Original Article

Interrelationship between serum 25-hydroxyvitamin D_3 concentration and lipid profiles in premenopausal Indian women

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ABSTRACT

Context: Vitamin D deficiency is prevalent worldwide, and observational studies have associated it with an atherogenic lipid profile. **Aim:** To determine the interrelationship between Vitamin D and lipid profile in apparently healthy premenopausal Indian women, considering confounding factors such as lifestyle that independently influence lipids. **Setting and Design:** Cross-sectional study. **Subjects and Methods:** One hundred and twenty healthy premenopausal women (20–45 year) were recruited from Gujarat, India. Data were collected on anthropometry, physical activity, sunlight exposure, and diet. Fasting blood samples were collected for the measurement of serum 25-hydroxyvitamin D_3 (25[OH]D), parathyroid hormone, and lipid profile. **Statistical Analysis:** Pearson's correlation coefficient was used to derive correlation between serum 25(OH)D concentrations and serum lipids. **Results:** Ninety-three percent women showed Vitamin D deficiency (serum 25[OH]D < 20 ng/ml). Serum 25(OH)D concentrations showed significant inverse correlation with total cholesterol (TC) (r = −0.202, P = 0.027), triglycerides (TG) (r = −0.284, P = 0.002), and low-density lipoprotein-cholesterol (LDL-C) (r = −0.184, P = 0.044) and positive correlation with high-density lipoprotein-cholesterol (HDL-C) (r = 0.250, P = 0.006). On dichotomizing the population according to median 25(OH)D concentration (11.1 ng/dl), no significant differences were observed between the groups for anthropometry, sunlight exposure, and lifestyle. Serum lipid profiles were significantly different, above median serum 25(OH)D concentration group showed favorable serum lipids (TC: 179.3 ± 30 vs. 191.8 ± 31.7 mg/dl; TG: 140 ± 39.1 vs. 165.5 ± 53.4 mg/dl; LDL-C: 100 ± 30.2 vs. 112 ± 32 mg/dl; HDL-C: 53 ± 14 vs. 47.6 ± 9.3 mg/dl)(P < 0.05). **Conclusions:** This study demonstrates that association of 25(OH)D concentrations with lipid profile even after considering lifestyle factors which independently influence lipids. Intervention trials would be required to prove this association to be causation.

Key words: Cholesterol, lifestyle factors, lipoprotein, triglycerides, Vitamin D

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Introduction

Vitamin D is a fat-soluble vitamin and a prohormone which has two isoforms, ergocalciferol (Vitamin D_2) available from

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plant sources and cholecalciferol (Vitamin D_3) produced by animals. In humans, more than 80% of the total Vitamin D of the body store is synthesized cutaneously through sunlight (ultraviolet B radiation) exposure while rest is obtained from the diet.[1-3] Cutaneously synthesized and ingested Vitamin D are immediately hydroxylated by liver to form 25-hydroxyvitamin D_3 (25[OH]D) which is the predominant form of circulating Vitamin D. A high prevalence of serum 25(OH)D deficiency has been reported among all age groups in the Middle East and Asian countries despite abundance of sunlight throughout the year. Many factors such as skin complexion, sunlight exposure, use of sunscreens and lack of vitamin D in diet are considered as major causes for high prevalence of vitamin D deficiency in sun-rich countries such as India.[4]

Vitamin D has an important role in calcium homeostasis and skeletal health and in addition, has now been implicated with various health and disease processes such as cardiovascular disease (CVD), hypertension, congestive heart failure, type 2 diabetes, and obesity.[3-7] Epidemiological studies have shown association of circulating 25(OH)D concentrations with adverse lipid profile which could mediate increased risk of CVD.[3,4,8] The mechanism of interrelationship between 25(OH)D and lipid profile is not clear. It has been hypothesized that 25(OH)D through various direct and indirect pathways influences the lipid profile.

Most studies on Asian Indians target specific groups including elderly or obese populations.[2,9] Women, especially of childbearing age, are more like to suffer from the consequences of Vitamin D deficiencies as compared to men.[10,11] In addition, Vitamin D deficiency and its relationship with serum lipids appear to vary by ethnicity and gender.[8] Some of the factors such as obesity and lifestyle factors can influence both 25(OH)D concentrations as well as the lipid profile. Thus, to study the association between vitamin D concentrations (as measured by serum 25[OH]D) and lipid profile, we undertook this study in a population of apparently healthy, premenopausal Asian Indian women with similar anthropometric data, and lifestyle to avoid confounding factors which can independently influence 25(OH)D concentration and lipid profile.

Subjects and Methods

A cross-sectional study in apparently healthy premenopausal women ($n = 120$) from offices, hospitals, nongovernmental organizations, colleges, and residential areas aged 20–45 years was carried out from March 2014 to April 2014 in Gujarat state, Western India.

