Vitamin D Status among Israeli Medical Residents

Hadar Moran-Lev MD[1,3], Dror Mandel MD[2,3], Yosef Weisman MD[1], Amit Ovental MD[2,3] and Ronit Lubetzky MD[1,3]

Departments of [1]Pediatrics and [2]Neonatology, Dana–Dwek Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT: **Background:** Israel is a country with a sunny climate; however, vitamin D deficiency and insufficiency are common findings in certain populations whose exposure to sunlight is limited. Medical residency is known for long indoor working hours, thus theoretically limiting the opportunities for sun exposure.
Objectives: To evaluate whether the vitamin D status among residents in a single medical center in Tel Aviv is below the normal range.
Methods: Forty-six residents (28 females, 18 males, average age 33.9 ± 2.8 years) in three residency programs (internal medicine, general surgery/obstetrics and gynecology, pediatrics) were recruited. Demographic data, personal lifestyle, physical activity details and sun exposure duration were obtained by a questionnaire. Serum levels for 25(OH)D were analyzed by a radioimmunoassay.
Results: The mean serum 25(OH)D concentration was 29.8 ± 5.8 ng/ml. According to Institute of Medicine definitions, none of the residents were vitamin D deficient and only two residents (4%) were vitamin D insufficient (15 ng/ml each). The level of 25(OH)D was similar among the various medical specialties. The 25(OH)D levels correlated with the duration of sun exposure and the number of offspring (regression analysis: $R^2 = 9.2\%$, $P < 0.04$ and $R^2 = 8.9\%$, $P < 0.04$, respectively), but not with nutritional data, blood chemistry, or extent of physical activity.
Conclusions: Most of the residents maintained normal or near normal 25(OH)D levels, indicating that the residency program itself did not pose a significant risk for vitamin D deficiency.

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KEY WORDS: vitamin D, 25(OH)D, medical residents' health, sun exposure, occupational medicine

Israel is a country with a sunny climate, but vitamin D deficiency and insufficiency can still be found among certain populations, such as Orthodox Jews [1], Bedouin [2], elderly people [3] and workers in the high tech industry [4], mainly due to their limited exposure to sunlight [5,6]. In 2010, Oren et al. [7] found that vitamin D insufficiency was common in the general population in Israel. Since vitamin D deficiency is a widespread entity, experts suggest screening for serum vitamin D among those at highest risk for deficiency to decrease the morbidity related to vitamin D deficiency [8]. Medical residency is known for long indoor working hours, thus limiting the opportunities for sun exposure. Therefore, we assumed that medical residents may also be at risk for vitamin D deficiency.

Serum 25(OH)D is the most abundant circulating metabolite of vitamin D. Serum 25(OH)D levels are determined mainly by exposure to sunlight rather than by dietary intake of vitamin D [9]. Almost all vitamin D produced in the skin or obtained from food or supplements is converted in the liver to 25(OH)D. Moreover, the serum half-life of 25(OH)D is nearly 2–3 weeks, thus measurement of 25(OD)D serum levels is a sensitive index of an individual's vitamin D status [10].

The aim of the present study was to measure serum 25(OH)D levels in Israeli medical residents and to examine whether vitamin D deficiency and insufficiency are common finding in this group.

PATIENTS AND METHODS

STUDY POPULATION AND DESIGN

This study was conducted in a single medical center located in Israel, which has a typical Mediterranean climate with small seasonal variation and about 300 sunny days per year. We recruited 46 medical residents who volunteered to participate in the study during May 2015. Of these residents, 28 (61%) were from the Department of Pediatrics, 7 (16%) from the Department of Internal Medicine, and 11 (23%) from Department of General Surgery (including obstetrics and gynecology). The study comprised 28 females and 18 males, mean age was 33.9 ± 2. 8 years (range 28–42 years). All participants were Caucasian non-Orthodox Jews. Exclusion criteria were a medical history of liver, renal, or metabolic bone diseases; clinically apparent malabsorption syndrome; obesity; use of vitamin D supplements or drugs known to affect vitamin D metabolism (e.g., anticonvulsants, glucocorticoids, diuretics); and pregnancy or nursing.

The study protocol was approved by the institutional review board and all participants provided written informed consent.

