Vitamin D Insufficiency in a Sunny Environment: A Demographic and Seasonal Analysis

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ABSTRACT: **Background:** Hypovitaminosis D has been shown to be extremely common in various regions around the world, mostly at high latitudes. Israel is characterized by certain features – cultural (e.g., ethnic isolates) and geographic (e.g., sunny climate) – that have been identified for their possible association with vitamin D status.

Objectives: To conduct an ecological study on a representative sample of the population of Israel, testing vitamin D status across age groups, genders, ethnic groups, and seasons.

Methods: We obtained serum samples from 195 healthy Israeli volunteers representing a broad demographic spectrum. Serum concentrations of 25(OH)D were measured with the commercial kit Liaison 25(OH)D Assay (DiaSorin, Italy).

Results: The mean vitamin D level for the entire cohort was surprisingly low (22.9 ± 10.1 ng/ml), with 149 subjects (78%) suffering from vitamin D insufficiency (< 30 ng/ml). Vitamin D status was better in infants than in older age groups. Differences by gender were significant only in the infant age group (i.e., vitamin D status was worse among females) and were not prominent across older ages. Israelis of Ashkenazi origin had higher vitamin D mean levels than those of Sephardic origin, who, in turn, had higher vitamin D levels than Arab subjects (31.4 ± 12, 24.1 ± 10, and 17.6 ± 9 ng/ml respectively). With regard to season, there were no differences between the samples collected in winter and the samples collected in summer.

Conclusions: The results suggest that hypovitaminosis D is common across all ages, genders and seasons in Israel, a country characterized by a sunny Mediterranean climate. Specific ethnic groups may be at especially high risk.

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In recent years, vitamin D has been attracting considerable attention. It is becoming increasingly clear that this vitamin has a wide range of biological activity in addition to the classic endocrine pathway, emphasizing the importance of this hormone in many aspects of general health. Studies suggest that vitamin D insufficiency plays a role in the development of cancer, autoimmune diseases, hypertension, infectious diseases, diabetes, cardiovascular disease, musculoskeletal disorders, asthma, as well as several psychiatric conditions such as schizophrenia, depression and dementia [1-5]. Unfortunately, it is estimated that as many as 1 billion people worldwide suffer from vitamin D deficiency or insufficiency (commonly defined as levels below 20 ng/ml and 30 ng/ml respectively), and this was shown to be prevalent across all age groups, genders, and geographic regions [1,6-13].

The aim of the present study was to assess vitamin D status in Israel. For this purpose the study population encompassed a representative demographic spectrum, enabling a comparative analysis of vitamin D levels across a range of age groups and both genders. Furthermore, Israel has unique cultural and geographic features, presenting the opportunity to investigate the associations between such factors and vitamin D status.

ETHNICITY IN ISRAEL AND VITAMIN D

The diversity of ethnic groups in Israel is extremely rich and thus ideal for investigating the effects of genetic and cultural factors on vitamin D levels. Israel's population comprises both Jewish and non-Jewish groups. The Jewish population of Israel is divided according to historical ethnic descent, namely Jews of European and American descent (known as *Ashkenazi* Jews), and Jews of North African (e.g., Morocco), Asian and Middle East descent (known as *Sephardic* Jews). The non-Jewish population living in Israel consists mostly of Arabs and particularly Moslem Arabs. These three main ethnic groups potentially vary in several parameters, which may exert differential effects on vitamin D status, such as skin color (due to typical genetic differences), dress code and customs (i.e., cultural variables) [1,6,13]. On the other hand, all ethnicities share

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Israel's small geographic size, and are thus subjected to similar environmental exposures (such as ultraviolet radiation). We thus sought to compare vitamin D levels among these three main distinctive ethnic groups living in Israel.

