Vitamin D status and hypercholesterolemia in Spanish general population

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Low serum 25-hydroxyvitamin D [25(OH)D] levels have been associated with increased prevalence of cardiovascular diseases. A possible relation between lipids and 25(OH)D might explain this association. This investigation aimed to determine the association between vitamin D and cholesterol, as well as the influence of statins on this association. This was a cross-sectional population-based study with 177 subjects aged 18–84 years. We collected demographics and data on sun exposure, sun protection habits, current medication including lipid-lowering drugs, and estimated vitamin D intake. Serum measurements included levels of 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting glucose. The mean 25(OH)D level was 24 ± 9 ng/ml. Young age ($P = 0.04$) and spending more than 1 h outdoors ($P = 0.04$) were independently associated with higher 25(OH)D levels. The 25(OH)D concentrations correlated negatively with total cholesterol ($P = 0.01$) and LDL cholesterol ($P = 0.04$) levels. The adjusted OR for total cholesterol > 200 mg/ml was 2.8 (range, 1.1–7.5). Receiving statins was associated with higher 25(OH)D levels ($P = 0.04$). In conclusion, this study supports an association between 25(OH)D levels and cholesterol. Further studies are required to explain this association.

Background

Although vitamin D can be obtained from diet or supplements, exposure to sunlight is the main source of this vitamin.[1] Solar UV radiation penetrates the skin and converts 7-dehydrocholesterol (7DHC) into previtamin D_3, which is rapidly transformed into vitamin D_3. Vitamin D from diet and from skin is hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D], the main determinant of vitamin D status. It is then metabolized in the kidneys in its active form, 1,25-dihydroxyvitamin D, in a tightly regulated process controlled by plasma parathyroid hormone (PTH) levels and serum calcium and phosphorus levels, among others.

Health promotion messages to limit UV exposure may lead to a growing prevalence of inadequate vitamin D status.[2] Low 25(OH)D levels have been linked to several conditions beyond a critical role in the development of osteoporosis. Vitamin D insufficiency has been associated with type 1 and type 2 diabetes, multiple sclerosis, autoimmune diseases, and infectious diseases.[1] Recently, researchers have identified vitamin D insufficiency as a possible risk factor for cardiovascular diseases, either directly or through a relation with other cardiovascular risk factors, including diabetes, hypertension, or obesity.[3-5] The effect of vitamin D status on serum lipids is especially interesting considering that vitamin D and cholesterol share a common precursor, 7DHC, although previous studies yielded divergent results.[3] The aim of this study was to investigate the association of vitamin D status with lipid profile, particularly on cholesterol levels.

Results

Of the 177 subjects who participated in this study, 132 (75%) were females. Their mean age was 47 ± 13 y and 40% of the participants were smokers. Sixteen percent of participants were obese (body mass index [BMI] > 30) and mean BMI was 25.3. **Table 1** summarizes baseline characteristics of all participants according to serum 25(OH)D tertiles. The lipid-lowering therapies considered were (n, mean daily dose) atorvastatin (6, 35 mg), simvastatin (3, 23 mg), fluvastatin (2, 40 mg), and pravastatin (1, 20 mg).

Globally, mean 25(OH)D level was 24 ± 9 ng/ml (to convert to nanomoles per liter, multiply by 2.496), and it was

Table 1. Baseline characteristics of participants according to serum 25(OH)D tertile categories [data expressed as *n* (%) or mean ± SD]