NUTRITIONAL AND LIFESTYLE QUESTIONNAIRES

All participants completed a validated questionnaire that was adjusted to our study and was designed to retrieve socio-demographic data (i.e., age, gender, marital status, number

of offspring), general health information (including medicine and supplement usage), anthropometric measurements (e.g., weight, height and body mass index), dietary intake, sun exposure, personal lifestyle, and working hours on weekdays and weekends. Specific personal lifestyle items included questions on smoking, physical activity (e.g., at least 90 minutes per week of physical exercise, for example in a gym, jogging, Pilates). Sun exposure-related factors (e.g., outdoor activities, skin type, use of sunscreen and sunglasses, and the extent of dress cover for religious reasons or for ultraviolet protection) were recorded and scored [11]. Dietary data included a standard food frequency questionnaire on dietary habits and consumption of foods with high levels of vitamin D (e.g., milk, cheese, fish, meat and cereals). Mean total vitamin D intake was estimated from the mean dietary intake [12]. A blood sample for 25(OH)D, electrolyte (calcium, phosphate), C-reactive protein, lipid profile and liver enzymes (alkaline phosphatase) was obtained from all participants.

LABORATORY EVALUATION

The concentration of 25(OH)D was measured by a radioimmunoassay commercial kit (25-Hydroxyvitamin D[125I] RIA kit, 68100E, DiaSorin, Via Crescentino, Italy), a method with a sensitivity of 1.5 ng/ml and coefficient of variance of 8.1% according to the manufacturer. Sera were separated and frozen at -20ºC until analyses were performed. Blood chemistry was measured by standard laboratory methods.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Minitab software version 16 (Minitab Inc, State College, PA, USA). Continuous variables were reported either by means and standard deviations, or by the median and the interquartile range.

Kruskal–Wallis test by ranks was used to compare characteristics and laboratory data about the three medical specialties. Regression analysis was performed to study potential correlations between vitamin D levels of the entire cohort and epidemiological and lifestyle parameters (i.e., duration of sun exposure, number of offspring, nutritional intake, smoking status, extent of physical activity or metabolic indices). A P value of 0.05 was considered significant.

RESULTS

Characteristics of all participants are presented in Table 1. Mean length of time into the residency program was 2.5 ± 1 years (range 0.5–5 years), mean number of working hours in a week was 64.57 ± 7.4 (range 50–70 hours), including 2.2 ± 0.6 hours during weekend shifts in the preceding month (range 0–4 days). Of the residents, 32 (69%) were married and 27 (58%) had children (two of the parents were not married) We found no significant differences among the three medical specialties in

terms of age, gender, marital status, number of offspring, smoking status and exposure to sun on weekdays. Surgical residents reported to work the longest hours, were more physically active and were less exposed to sun during weekends. ($P < 0.001$, $P = 0.03$, $P = 0.02$, respectively). However, there was no significant difference between the residents' 25(OH)D level and field of specialty ($P = 0.89$, Table 2).

The cohort's mean ± SD 25(OH)D level was 29.76 ± 5.79 ng/ml (range 15–40 ng/ml). The mean ± SD 25(OH)D level of the pediatric residents, the internal medicine residents and surgery residents was 29.86 ± 5.7 ng/ml, 29.86 ± 5.7 ng/ml and 30.2 ± 5.2 ng/ml, respectively. According to the Institute of Medicine (IOM) definitions [13], only two residents were vitamin D insufficient (15 ng/ml each) and the others had normal levels of 25(OH)D. However, according to the Endocrine Society definitions, these two residents were vitamin D deficient, and another 14 residents (30%) were vitamin D insufficient (25(OH)D with levels between 20 and 30 ng/ml [8]. The levels of the biochemical tests were within the normal range except for hypertriglyceridemia in five participants (10%) residents [Table 2].

The vitamin D levels of the entire cohort correlated with the average duration of sun exposure and the number of offspring ($R^2 = 9.2\%$, $P < 0.04$, and $R^2 = 8.9\%$, $P < 0.04$, respectively). Finally, we found no significant correlation between vitamin D level and nutritional intake, smoking, extent of physical activity or metabolic indices (level of LDL, HDL, triglyceride and CRP).

