α-hydroxylase and reduced prostate cancer cell proliferation in vitro [45•].

Although intestinal calcium absorption and skeletal mineralization have become the principle actions of vitamin D, the presence of ectopic 1α-hydroxylase and wide distribution and function of the VDR raises the issue of a complex, integrative physiology [7, 46•]. Thus, a systems perspective of vitamin D physiology is rooted in data from evolutionary biology.

Examination of the role of vitamin D and its effects on adipocytes and intermediary metabolism may provide useful insight into risk factors for T2D and CVD. There is an increasing understanding of the connection between vitamin D levels and obesity. Obesity limits sun exposure indirectly via decreased mobility, contributing to decreased vitamin D levels in the GCC. The enhanced fat solubility and decreased bioavailability of vitamin D produces low serum levels (10–20 ng/mL) with obesity [10, 46•, 47, 48]. The complexity of vitamin D's effects is evident in leptin-inflammatory networks [49, 50]. Kong et al. [51] demonstrated that vitamin D was unable to block peroxisome proliferator-activated receptor-γ expression and associated adipocyte differentiation. VDR mRNA concentrations are also elevated in differentiating adipocytes [52]. The bidirectional relationship between obesity and vitamin D is evident in studies in the Persian Gulf region: vitamin D deficiency is prevalent in obese subjects and vitamin D is more bioavailable with weight loss [46•, 53].

Vitamin D studies using animal models have helped explain the vitamin's effects on the immune system and its consequent role on pancreatic β-cell health. Rat studies have demonstrated that vitamin D protects against interleukin-1β and γ-interferon–mediated autoimmune destruction of β cells. Pino-Montes et al. [54] looked beyond the protective effects and examined the therapeutic effects of vitamin D on streptozotocin-induced nonobese diabetic mice after diabetes developed. The study found that vitamin D decreased the mean insulin required by the rats that were diabetic, compared with the untreated diabetic controls. The number of β cells per section of pancreatic tissue was 27±0.8 in nondiabetic control rats, 9.5±0.6 in untreated diabetic control rats, and 17±0.8 in vitamin D–treated diabetic mice [51]. Vitamin D levels may also play a physiologic role in the pathophysiology of T2D, in which low vitamin D levels are associated with impaired osteoblast osteocalcin (OCN) production, β-cell function, and insulin secretion [7, 9]. OCN levels are lower with T2D and β cells express the VDR and vitamin D–dependent calcium-binding proteins [8]. Vitamin D supplementation enhances β-cell function via nonselective voltage-dependent calcium channel activation that promotes endopeptidase cleavage of proinsulin to insulin [55]. Animal studies of vitamin D have helped elucidate its effects on the immune system that may be implicated with β-cell health. These human and murine model studies provide strong evidence for the direct role of vitamin D in promoting glucose homeostasis through immunoprotective mechanisms. Studies have correlated hypovitaminosis D with T2D in women, impaired insulin secretion in a population at risk for diabetes, and hyperresponsive insulin secretion after glucose challenge in older men [56]. Chiu et al. [56] also used the hyperglycemic clamp technique in glucose-tolerant subjects to demonstrate a positive correlation of serum vitamin D concentration with the insulin sensitivity index (ratio of average glucose infusion rate by average plasma insulin concentration).

Vitamin D has recently been tied to CVD risk. The cardiac VDR modulates renin gene expression, vascular smooth muscle cell and cardiomyocyte growth, and macrophage uptake of atherogenic low-density lipoprotein cholesterol [57, 58]. Suppression of vitamin D production in wild-type mice results in the overexpression of renin [57]. Transgenic rats with enhanced vitamin D metabolic clearance exhibit extensive atherosclerosis [57]. Polymorphisms of the VDR lead to increased cardiac hypertrophy [58].

Vitamin D insufficient or deficient individuals from the Framingham Offspring Study showed an adjusted risk for components of CVD such as “myocardial infarction, coronary insufficiency, and heart failure” to be 62% higher than those with normal levels [59]. A study involving patients with end-stage heart failure and vitamin D deficiency showed that those with the lowest vitamin D levels (< 0.016 ng/mL) had a 1-year mortality rate of about 33% compared with those who had the highest vitamin D levels (mean: 0.434 ng/mL) and a mortality rate of 3.9% [59]. Individuals with pre-existing hypertension and low vitamin D levels of 16 ng/mL had twice the risk of CVD events [57].

Conclusions

We now appreciate the extraskeletal roles of vitamin D in pathophysiology. The conspicuous coincidence of a unique lifestyle, population genetics, vitamin D undernutrition, and high prevalence rates of obesity and diabetes in the Persian Gulf raise important questions. Does vitamin D undernutrition influence the natural history of obesity, T2D, and CVD in the Persian Gulf? How does increased adiposity contribute to vitamin D undernutrition in the region? Can the socioeconomic climate of the region account for the phenotype of observed metabolic disease? Should inhabitants of the region be routinely supplemented with vitamin D and if so, to what level? Knowledge gleaned from studies in the Persian Gulf may enlighten us regarding the integrative physiology of vitamin D and help answer these questions.

Disclosure Conflicts of interest: J. Fields: none; N. Trivedi: none; E. Horton: has been on the advisory board for Amylin; has been a consultant for Gilead; has been on the research steering committee for Medtronic; has been on the advisory board and speakers’ bureau for Merck; has been on the advisory board for Roche; has received grant support from Amylin and Eli Lilly; has received honoraria from Amylin, Gilead, Medtronic, Merck, and Roche; and has received travel/accommodations expenses covered or reimbursed from Amylin, Gilead, Medtronic, Merck, and Roche; J.I. Mechanick: has been a consultant, received honoraria, received payment for development of educational presentations including service on speakers’ bureaus, and received travel/accommodations expenses covered or reimbursed by Abbott Nutrition and Nestle Nutrition; and has received grant support from Select Medical Corporation.

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