Category	Serum 25(OH)D tertile			p
	I	II	III	
	(< 20.00)	(20.01–27.00)	(> 27.01)	
Participants	61 (35)	54 (31)	62 (35)	0.62
Female sex	50 (82)	36 (67)	46 (74)	0.17
Age (yrs)	48 ± 13	47 ± 13	47 ± 13	0.76
Skin phototype				
1–2	29 (37)	24 (30)	26 (33)	
3	22 (30)	24 (32)	28 (38)	
4	10 (42)	6 (25)	8 (33)	0.81
BMI (kg/m²)	25 ± 4	26 ± 5	25 ± 4	0.51
Sun protection				
Always	27 (44)	18 (29)	17 (27)	
Occasionally	18 (32)	17.(30)	22 (40)	
Never	14 (25)	18 (33)	23 (42)	0.32
Sun exposure (h/d)				
> 2	15 (26)	18 (31)	25 (43)	
1–2	19 (32)	19 (32)	21 (36)	
< 1	26 (44)	17 (32)	16 (26)	0.32
Current smokers	31 (51)	22 (29)	18 (31)	0.11
Vitamin D intake (μg/d)	5.5 ± 3.4	5.5 ± 1.9	5.2 ± 1.8	0.85
Menopause	17 (28)	15 (28)	19 (31)	0.37
Vitamin D supplements	—	7 (13)	6 (10)	0.02
Lipid-lowering drugs	—	4 (7)	8 (13)	0.02
Serum 25(OH)D$_3$ (ng/ml)	15 ± 4	24 ± 2	33 ± 6	0.001
PTH (pg/ml)	46 ± 24	41 ± 15	44 ± 12	0.22
Calcium (mg/dl)	9.5 ± 0.3	9.5 ± 0.4	9.4 ± 0.9	0.51
Total cholesterol (mg/dl)	206 ± 37	205 ± 31	195 ± 10	0.09
HDL cholesterol (mg/dl)	53 ± 12	59 ± 19	54 ± 12	0.18
LDL cholesterol (mg/dl)	129 ± 37	132 ± 28	122 ± 26	0.32
Triglycerides (mg/dl)	106 ± 53	104 ± 78	93 ± 38	0.44
Glucose (mg/dl)	99 ± 15	95 ± 10	97 ± 12	0.36

—, no data.

significantly higher in the youngest age group (18–35 y) (*P* = 0.04) and for those who spent more than 1 h outdoors each day (*P* = 0.04). We detected an increased risk of vitamin D insufficiency (< 30 ng/ml) among smokers (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.00–3.35). Smoking correlated negatively with PTH levels (*r* = −0.24; *P* < 0.001). An inverse correlation existed between 25(OH)D and PTH levels, which reached significance only in nonsmokers (*r* = −0.220; *P* < 0.025).

The 25(OH)D levels correlated negatively with total cholesterol concentrations (*r* = −0.196; *P* = 0.01). This association remained essentially unaltered after adjustment for sun exposure (*P* = 0.03). Their adjusted OR with 25(OH)D < 15 ng/ml for total cholesterol > 200 mg/dl was 2.83 (95% CI, 1.06–7.51) after adjustment for lipid-lowering therapy, age, and smoking. We found no correlation between the 25(OH)D and HDL cholesterol concentrations (*P* = 0.73) or the HDL/LDL cholesterol ratio (*P* = 0.61). Participants with 25(OH)D < 15 presented higher LDL cholesterol levels (125 ± 28 vs. 138 ± 39 mg/dl) (*P* = 0.04) (**Table 2**). No significant association existed between 25(OH)D and BMI (*P* = 0.88) or triglycerides (*P* = 0.29).

Subjects with untreated high cholesterol presented lower 25(OH)D levels than participants without high cholesterol (**Table 3**). The highest serum 25(OH)D levels occurred in high-cholesterol subjects receiving statins (*P* = 0.04). No subjects receiving statins presented total cholesterol of > 200 mg/dl. Those participants being treated with statins displayed similar vitamin D levels, irrespective of whether they achieved their goal of achieving total cholesterol of < 200 mg/dl (28.0 ± 4.1 vs. 28.0 ± 5.9) (*P* = 0.98).

