

Vitamin D deficiency is an independent predictor of elevated triglycerides in Spanish school children

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Received: 23 July 2010 / Accepted: 2 November 2010 / Published online: 20 November 2010
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Abstract

Purpose To determine the association between vitamin D status and the serum lipid profile in children.

Methods The subjects of this cross-sectional study were 149 Spanish school children (8–13 years of age). The anthropometric data collected were weight and height, from which the body mass index (BMI) was calculated. Serum 25(OH)D concentrations were measured by chemiluminescent assay. Triglycerides were determined by enzyme colorimetry; total cholesterol and HDL-cholesterol were determined by the cholesterol esterase method. The LDL-cholesterol concentrations were determined mathematically.

Results Compared to children with serum 25(OH)D concentrations in the fourth quartile, those in the first had higher triglyceride (86.0 ± 35.7 vs. 64.1 ± 26.7 mg/dL; $p < 0.05$). After adjusting for age, sex, BMI, and physical activity, the serum 25(OH)D level was found to be inversely proportional to the triglyceride ($r = -0.857$; $p = 0.010$). While age, sex, BMI, and physical activity explained 12% of the variance of the HDL-cholesterol figures, the inclusion of serum 25(OH)D allowed 23% of the variance to be explained.

Conclusion A low serum vitamin D levels in children is associated with high triglyceride levels.

Keywords 25(OH)D · Serum lipids · Children

Introduction

Vitamin D has long been known involved in the regulation of calcium, phosphate, and alkaline phosphate levels, and the mineralization of bone [1]. In recent years, however, an adequate vitamin D status has been related to the prevention of certain types of cancer, diabetes mellitus, autoimmune disorders, and cardiovascular disease [1, 2].

Recent studies in adults have shown a relationship between vitamin D deficiency and a greater prevalence of self-reported angina, myocardial infarction, coronary heart disease, heart failure and peripheral vascular disease [3, 4]. Different mechanisms could be involved in these relationships, such as the regulation of blood pressure [5, 6], glycaemia [6], percentage body fat [7], and serum lipids [4] by vitamin D.

Some studies have examined the relationship between vitamin D and serum lipids, most of them have involved normal weight [4, 8] and obese adults [9, 10], but few in children [11–13]. The aim of the present study was to determine the association between vitamin D status and the serum lipid profile in children.

Experimental methods

Subjects

Sample recruitment: the study was carried out in 3 schools from Madrid (Spain) (latitude 40°23'N), and they were randomly selected from a list of all primary schools from Madrid. The directors were contacted by phone to arrange an interview during which the characteristics and the importance of the study were explained. Permission was requested to meet with the parents of the children in the age

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group of 8–13 years. Parents of 276 children between 8 and 13 years were contacted and explained the details of the study, and all questions were answered. Only the parents of 178 children gave permission to include their children in the study. Parents of the remaining 98 children did not agree them to take part in the study because of different reasons: they did not agree to take blood from the children, they were not interested in the study, etc. Twenty-nine children were excluded because of different reasons: presence of celiac disease, fish and egg allergy, lactose intolerance, and diabetes and did not attend on days when tests were performed. Thus, the study sample was 149 children.

The exclusion criteria were:

- A lack of authorization to take part or the non-acceptance of any of the conditions required for the study to proceed.
- Non-attendance on days when the tests or interviews were performed.
- Clinical problems that advised against inclusion or that might modify the results.

The study was approved by the Human Research Review Committee of the Pharmacy Faculty, Complutense University of Madrid.

Methods

Physical activity

Information about the subjects' physical activity was obtained using a questionnaire that recorded the length of time spent sleeping, eating, and playing sport, etc. [14]. An activity coefficient was established for each subject by multiplying the time spent in each activity by established coefficients [15, 16]—1 for sleeping and resting, 1.5 for very light activities (those that can be done sitting or standing up such as studying, doing homework, or painting), 2.5 for light activities (e.g., walking), 5 for moderate activities (e.g., playing tennis, skiing, dancing), and 7 for intensive activities (e.g., playing basketball)—and then dividing by 24 h.

Anthropometric survey

All measurements were taken at the schools in the morning, and following norms set out by the World Health Organization [17].

Weight and height were determined using a digital electronic balance (SECA ALPHA, GMBH & Co., Igny, France) (range 0.1–150 kg, precision 100 g) and a Harpenden digital stadiometer (Pfifter, Carlstadt, NJ, USA)

(range 70–205 cm, precision 1 mm) respectively. For these measurements, subjects were barefoot and wore only underwear. Subject body mass index (BMI) was calculated as weight (kg)/height² (m²).

Biochemical survey

The study was undertaken during winter (specifically on February), and blood was taken in that season. Blood samples were drawn by venipuncture after 12 h of fasting, between 8 and 9 am in the morning. Adequacy of the fasting period was checked by nurses before blood was collected.