SEASONS IN THE SUNNY REGION AND VITAMIN D

Israel is situated in a coastal area and is characterized by a warm Mediterranean climate that is mostly sunny year round. The sunny weather notwithstanding, due to the country's distance from the equator (latitude 30–33°N), radiation from the sun in the summer is approximately double that in the winter. As sunlight exposure is the key factor in vitamin D synthesis, it is plausible that a winter trough in vitamin D levels may manifest even in this sunny region [10,14]. Furthermore, while high-latitude regions are traditionally associated with inadequate levels of vitamin D, in recent years accumulating reports from various sunny countries demonstrated that this hormone insufficiency is common in tropical and subtropical regions as well. This suggests that vitamin D insufficiency is only partly explained by season and latitude [10-13]. In order to ascertain whether there are seasonal variations in vitamin D levels in Israel, we obtained serum samples in different seasons – summer and winter.

SUBJECTS AND METHODS

We obtained serum samples from 195 healthy Israeli volunteers: 100 females, 95 males. Age was available for most of the subjects (N=191): 21 were under 5 years old (called Infants), 34 were between the age of 5 and 20 (Children), 121 were 20–50 (Adults), and 15 subjects were over 50 (Older Adults).

Ethnic origin was provided by 98 of the subjects, 8 of whom had mixed ethnic origin (i.e., offspring of Ashkenazi and Sephardic admixture) and were not included in the final ethnic analysis. Of the remaining 90 subjects, 26 were Ashkenazi Jews, 38 were Sephardic Jews, and 26 were of Arab origin.

SEASONAL ANALYSIS

Definition of 'season' in this region of the world may follow a three-season model, with February-May as spring, June-September as summer, and October-January as winter (i.e., combining autumn and winter into a single "cold" season, more accurately reflecting the actual changing of the temperatures in this region). The serum samples of 58 of the subjects were collected during two distinct seasons for the purpose of comparing vitamin D status, 35 of which were collected in the winter months (between November and January) and 23 in the summer months (between June and July).

VITAMIN D MEASUREMENT

We used the commercial kit LIAISON® 25(OH)D Assay (DiaSorin, Italy) to measure serum concentration of 25(OH) D in sera. The method for quantitative determination of 25(OH)D is a direct, competitive chemiluminescence immunoassay. Specific antibody to vitamin D is used for coating magnetic particles (solid phase) and vitamin D is linked to an isoluminol derivative. During the incubation, 25(OH)D is dissociated from its binding protein and competes with labeled vitamin D for binding sites on the antibody. After the incubation, the unbound material is removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescent reaction is initiated. The light signal is measured by a photomultiplier as relative light units (RLU) and is inversely proportional to the concentration of 25(OH) D present in calibrators, controls, or samples.

As different investigators defined the normal lower limit in the serum as 25(OH)D levels below 12 ng/ml (30 nmol/L) or below 20 ng/ml (50 nmol/L) [1,10], in the present study we defined vitamin D deficiency as levels of 25(OH)D below 15 ng/ml. Vitamin D insufficiency was defined as levels below 30 ng/ml (75 nmol/L) [1].

STATISTICAL ANALYSIS

Comparison of prevalence rates (i.e., vitamin D deficiency and insufficiency percentages) between groups was performed by the chi-square test or Fisher exact test (two-tailed), as appropriate. Continuous variables are expressed as mean ± standard deviation. A two-tailed ANOVA was performed for comparison of vitamin D levels between groups. The Bonferroni correction was applied in cases of multiple comparisons. For all tests P values < 0.05 were considered statistically significant and the StatSoft-STATISTICA (v6.0) software was used for all analyses.

RESULTS

Serum vitamin D (25(OH)D) levels were normally distributed around a mean value of 22.9 ± 10.1 ng/ml for the entire cohort [Figure 1]. Of the 195 subjects who participated in this