Discussion

The results of this study indicate that vitamin D insufficiency is prevalent in our study population and that living in such a sunny area as Spain does not necessarily guarantee an adequate vitamin D status, even in summer. This fact must be taken into account when recommending sun avoidance in high-risk populations. In agreement with previous studies,[6] we found that elderly people and smokers have insufficient

Table 2. Serum levels of total cholesterol and serum lipoprotein cholesterol fractions (using the cutoff of 15 ng/ml vitamin D deficiency)

Category	25(OH)D (ng/ml)	n	Total cholesterol (mg/dl)	HDL cholesterol (mg/dl)	LDL cholesterol (mg/dl)
All participants	> 15	148	199 ± 33	56 ± 15	125 ± 28
	< 15	25	216 ± 36	54 ± 13	138 ± 39
	p	0.008	0.008	0.64	0.04
With statins	< 15	—			
	> 15	12	190 ± 21	54 ± 9	113 ± 16
	p				
Without statins	< 15	26	218 ± 36	54 ± 13	138 ± 39
	> 15	139	199 ± 33	56 ± 15	125 ± 28
	p	0.009	0.007	0.61	0.22

—, no data.

Table 3. Serum levels of total cholesterol and 25(OH)D (mean ± SD) across cholesterol status and lipid-lowering agents

Serum total cholesterol > 200 mg/dl	Current lipid-lowering therapy	n	25(OH)D (ng/ml) (P = 0.04)	Total cholesterol (mg/dl) (P = 0.23)
No	No	86	24 ± 9	175 ± 17
Yes	No	79	23 ± 9	231 ± 24
Yes	Yes	12	29 ± 4	190 ± 21

vitamin D levels more often than young adults and nonsmokers, even when immunoassay methods—which often overestimate 25(OH)D levels in smokers—are used to measure these levels.[7,8] PTH levels are also lower in smokers because tobacco suppresses the PTH–calcitriol axis.[9] We did not find a significant relationship between BMI and 25(OH)D levels, in contrast to previous studies[3] that reported lower 25(OH)D concentrations in obese subjects. This lack of statistical significance might be due to our study's small number of obese subjects.

Our results suggest that high cholesterol is more frequent in people with lower 25(OH)D levels. This relation cannot be accidental if we consider that cholesterol and vitamin D follow the same metabolic pathway from hydroxymethylglutaryl-coenzyme A (HMG-CoA) to 7DHC. Bogh and colleagues[10] showed that vitamin D synthesis after UVB exposure correlates positively with baseline total cholesterol level. Furthermore, LDL receptor expression in the epidermis is higher in the basal layer, whereas keratinocyte differentiation is accompanied by loss of plasma membrane LDL receptor activity.[11] Notably, vitamin D_3 synthesis occurs mainly in deeper epidermis layers.[12] This finding suggests that LDL cholesterol plays an important role as a precursor of previtamin D, besides de novo biosynthesis. The inverse relation between serum LDL cholesterol and vitamin D status might be explained by a defect in LDL cholesterol uptake by keratinocytes. Therefore, both low levels of 25(OH)D and high levels of LDL cholesterol may be the result of this defect in LDL cholesterol uptake. Our findings coincide with those of previous studies that investigated the relation between vitamin D and cholesterol or metabolic syndrome.[3,13] Some studies found an inverse relation

between serum 25(OH)D and total cholesterol,[14] LDL cholesterol,[14] or triglycerides,[13,14] and a positive association with HDL cholesterol[15,16] and apolipoprotein A1.[17] We found no relation with either triglycerides or HDL cholesterol, although statistical power may have limited our analysis. A common conclusion of all these studies is the association between higher 25(OH)D levels and a better lipid profile, in agreement with our idea of a relation between vitamin D synthesis and cholesterol metabolism. We could not establish the causal relation between cholesterol and 25(OH)D because of the cross-sectional nature of this study. However, vitamin D repletion in clinical trials did not demonstrate a significant effect on cholesterol levels,[18,19] supporting our hypothesis of the influence of skin uptake of cholesterol on vitamin D metabolism. Nevertheless, interventional studies are scarce, heterogeneous, and usually with insufficient doses of vitamin D supplementation.[3,18,20]

Although few participants in our study were being treated with statins, serum vitamin D was significantly higher among those taking statins. Statins inhibit HMG-CoA reductase activity.[21] This enzyme participates in the cholesterol synthesis pathway, which leads to 7DHC synthesis. At the same time, 7DHC can be transformed into cholesterol by the action of 7DHC reductase or into previtamin D by isomerization when people are exposed to UVB radiation. Although one might expect reduced 25(OH)D synthesis with statins, this study shows the opposite, and others have reported similar results.[22-26]