Study population

From the study regions, approximately 60 sites comprising different institutes, hospitals, nongovernmental organizations, offices, colleges, and residential areas were approached. Out of these 60 sites, 40 (two-thirds) provided the consent, of which 35 sites were selected randomly.

From the 35 selected sites, a total of 1109 women were randomly selected and approached by our team. A total of 580 (52.2%) women provided consent for blood analysis and to take part in the study. These women completed a screening questionnaire to check for eligibility (i.e., age, education, socioeconomic strata, etc.). Inclusion criteria were apparently healthy premenopausal women within the age group of 20–45 years. Women with any history of using medication which would affect Vitamin D and lipid metabolism or diseases such as hyper/hypothyroidism, hypertension, diabetes, premature loss of ovarian function, other gynecological problems, pregnancy, lactation, or any major surgery were excluded from the study. A total of 197 women (34%) satisfied the inclusion criteria and thus were eligible for the study. A total of 120 apparently healthy women were randomly selected by a computerized random number generation (participation rate was 61%). With a sample size of 120, based on the variation in total cholesterol (TC), a level of significance of 5% and to detect the difference of >7%, the resultant power of the present study is 80%.

Ethical approval and consent

Ethical approval to perform this study was obtained from the Ethics Committee of GMERS (GMERS Medical College, Civil Hospital Campus, Near Pathikashram, Sector-12, Gandhinagar-382012, Gujarat, India. ECR/535/Inst/GJ/2014). All the procedures performed in the study were in accordance with the ethical standards of the Ethical Committee and with the Helsinki Declaration of 1975 (revised in 2000) and its later amendments or comparable ethical standards. The purpose and importance of the study were explained, and an informed written consent was obtained from all the participants.

Anthropometry

Height was measured (nearest 1 mm) using a stadiometer (Leicester Height Meter, Child Growth Foundation, UK, range 60–207 cm). Weight (nearest 0.1 kg), body mass index (BMI), and body fat percentage were measured using high capacity body composition monitor (SC240 MA, Tanita, India). All measurements were taken with participants wearing light clothing and without shoes.

Dietary calcium and fat intake and physical activity

Three-day diet was recorded through a 24-h diet recall taken for three nonconsecutive days (2 weekdays and a Sunday). Nutrient intakes as well as dietary calcium and fat intakes were calculated using a nutrient analysis software (C-Diet version 2.1, Xenios Technology, 2012) of cooked and raw food databases.[12,13] Validated questionnaire[14] was used for collecting data on physical activity. The physical activity questionnaire comprised type of activity, duration by sessions in minutes, and weekly frequency for different activities. Assessment of time expended in light activities (<3 metabolic equivalent [MET]) as well as moderate to vigorous activities (>3 MET) was performed.[15,16] Sunlight exposure was recorded using a validated questionnaire, and hours were calculated using the time spent in the sunlight during the day between 7 am and 7 pm.[17]

Biochemical estimations

To minimize the seasonal variation and change in sunlight exposure, all samples were obtained during the same season, i.e., during spring (March–April 2014). After an overnight fast, blood samples were collected between 7:30 and 8:00 am in the morning. Serum 25(OH)D concentrations were measured by chemiluminescent microparticle immunoassay (Abbott, Architect, India; Coefficient of variance 3.7% ± 0.7%). Intact serum parathyroid hormone (PTH) concentrations were measured by chemiluminescent immunoassay (Siemens, India; coefficient of variance 3%). Serum lipid concentrations were measured using Siemens auto analyzer (Date dimension RXL Max) with enzymatic procedures for the measurement of TC (<220 mg/dl), triglycerides (TG) (<150 mg/dl).

Statistical analysis

Descriptive characteristics (mean and standard deviations) were computed for anthropometric measures, serum lipids (TC, TG), high-density lipoprotein-cholesterol (HDL-C) and Low-Density Lipoprotein-cholesterol (LDL-C)] and calories, protein, carbohydrates, fat and calcium intakes for the study population. Data were dichotomized according to median serum 25(OH)D concentrations (11.1 ng/dl). Independent sample *t*-test was used to compare the means of serum lipid concentrations among two groups. Pearson's correlation coefficient was used to derive correlation between serum 25(OH)D and serum lipid concentrations. All analyses were performed using SPSS version 18.0, and the significance level was set at $P < 0.05$.

Results

In our study, 93% of women had vitamin D deficiency (serum 25(OH)D concentration <20 ng/ml);[18] 59% had serum 25(OH)D concentrations below 12 ng/dl, 34% had between 12-20 ng/dl, and only 7% had above 20 ng/dl [Figure 1].