Figure 1. Distribution of vitamin D levels among 195 healthy Israeli subjects

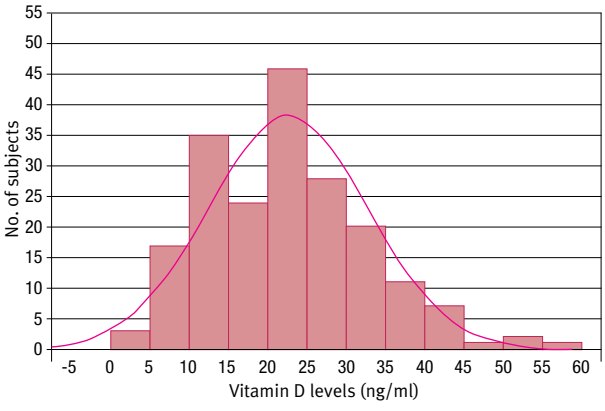

Table 1. Comparison of vitamin D status according to age

Age/Vitamin D status	All (n=191)	Infants: Age < 5 yrs (n=21)	Children: Age > 5 and < 20 yrs (n=34)	Adults: Age > 20 and < 50 yrs (n=121)	Older adults: Age > 50 yrs (n=15)	*P* value
Vitamin D level (ng/ml) (mean ± SD)	22.9 ± 10.1	28.6 ± 13.54*	22.53 ± 9.09	22.56 ± 9.66	17.8 ± 7.81	0.05*
Prevalence of vitamin D insufficiency (< 30 ng/ml)	149 (78%)	11 (52.4%)#	27 (79.4%)	98 (80.1%)	13 (86.7%)	< 0.05#
Prevalence of vitamin D deficiency (< 15 ng/ml)	52 (27.2%)	4 (19%)	9 (26.5%)	33 (27.3%)	6 (40%)	NS

*Vitamin D mean levels in infants were higher than in older age groups ($P < 0.05$)
#The prevalence among infants was lower than in older age groups ($P < 0.05$)
NS = No significant differences ($P > 0.05$)

study 149 (78%) had insufficient vitamin D levels (< 30 ng/ml), and among them 52 (27% of the entire cohort) suffered from vitamin D deficiency (< 15 ng/ml).

Comparison of vitamin D levels between different age groups showed that vitamin D status was better (i.e., higher mean levels and lower insufficiency rates) among infants (age < 5 years old) than in older age groups [Table 1]. While vitamin D levels declined and insufficiency rates rose as the age increased, these differences did not reach statistical significance for subjects older than 5 years of age (i.e., when comparing children, adults and older adults).

Comparison by gender of subjects under the age of 20 showed that the vitamin D insufficiency percentage among girls was significantly higher than among boys ($P < 0.05$), and the girls' vitamin D levels were lower than those of the boys ($P = 0.06$) [Table 2]. On the other hand, comparison by gender for the entire cohort (i.e., including adults, age > 20) did not yield significant differences in vitamin D status between males and females.

Table 2. Comparison of vitamin D status by gender according to age group

Gender/Vitamin D status (all ages)	Male (n=95)	Female (n=100)	*P* value
Vitamin D level ng/ml (mean ± SD)	23.8 ± 10	21.4 ± 10.4	NS
Prevalence of vitamin D insufficiency (< 30 ng/ml)	71 (74.8%)	82 (82%)	NS
Prevalence of vitamin D deficiency (< 1 5ng/ml)	23 (24.2%)	32 (32%)	NS
Gender/Vitamin D status (ages < 20 yrs)	**Boys (n=29)**	**Girls (n=26)**	***P* value**
Vitamin D level (ng/ml) (mean ± SD)	27.57 ± 11.27	21.82 ± 10.7	0.06
Prevalence of vitamin D insufficiency (< 30 ng/ml)	16 (55.2%)	22 (84.6%)	< 0.05
Prevalence of vitamin D deficiency (< 15 ng/ml)	7 (24.1%)	6 (23.1%)	NS

NS= No significant differences ($P > 0.05$)

As detailed above, we attempted to compare the vitamin D status of three distinct ethnic groups in Israel [Table 3]. A significant gradient was evident, as Ashkenazi Jews had higher vitamin D levels (and lower insufficiency rates) than Sephardic Jews, who in turn had higher vitamin D levels (and lower insufficiency rates) than Israeli Arabs ($P < 0.05$). Of note, this ethnic gradient was even more pronounced when the analysis was performed in the adult age groups (i.e., ages > 20 and < 50) [Table 3].