The effect of statins on increasing LDL cholesterol uptake in cells can account for this apparent contradiction. Inhibiting this pathway increases the gradient between cells and the

bloodstream to promote penetration of LDL cholesterol into the cell.[21] Furthermore, statins increase LDL cholesterol receptor expression in the membrane cell.[21,27]

In conclusion, our study yields further evidence for the unfavorable lipid profile among vitamin D–deficient individuals and offers a new possible explanation for this association. Given the prevalence of vitamin D insufficiency and the detrimental consequences of an unfavorable lipid profile, investigation and correction of vitamin D status may be indicated in high-risk populations. Further research needs to be done to establish the effect of vitamin D supplementation on the lipid profile and elucidate the mechanisms that explain the link between vitamin D and lipids.

Patients and Methods

Study design and subjects

This was a cross-sectional study performed in a seaside city in eastern Spain at a latitude of 39°N. We recruited participants from the adults accompanying patients who came to our hospital clinic in the summers during 2008–2010. Exclusion criteria included having a previous diagnosis of renal failure, hyperparathyroidism, familial hypercholesterolemia, preexisting heart disease, taking medication that causes photosensitivity, and pregnancy. Ultimately, 177 individuals participated and gave written informed consent. The hospital's ethics committee approved the study protocol.

We asked study participants to complete an interview with the principal investigator about demographic data, medical history and current medical status, drugs, treatment duration, smoking habits, weight and height (from which we calculated BMI), and Fitzpatrick skin phototype.[28] We recorded sun exposure by estimating the mean number of hours spent outdoors, and we divided subjects into three groups: (1) ≤ 1 h daily, (2) 1–2 h daily, and (3) > 2 h daily. We asked participants about sun protection and sun avoidance in the last month and divided them into three categories: (1) "always" wearing protective clothing or applying sunscreen of factor 15 or above at least 75% of the time, (2) "occasionally" wearing protective clothing or applying sunscreen of factor 15 or above 25–75% of the time, and (3) "never" wearing protective clothing or applying sunscreen of factor 15 or above < 25% of the time. We measured vitamin D intake by using a food frequency questionnaire and self-reported supplemental intake during a visit as part of the study. Participants with high cholesterol were defined as those having a total cholesterol level of > 200 mg/dl and/or those receiving lipid-lowering therapy.

Biochemical measurements

We used a blood test to measure the following levels: 25(OH)D, PTH, calcium, phosphorus, fasting blood glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. We determined 25(OH)D levels by using the Liaison 25OH vitamin D TOTAL (Diasorin Inc., Stillwater, MN, USA), a chemiluminescence immunoassay with an interassay coefficient of variation of 7.0% at 18 ng/ml and 6.3% at 37 ng/ml. We measured total cholesterol and triglycerides by means of enzymatic assays, and we recorded HDL cholesterol concentrations with a Beckman LX-20 autoanalyzer (Beckman Coulter, La Brea, CA, USA) by using a direct method. We calculated LDL cholesterol values by using the Friedewald equation.

Statistical Analysis

Continuous variables with normal distribution are expressed as mean ± standard deviation (SD), and categorical variables are expressed as a percentage. We evaluated differences in baseline characteristics across tertiles of 25(OH)D levels by using a chi-square test for categorical variables and analysis of variance for continuous variables. We assessed the correlation between 25(OH)D and lipid levels with the Pearson correlation coefficient. We used partial correlation and linear regression coefficients to examine the relationship between variables. We included those variables associated with 25(OH)D levels in the univariate analyses in the regression models for the multivariate analysis. These variables were age, sun exposure, smoking, and lipid-lowering therapy. We calculated crude ORs, adjusted ORs, and corresponding 95% confidence intervals by univariate and conditional multivariate logistic regression. We analyzed data by using SPSS package procedures (SPSS v19; Chicago, IL, USA). All tests were two-tailed and a p-value threshold of < 0.05 was set for statistical significance.

of Dermatology of University Hospital Doctor Peset for their assistance in this study.

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