Serum 25(OH)D levels were measured by chemiluminescent assay [18, 19]. Serum was incubated with anti-vitamin D-coated microparticles and isoluminol derivative-conjugated 25(OH)D prior to the measurement of the chemiluminescent signal (C.V. = 8%).

A serum level of <20 ng/mL (50 nmol/L) was taken to indicate a vitamin D deficiency [20, 21].

The children were grouped into quartiles depending on their serum vitamin D levels; Quartile 1 = 25(OH)D <17.4 ng/mL, Quartile 2 = 17.4–22.6 ng/mL, Quartile 3 = 22.6–27.6 ng/mL, and Quartile 4 = ≥27.6 ng/mL.

Triglycerides were determined by enzyme colorimetry (GPO-PAP) (C.V. = 2.8%) [22]. Total cholesterol (C.V. = 2.2%) and HDL-cholesterol (C.V. = 2.4%) were determined by the cholesterol esterase method [23], the latter after precipitation from the serum with phosphotungstic acid and magnesium ions [24]. The concentration of VLDL-cholesterol was obtained mathematically from the triglyceride level (dividing this by five) [25], and the LDL-cholesterol concentration using the formula of Friedewald et al. [26]:

$$\text{LDL-cholesterol (mg/dL)} = \text{total cholesterol} \\ - (\text{VLDL-cholesterol} \\ + \text{HDL-cholesterol}).$$

The following were considered the thresholds of normality: total cholesterol <170 mg/dL, triglycerides <75 mg/dL (in those under 10 years of age) or <90 mg/dL (in those 10 and over), HDL-cholesterol ≥45 mg/dL, LDL-cholesterol <110 mg/dL, and VLDL-cholesterol <15 mg/dL (in those younger than 10 years of age) or <18 mg/dL (in those 10 or over) [27].

Statistical analysis

Means and standard deviations (SD) were calculated for all variables. One-way ANOVA and the Newman–Keuls post hoc test were used to identify significant differences between the groups. Comparisons between proportions were detected using the χ^2 test. Multiple regression

analysis was performed to determine the vitamin D levels that predicted serum lipid levels, taking into account age, sex, BMI, and physical activity. Results were recorded with the 95% confidence interval (95% CI). All calculations were made using RSIGMA BABEL Software (Horus Hardware, Madrid). Significance was set at $p < 0.05$.

Results

The mean serum vitamin D concentration for the subjects as a whole was 23.1 ± 8.2 ng/mL; 37.6% of the children had deficient concentrations.

The mean cholesterol, triglycerides, and HDL-, LDL-cholesterol concentrations were 168.5 ± 24.9 , 74.2 ± 31.6 , 64.0 ± 14.9 , and 89.6 ± 20.8 mg/dL respectively. Some 47.7% of the children had high cholesterol levels; 24.2% had high triglyceride levels. Some 5.4 and 15.4% of the children had inadequate HDL- and LDL-cholesterol concentrations.

Dividing the population into quartiles with respect to serum vitamin D showed that the children in the first, second, and third quartiles were older, heavier, and had a higher BMI than those of the fourth quartile. In addition, those of the first and third quartiles had lower activity coefficients than those in the fourth (Table 1). The children in the first quartile had higher triglyceride levels than those in the fourth (Table 2).

After adjusting for age, sex, BMI, and physical activity, serum 25(OH)D was found to be inversely associated with triglyceride levels. For every 1 ng/mL increase in 25(OH)D, triglycerides fell by 0.857 mg/dL (Table 3). Although serum vitamin D was not significantly associated with the HDL-cholesterol level, the former's inclusion in the regression analysis (Table 3) improved the capacity to predict the HDL-cholesterol level. While age, sex, BMI, and physical activity explained 12% of the variance of the HDL-cholesterol figures, the inclusion of serum 25(OH)D allowed 23% of the variance to be explained.

Table 1 General characteristics of the study population with respect to vitamin D quartile (means $\pm$ SD)