Table 3. Comparison of vitamin D status by ethnicity according to age

Ethnic origin/ Vitamin D status (all ages)	Ashkenazi Jews (n=26)	Sephardic Jews (n=38)	Arabs (n=26)	*P* value
Vitamin D level (ng/ml) (mean ± SD)	31.4 ± 11.7	24.1 ± 10.3	17.6 ± 9.5	< 0.05*
Prevalence of vitamin D insufficiency (< 30 ng/ml)	14 (53.8%)	29 (76.3%)	22 (84.6%)	< 0.05#
Prevalence of vitamin D deficiency (< 15 ng/ml)	3 (11.5%)	8 (21.1%)	12 (46.2%)	< 0.05##
Ethnic origin/ Vitamin D status (ages > 20 and < 50 yrs)	**Ashkenazi Jews (n=17)**	**Sephardic Jews (n=21)**	**Arabs (n=17)**	***P* value**
Vitamin D level (ng/ml) (mean ± SD)	31.3 ± 10.2	21.4 ± 8.3	15.9 ± 8.9	< 0.05*
Prevalence of vitamin D insufficiency (< 30 ng/ml)	9 (52.9%)	18 (85.7%)	16 (94.1%)	< 0.05#
Prevalence of vitamin D deficiency (< 15 ng/ml)	1 (5.9%)	6 (28.6%)	10 (25.3%)	< 0.05#

* Vitamin D mean levels in Ashkenazi Jews > Sephardic Jews > Arabs ($P < 0.05$ for each comparison)
#Prevalence among Ashkenazi Jews < Sephardic Jews < Arabs ($P < 0.05$ for each comparison)
##Prevalence among Ashkenazi and Sephardic Jews < Arabs ($P < 0.05$)

Finally, we compared vitamin D status between serum samples collected during the winter season and samples collected during the summer season in Israel (as detailed above). Vitamin D mean levels (21.6 ± 8 vs. 23.9 ± 8 ng/ml), insufficiency rates (82.9% vs. 82.6%) and deficiency rates (22.9% vs. 21.7%) were similar in the winter season and summer season respectively ($P > 0.05$ for all comparisons).

DISCUSSION

A low serum vitamin D level (< 30 ng/ml) is a worldwide predicament, ranging from 30% to over 80% in various populations [1,2,9]. Traditionally, vitamin D insufficiency has been mainly associated with high latitude and is attributed to reduced ultraviolet radiation exposure in regions far from the equator [3]. However, recent studies show that this problem is not limited to sun-deprived areas of the world but is also common in sunny regions such as Florida (USA), Turkey, New Zealand, Australia, Brazil, India, Lebanon, Tunisia, Jordan and Saudi Arabia [10-13]. In accordance, this study found that 78% of the healthy subjects living in Israel, a sunny Mediterranean country, have suboptimal vitamin D serum levels, and 27% are vitamin D deficient. The mean vitamin D level for the entire study population (22.8 ± 10 ng/ml) was found to be in the range considered to be insufficient (< 30 ng/ml) for maintenance of optimal health [1,16].

The insufficiency status in the present study was somewhat milder among infants under 5 years old when compared with that of older subjects. Similar findings were recently reported by large demographic analyses conducted in the U.S. [8]. Historically, vitamin D deficiency in young children was commonly associated with rickets. For this reason, since the early 20th century, it has been common for infants in industrial countries to receive preventive treatment against vitamin D deficiency [1]. Plausibly, this widespread nutritional supplement accounts for the observed lower deficiency rates in younger Israeli children. Of note, despite the fact that vitamin D insufficiency might be less prevalent among infants, we found that even in this population over 50% of the subjects had suboptimal levels of vitamin D in the serum. In other words, the lower prevalence in this age group may perhaps be only relative to the exceptionally high occurrence of vitamin D deficiency that we found among the general older population.