DISCUSSION

Vitamin D is traditionally associated with systemic calcium homeostasis and bone mineralization, as well as many non-classic biologic actions, such as assisting in gene regulation and having a significant role in the modulation of cell proliferation, differentiation and apoptosis in many normal and cancer cells [14,15]. Recent data have demonstrated an association between vitamin D status and the prevalence of extra skeletal diseases, such as cancer, cardiovascular diseases and autoimmune diseases [16-19], emphasizing the importance of maintaining normal vitamin D levels for good overall health. The demonstration of subjects with serum 25(OH)D levels > 30 ng/ml being at lowest risk for such diseases has led the Endocrine Society to a revised definition of vitamin D deficiency and insufficiency: vitamin D deficiency is currently defined as serum 25(OH)D levels < 20 ng/ml (50 nmol/l) and vitamin D insufficiency is defined as serum 25(OH)D levels < 30 ng/ml (75 nmol/l) [8]. In contrast, the IOM, a division of the American National Academy of Science, indicated that serum 25(OH)D levels > 20 ng/ml are enough to sustain normal calcium absorption and bone density as well as to minimize the risk of osteomalacia and rickets and that there is no evidence base to establish the optimal level of 25(OD)D > 20 ng/ml for extra skeletal diseases [13].

The debate in the vitamin D research community between those who support the IOM definitions of vitamin D deficiency and insufficiency and those who support the Endocrine Society's definition is still going on [20] and analysis of the results from recent studies, including the present study, shows that emerging conclusions may be different depending on whether the IOM or Endocrine Society's definition is used.

In the present study two residents had vitamin D levels that were below the recommended norm. However, analysis of serum 25(OH)D according to the Endocrine Society's definition, categorized 14 other residents (30%) as being vitamin D insufficient.

Our results are somewhat different from those of other studies that addressed this population in Israel and abroad [21-23]. Mendoza et al. [21] studied house staff physicians in Mexico City, an area located in a more southern latitude that is known to have more seasonal variation. Their results showed that vitamin D and calcium levels were significantly lower among medical residents compared to controls (16.9 ± 5.1 vs. 21.5 ± 7.1 ng/ml) . No differences were found within the two groups in metabolic indices (such as glucose insulin and low-density lipoprotein cholesterol levels) except for an inverse correlation between triglyceride concentration and vitamin D ($R = 0.31$, $P = 0.04$). In our study, hypertriglyceridemia did not correlate with low vitamin D level, presumably due to the small sample size of vitamin D deficient participants.

In a study by Haney and colleagues [22] on residents living in the U.S. state of Oregon, 20% of the participants had vitamin D deficiency, with 25(OH)D levels < 20 ng/ml. The differences between their results and ours may be attributed to the differences in the number of sunny days in Israel vs. Oregon, a state located at more northern latitude than Israel. The results from Munter and co-authors [23] revealed vitamin D deficiency, with 25(OH)D < 20 ng/ml, in 77% of the cohort of comparable residents in Jerusalem. Importantly, 49% of their cohort was religious and 21% were from different ethnic origins, both known as having independent risk factors for vitamin D deficiency [24]. This finding may support our assumption that vitamin D levels are more related to lifestyle aspects (such as religious dress code), geographical area of living and family structure, which may change the habits in the leisure time and hence the sun exposure, rather than to the medical residency time period itself.

The strength of our study is its prospective design. However, our study is limited by recruitment of participants at a single institution, the relatively small number of subjects and the lack of a control group, which was not recruited since our aim was to compare the vitamin D levels to the established recommended norms.

CONCLUSIONS

Vitamin D deficiency is not a common finding in medical residents from the Tel Aviv area. However, because 25(OH)D levels > 30 mg/ml may reduce the risk of extraskeletal disease, targeting to such levels may be of benefit.

Table 1. Participants' demographic characteristics

Characteristic	All residents (N=46)	Pediatrics (N=28)	Internal medicine (N=7)	Surgery/ obstetrics & gynecology (N=11)
Age (years) (range)	33.9 ± 2.8 (28–42)	33.5 ± 1.9 (31–39)	34.4 ± 3.4 (28–41)	35 ± 4.4 (30–42)
Gender (female:male)	28:18	20:8	5:2	2:9
Years into residency program (range)	2.5 ± 1 (0.5–5)	2.2 ± 1.1 (0.5–5)	2.8 ± 0.6 (1–5)	2.8 ± 1.2 (0.9–5)
Working hours per week (range)	64.6 ± 7.4 (50–70)	62.1 ± 4.1 (60–70)	59.2 ± 6.6 (50–70)	74.1 ± 6.0[c] (60–80)
Weekends shifts[a] (range 0–4)	2.2 ± 0.6 (0–4)	2.1 ± 0.47 (2–4)	2 ± 1 (2–3)	2.5 ± 0.5 (0–3)
Marital status (% married)	32 (69)	22 (78)	4 (57)	6 (54)
Number of children (range)	1 ± 0.98 (0–3)	1.2 ± 1 (0–3)	0.71 ± 0.95 (0–2)	0.54 ± 0.8 (0–2)
Physically active (%)[b]	26 (56)	13 (46)	3 (42)	10 (90)[d]
Smoker (%)	10 (21)	8 (28)	0	2 (18)
›1 hour sun exposure per week, n (%)	37 (80)	22 (78)	6 (86)	9 (81)
‹1 hour sun exposure per weekend, n (%)	14 (30)	4 (14)	3 (42)	7 (63)[e]