	Total	Quartile 1 ($n = 37$)	Quartile 2 ($n = 37$)	Quartile 3 ($n = 37$)	Quartile 4 ($n = 38$)	AN1
Age (years)	10.79 ± 1.05	10.91 ± 0.97^a	11.10 ± 1.06^a	10.93 ± 0.97^a	10.22 ± 1.03^b	0.0020
Sex						
Boys (%)	47.7 ± 4.1	40.5	52.8	37.8 ^a	62.2 ^b	
Weight (kg)	39.8 ± 10.5	41.7 ± 11.7^a	42.4 ± 9.0^a	42.1 ± 10.3^a	33.2 ± 8.0^b	<0.001
Height (m)	1.43 ± 0.09	1.44 ± 0.09^a	1.45 ± 0.08^a	1.46 ± 0.09^a	1.39 ± 0.09^b	0.0020
BMI (kg/m ²)	19.1 ± 3.5	19.8 ± 4.2^a	20.1 ± 3.2^a	19.5 ± 3.3^a	17.0 ± 2.5^b	<0.001
Activity coefficient	1.48 ± 0.07	1.47 ± 0.06^a	1.49 ± 0.06	1.45 ± 0.08^a	1.51 ± 0.07^b	0.0099
25(OH)D (ng/mL)	23.1 ± 8.2	13.6 ± 2.8^a	19.9 ± 1.6^b	24.6 ± 1.4^c	33.9 ± 5.8^d	0

Means with different letters are significantly different (Newman–Keuls' post hoc test)

Quartile 1, 25(OH)D <17.4 ng/mL; Quartile 2, 25(OH)D: 17.4–22.6 ng/mL; Quartile 3, 25(OH)D: 22.6–27.6 ng/mL; Quartile 4, 25(OH)D $\geq$ 27.6 ng/mL

AN1 one-way ANOVA

Table 2 Serum lipid concentration with respect to vitamin D quartile (means $\pm$ SD)

	Total	Quartile 1 ($n = 37$)	Quartile 2 ($n = 37$)	Quartile 3 ($n = 37$)	Quartile 4 ($n = 38$)	AN1
Cholesterol (mg/dL)	168.5 ± 24.9	169.8 ± 21.5	165.0 ± 30.5	168.5 ± 25.8	170.3 ± 21.7	NS
Triglycerides (mg/dL)	74.2 ± 31.6	86.0 ± 35.7^a	73.4 ± 28.1	74.0 ± 32.4	64.1 ± 26.7^b	0.028
HDL (mg/dL)	64.0 ± 14.9	62.5 ± 14.6	60.4 ± 12.0	64.6 ± 13.4	68.4 ± 17.9	NS
LDL (mg/dL)	89.6 ± 20.8	90.2 ± 18.4	89.9 ± 25.3	89.1 ± 22.5	89.1 ± 17.3	NS
LDL/HDL ratio	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	1.4 ± 0.5	1.4 ± 0.4	NS
CL/HDL ratio	2.7 ± 0.6	2.8 ± 0.7	2.8 ± 0.6	2.7 ± 0.6	2.6 ± 0.5	NS

Means with different letters are significantly different (Newman–Keuls post hoc test)

Quartile 1, 25(OH)D <17.4 ng/mL; Quartile 2, 25(OH)D: 17.4–22.6 ng/mL; Quartile 3, 25(OH)D: 22.6–27.6 ng/mL; Quartile 4, 25(OH)D $\geq$ 27.6 ng/mL

AN1 one-way ANOVA, CL cholesterol (mg/dL)

Table 3 Results of a multiple regression analysis with vitamin D as the dependent variable and serum lipids as the independent variable

	β^a	Error	<i>p</i> for the variable	R^2
Cholesterol (mg/dL)	−0.551	0.310	0.078	0.107
Triglycerides (mg/dL)	−0.857	0.376	0.024	0.117
HDL (mg/dL)	0.011	0.170	0.950	0.230
LDL (mg/dL)	−0.389	0.266	0.146	0.044

β Constant or intercept

^a Analysis adjusted for sex, age, BMI, and physical activity

Discussion

The present results agree with those of other authors [28–30] and show that vitamin D deficiency is a common problem among children and adolescents.

Because of the magnitude of this problem, some authors recommend increase the exposure to the sun to improve vitamin D status, since it is the main source of the vitamin [31]. However, this is not always enough. For example, in some countries, there may be insufficient sunshine to maintain appropriate vitamin D levels, and many people (even in sunny countries) live in urban settings in which the amount of light they receive is inadequate. The use of sun creams—although essential for preventing skin cancers, including melanoma—may also reduce the amount of solar radiation received [32]. Because of the sun exposure problems and because in many studies the intake of vitamin D has been related to the serum 25(OH)D concentration [33, 34], even when exposure to the sun is taken into account [33], it seems that to maintain an appropriate serum 25(OH)D concentration vitamin D intake needs to be adequate. Nevertheless, some authors believe it would be difficult to make school children increase their consumption of foods rich in vitamin D, and given the dangers involved in prolonged exposure to the sun, they recommend the use of dietary supplements to cover vitamin D needs [35, 36].

Apart from that, other authors [37, 38] report that overweight/obesity and the lack of physical activity predispose individuals to serum vitamin D deficiency; which is confirmed in the present study (Table 1). Excess body fat sequesters circulating vitamin D, which could lead to its deficiency [39]. Exercise modifies the levels of hormones such as 1,25(OH)₂D, which could potentiate the effect of vitamin D [40].