Another population that is traditionally considered at risk for vitamin D deficiency is the elderly, especially postmenopausal women. In this study, while the age gradient related to a somewhat lower level of vitamin D and higher occurrence of vitamin D insufficiency and deficiency, it failed to reach statistical significance. The lack of a clear age gradient could be attributed to either the recent policy of vitamin D supplementation for the elderly (due to their tendency to suffer from osteoporosis), resulting in higher vitamin D levels among this population [9,16], or is due to the lowering of vitamin D levels in the younger general population [1,9]. This result is consistent with a large demographic analysis recently conducted in the U.S. by Ginde et al. [6], showing that age differences that existed in the National Health and Nutrition Examination Survey (NHANES III) conducted during 1988 through 1994 were attenuated in the NHANES study 2001–2004. It was suggested that this trend might be due to a radical drop in vitamin D levels across all age groups [6]. On the other hand, when testing the elderly population in England, Hirani and co-authors [9] found that the odds of hypovitaminosis D significantly increased by age group, as it was lower among those aged 75–79 in comparison to those aged 85 and older. Unfortunately, these advanced age groups were not tested in our study due to the relatively small number of elderly participants (15 subjects over the age of 50), none of whom were over 65. Recently, Ish-Shalom et al. [17] conducted a study among elderly hip fracture patients in Israel (mean age 81 ± 9). Although the aim of the study was to assess different dosing protocols of vitamin D supplementation, they found that the baseline serum 25(OH)D concentration of study subjects was 15.7 ± 9 ng/ml, only slightly lower than the values among subjects aged 50–65 in the current study. Thus, future studies should confirm whether indeed the elderly in Israel have an especially alarming vitamin D status.

Gender differences in vitamin D status, which are commonly assumed to exist, seem to have diminished in recent years [6,18]. On the one hand we found that young females (under the age of 20) had lower vitamin D levels than males of the same age group. Similar results were recently shown by Mansbach et al. [8] in a demographic analysis of U.S. children. On the other hand, we also found that these gender differences attenuated with age in our study population. This finding is in accordance with the findings of the earlier mentioned NHANES study among the non-juvenile population [6], as differences by gender detected during NHANES III (1988-1994) equalized during NHANES 2001–2004. To the best of our knowledge, the possible effect of age on gender differences in vitamin D status has yet to be reported in a single-study population.

In its 60 years of existence, Israel has become a melting pot for Jews from different countries around the globe. Genetic differences between Ashkenazi Jews of European and North American origin, and Sephardic Jews of North African, Middle Eastern and Asian origin are commonly demonstrated by different genetic disorders typical to each group [19]. Moreover, DNA tests have demonstrated substantially less intermarriage in most of the various Jewish ethnic groups over the last 3000 years than in other populations [20]. Although the different ethnic groups originally practiced

NHANES = National Health and Nutrition Examination Survey

different customs, this is no longer the case in modern-day Israel. The secular Jewish population today shares a similar dress code, type of housing, diet and customs. For this reason, Israel represents a unique opportunity to examine genetic differences. The window of opportunity for such studies is rapidly closing, since inter-ethnic marriages are becoming increasingly common, progressively diluting the historical genetic isolation of the different Jewish groups.

Comparing the vitamin D levels between the Jewish ethnic groups, this study shows a much more severe status of vitamin D among Sephardic Israelis when compared to Ashkenazi Israelis. Phenotipically, Sephardic Jews are characterized by a darker skin pigmentation than that of Ashkenazi Jews. In dark skin individuals, melanin absorbs ultraviolet B radiation, resulting in reduced skin synthesis of vitamin D [1,15]. Indeed, studies from northern hemisphere regions suggest that darker skin ethnic groups suffer more from vitamin D insufficiency than lighter skin populations in the same geographic region [3,6,15]. Our study proposes that darker skin pigmentation may also have negative outcomes on vitamin D status in sunny regions; however, other genetic influences besides phenotypic skin pigmentation cannot be ruled out.