Values are given ± standard deviation unless otherwise indicated
[a]Weekend shifts during the preceding month
[b]At least 90 minutes per week of actual exercise (e.g., in a gym, jogging outside, Pilates)
[c]$P < 0.001$
[d]$P = 0.03$
[e]$P = 0.02$

Table 2. Laboratory data of the participants recorded as number ± standard deviation (range)

Subjects	All residents (N=46)	Pediatrics (N=28)	Internal medicine (N=7)	Surgery/obstetrics & gynecology (N=11)	P value
25(OH)D (ng/ml)	29.76 ± 5.8 (15–40)	29.86 ± 5.7 (15–40)	29.86 ± 5.7 (15–40)	30.2 ± 5.2 (22–40)	0.89
Calcium (mg/dl)	9.5 ± 0.3 (9.5–10.2)	9.48 ± 0.3 (9–10.2)	9.4 ± 0.29 (9–9.8)	9.6 ± 0.23 (9.2–10)	0.2
Phosphorous (mg/dl)	3.56 ± 0.5 (2.8–4.6)	3.57 ± 0.5 (2.8–4.6)	3.8 ± 0.3 (3.2–4.3)	3.3 ± 0.5 (2.8–3.8)	0.07
LDL (mg/dl)	94.6 ± 22.2 (58–159)	93.88 ± 25.8 (58–159)	87.43 ± 5.6 (77–94)	101.09 ± 19.3 (73–131)	0.24
HDL (mg/dl)	56.25 ± 18.4 (32–110)	58.35 ± 19.1 (32–110)	61.2 ± 23.6 (32–90)	48.09 ± 10.6 (33–70)	0.28
Triglyceride (mg/dl)	100.2 ± 62.2 (39–295)	84.58 ± 43.1 (39–203)	140.9 ± 108.4 (48–295)	111.3 ± 55 (46–216)	0.26
ALP (U/l)	61.2 ± 17.2 (26–125)	60.6 ± 12.4 (42–83)	60.7 ± 31.1 (26–125)	63 ± 18.5 (31–93)	0.27
CRP (mg/dl)	1.71 ± 2.7 (0.06–14)	1.9 ± 3.1 (0.06–14)	2.03 ± 3.02 (0.06–8.2)	0.9 ± 0.9 (0.07–2.34)	0.55

25(OH)D = 25-hydroxyvitamin D, LDL = low-density lipoprotein,
HDL = high-density lipoprotein, ALP = alkaline phosphatase, CRP = C-reactive protein

Correspondence
Dr. H. Moran-Lev
Dept. of Pediatrics, Dana–Dwek Children's Hospital, Tel Aviv Sourasky
Medical Center, Tel Aviv, 6423906 Israel
Phone: (972-3) 697-4271
Fax: (972-3) 697-4547
email: hadarm@tlvmc.gov.il

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Capsule

A more pathological amyloid-β oligomer

Amyloid-β (Aβ) oligomers promote the aggregation of the cytoskeletal protein tau, which is associated with neuronal death and impaired cognition in neurodegenerative disorders, including Alzheimer's disease. Various oligomeric forms of Aβ emerge at different stages of the disease. Amar et al. found that the 56-kDa oligomer Aβ*56, but not Aβ dimers or trimers, stimulated Ca^{2+} influx, which triggered the phosphorylation and aggregation of tau in mice and neurons. The findings suggest that targeting this specific amyloid form may prevent the tau pathology underlying Alzheimer's disease.

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Eitan Israeli

Capsule

Small molecules to target parasite organelle

The glycosome is a peroxisome-like organelle that packages glycolytic enzymes of the parasites that cause sleeping sickness, Chagas disease, and leishmaniases. Dawidowski and co-authors designed small-molecule inhibitors to disrupt interactions between two of the proteins involved in peroxisome biogenesis (PEX5 and PEX14), which permit import of glycosomal matrix proteins from the cytoplasm. The small peptide-mimicking molecules kill the trypanosome parasites by causing metabolic collapse without interfering with human PEX homologs. Preliminary studies in mice confirmed an anti-parasitic effect.

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Eitan Israeli