The most important finding of the present study was the association between serum vitamin D and triglycerides, confirming the results reported in other studies. In the third National Health and Nutrition Examination Survey, which involved 18,825 adults over 20 years of age, the adjusted prevalence of high serum triglycerides was significantly

higher in the first quartile (25(OH)D <21 ng/mL) than in the fourth quartile (25(OH)D >37 ng/mL) of serum 25(OH)D concentrations [OR = 1.47 (1.30–1.65); $p < 0.001$] [41]. Similarly, in a recent study of 3577 adolescents aged 12–19 years, undertaken by the National Health and Nutrition Examination Survey (NHANES 2000–2004), it was reported that subjects with serum 25(OH)D in the lowest quartile (<15 ng/mL) were at greater risk of hypertriglyceridemia than those in the highest (>26 ng/mL) [OR = 1.00 (1.33–2.39)] after adjusting for age, sex, race, BMI, socioeconomic status, and physical activity [12]. In a group of 73 women with morbid obesity, those with vitamin D deficiencies (25(OH)D <20 ng/mL) had higher triglyceride levels than those with an adequate serum vitamin D status (25(OH)D ≥20 ng/mL) (163.3 ± 81.5 vs. 95.1 ± 24.2 mg/dL; $p = 0.001$) [9]. A significant negative association was also found between serum vitamin D and triglycerides ($r = -0.364$; $p = 0.015$). Similar observations have been made in intervention studies. For example, in a study involving 200 overweight subjects who received 83 µg/day vitamin D or placebo while participating in a weight-reduction program for 12 months, a more pronounced reduction in serum triglycerides occurred in the vitamin D group than in the placebo group (−13.5% compared with +3.0%; $p < 0.001$) [42]. According to Zittermann et al. [42], two mechanisms might be involved in the vitamin D-mediated reduction in serum triglycerides: (1) vitamin D increases intestinal calcium absorption [43] and thus the amount of absorbed calcium. This calcium could then reduce serum triglycerides by reducing hepatic triglyceride formation and secretion [44]; (2) via a suppressive effect of vitamin D on serum PTH concentrations. Since elevated PTH concentrations are accompanied by a reduction in plasma post-heparin lipolytic activity [45], a reduction in serum PTH may reduce serum triglycerides via increased peripheral removal. A third mechanism might also be involved, in which vitamin D induces the expression of VLDL-cholesterol receptors in some types of cell [46]. A fourth possible mechanism to explain the association between 25(OH)D and triglycerides would be across the insulin resistance: when vitamin D deficiency is present the risk of insulin resistance increases [47], and this situation is associated with an elevation of the levels of VLDL and triglycerides [48].

Although no direct relationship was found between serum 25(OH)D and HDL-cholesterol levels in the present study, the literature suggests it has some influence. In the most recent NHANES 2000–2004 survey, vitamin D deficiency (<15 ng/mL) was associated with lower HDL-cholesterol [OR = −3.03 mg/dL (−5.02 to −1.04)] levels—an association not seen in those with 25(OH) levels ≥30 ng/mL [3]. In the above study involving 73

women with morbid obesity [9], those with a 25(OH)D concentration of <20 ng/mL had lower HDL-cholesterol levels than those with a higher concentration (37.0 ± 7.8 vs. 44.9 ± 8.7 mg/dL; $p = 0.003$). Further, a significant, positive relationship was found between vitamin D levels and HDL-cholesterol levels ($r = 0.325$; $p = 0.033$). The effect of vitamin D on HDL-cholesterol might be explained by its requirement in order to maintain adequate levels of apolipoprotein A-1 (the main component of high-density lipoprotein) [12]. In addition, it has been suggested that the modulators of the vitamin D receptor might be potent apo-AI gene inducers [49]. Certainly, in a study of 358 adults, an independent and highly significant positive correlation was observed between the serum concentrations of 25(OH)D and apolipoprotein A-I and HDL-cholesterol levels [50].

The present study suffers the limitation of the non-measurement of the PTH concentration. It is therefore impossible to determine the relationship between low vitamin D levels and PTH or to determine whether a low PTH concentration is associated with a lower triglyceride level. Another limitation of this study is the relatively small sample, which may have prevented the detection of associations between 25(OH)D and other lipids like HDL.

In conclusion, low serum vitamin D levels in children are associated with high triglyceride levels and could be associated with low HDL-cholesterol levels. These associations mean that children with low vitamin D levels could be at greater long-term risk of cardiovascular disease.

Acknowledgments This work was partially supported by the research projects FISS PI060318 and UCM-BSCH GR58/08-920030 (Research Group VALORNUT, Spain).

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