Israeli Arabs are typically of dark skin complexion. However, they also differ from the previously described two Jewish ethnicities in terms of several cultural factors. A significant proportion of the Israeli Arab population lives in all-Arab villages, most of which are located outside the main Israeli urban area, and traditionally wears long-sleeved clothes (especially the women). Studies from several Arab countries in the Middle East have similarly reported a high prevalence of vitamin D insufficiency, in the range of 50–97%. These findings have been attributed mainly to the customary clothing that covers almost the entire body [1,13]. Thus, it is plausible that this specific cultural factor joins the phenotypic dark pigmentation and other (unexplored) genetic factors, suggesting that the Israeli Arab ethnic group has the lowest levels of vitamin D and the highest prevalence of vitamin D insufficiency (94%) of all three ethnicities studied here.

Of note, it was previously hypothesized that there may be an association between the fact that African and Hispanic Americans, having a markedly higher prevalence of vitamin D insufficiency (when compared with Caucasian Americans), also have a higher incidence and worse outcomes for cardiovascular disease, certain cancers, diabetes mellitus, systemic lupus erythematosus, and renal disease, all of which have been linked to vitamin D insufficiency [3,6,21]. Similarly, it seems that Israelis of Ashkenazi origin develop coronary artery disease later in life than other ethnicities living in Israel [22], and that Israelis of Sephardic origin are more susceptible to stroke and diabetes when compared with Ashkenazi Israelis [23]. Furthermore, recent evidence suggests that Arab Israelis carry the highest risk of cardiovascular morbidity as well as diabetes, when compared to the Jewish residents of Israel [24]. The possible role of vitamin D status in predisposing certain ethnicities living in Israel to certain conditions (associated with diminished levels of this vitamin) warrants further exploration.

Finally, Israel is a country blessed with a climate that is sunny all year round, which implies relatively high levels of ultraviolet B radiation in the winter and double that in the summer. The samples collected in this study during the two distinct seasons were nearly identical in all tested parameters: average vitamin D level, percentage of deficiency and percentage of insufficiency. On both occasions (i.e., in both seasons) the samples revealed a strong tendency towards suboptimal levels of vitamin D. Due to the small sampling group (samples from 58 subjects obtained in the two seasons) these results suggest that there is no significant seasonality in vitamin D levels in Israel. This finding stands in contrast to data gathered in high-latitude countries, where undetectable amounts of ultraviolet radiation in the winter (due to the distance from the equator) significantly lowers vitamin D serum levels [15]. Nonetheless, other studies conducted in sunny areas are inconclusive regarding the season's influence on vitamin D levels in the serum [10,11]. In these regions, the major effect on vitamin D levels seems to come from vitamin D supplementation, long-sleeved clothing, outdoors lifestyle, and use of sunscreen [1,12,14,25]. These variables are relevant to Israel, where a sharp increase in malignant melanoma in previous years has raised public awareness, leading to a dramatic increase in sunscreen use and avoidance of sun exposure, especially during the summer months. In light of these preliminary results, further study should examine the possibility that in Israel vitamin D insufficiency in the summer is indeed as common and as worrying as in the winter.

CONCLUSIONS

Vitamin D deficiency was historically considered to be rare in sunny Israel. Consequently, vitamin D testing is not routinely performed. The results of our study suggest that vitamin D insufficiency may be widespread across all ages, ethnic groups, genders and seasons in this country. Demographic variance was evident, as the youngest age group (i.e., infants) displayed better vitamin D status than the elders. Israeli Arabs seemed especially at risk for hypovitaminosis D, followed by Israelis of Eastern (Sephardic) origin. Israelis of European (Ashkenazi) descent seemed to be the only group with adequate mean vitamin D serum levels, though in this group as well most of the subjects had suboptimal serum levels of this vitamin.

The findings of this study, while raising serious concerns regarding the vitamin D status of the Israeli population and particularly of specific ethnic groups, should be interpreted

as preliminary due to the modest sample size and lack of data on the nutritional status of the subjects. Nevertheless, on the basis of our results, a larger scale population-based screening endeavor seems justified to confirm whether a considerable proportion of the dwellers of this sunny region could benefit from vitamin D supplementation. Considering that vitamin D enrichment of dairy products is routine in most Western countries, even sunny ones, perhaps it is time to adopt this simple means of supplementation in Israel as well.

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