Since our aim was to examine the impact of serum 25(OH) D concentrations on serum lipid concentrations, the population was dichotomized according to median serum 25(OH)D concentrations (11.1 ng/dl). No significant difference was observed for age, weight, BMI, total body fat %, visceral fat levels, time spent in moderate to vigorous activity, sunlight exposure and mean dietary intakes of calories, fat, protein, carbohydrates, and calcium among the two groups ($P > 0.05$ for all) [Table 1]. All the women met the recommended guidelines for physical activity (30-60 min per day).[16] Mean serum concentrations of TC, TG, LDL-C, HDL-C, and PTH among study population were 185.6 ± 31.4 mg/dl, 152.8 ± 48.3 mg/dl, 106 ± 31.6 mg/dl, 50.3 ± 12.1 mg/dl, and 49.4 ± 24.6 pg/ml, respectively [Table 2]. The serum lipid concentrations were significantly different between the two groups ($P < 0.05$). The above median serum 25(OH)D concentration group showed lower TC, TG, and LDL-C and higher HDL-C serum concentrations as compared to the below median serum 25(OH)D concentration (TC: 179.3 ± 30 vs 191.8 ± 31.7 mg/dl; TG: 140 ± 39.1 vs 165.5 ± 53.4 mg/dl; LDL-C: 100 ± 30.2 vs 112 ± 32 mg/dl; HDL-C: 53 ± 14 vs 47.6 ± 9.3 mg/dl) [Table 2]. The ratios of TG, TC, and LDL-C with HDL-C were also significantly different between the two groups, women having above median serum 25(OH)D concentration showed lower lipid ratios as compared to the below median serum 25(OH)D concentration (i.e., TG/HDL-C: 3.7 ± 1.7 vs. 2.7 ± 1.0, TC/HDL-C: 4.1 ± 1.1 vs. 3.5 ± 0.8, LDL-C/HDL-C: 2.4 ± 0.9 vs. 1.9 ± 0.7).

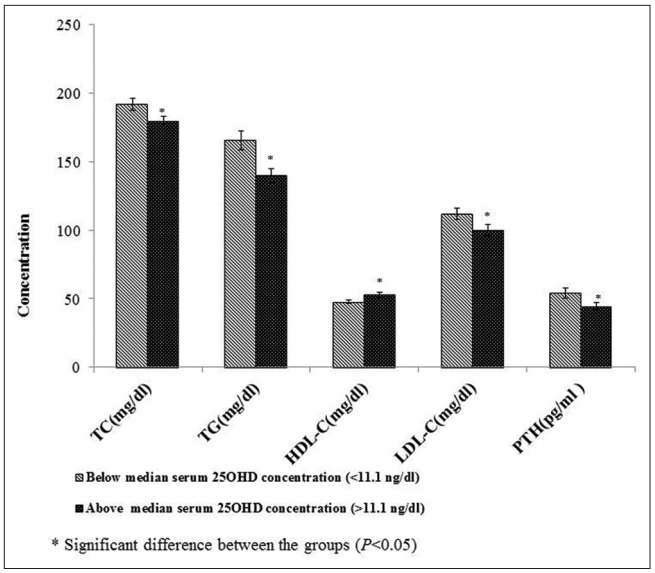

Figure 1: Serum lipid and serum parathyroid hormone concentrations in the study groups

Table 1: Lifestyle characteristics of women dichotomized by median 25-hydroxyvitamin D_3 concentration

Parameters	Vitamin D Level		Total (*n*=120)	*P*
	Below median serum 25(OH)D concentration (<11.1 ng/dl) (*n*=60)	Above median serum 25(OH)D concentration (>11.1 ng/dl) (*n*=60)		
Age (years)	33.9±5.8	33.7±5.6	33.8±5.7	0.84
Weight (kg)	60.3±9.8	58.6±10.9	59.5±10.4	0.37
BMI (kg/m^2)	24.5±3.8	24.4±4.2	24.5±4	0.84
Body fat %	34.7±5.2	34.5±6	34.5±5.6	0.81
Visceral fat level	5.8±2.3	5.6±2.6	5.7±2.5	0.68
Moderate to vigorous activity (h/day)	1.7±0.8	1.8±0.8	1.7±0.8	0.55
Sun light exposure (min/day)	51.9±40.4	53.2±30.6	52.5±35.7	0.83
Diet				
Energy (kcal/day)	1507±352	1524±436	1516±395	0.82
Proteins (g/day)	37±9	38±13	38±11	0.50
Fat (g/day)	48±16	48±16	48±16	0.95
Carbohydrates (g/day)	231±52	234±67	233±60	0.78
Calcium (mg/day)	473±168	474±161	473±163	0.98

No significant differences between the groups for all the parameters (*P*>0.05 for all). BMI: Body mass index, 25(OH)D: 25-hydroxyvitamin D_3

Table 2: Serum lipid profile and serum parathyroid hormone (biochemical parameters) in the study population stratified by median 25-hydroxyvitamin D_3 concentrations

Parameters	Vitamin D Level		Total (*n*=120)	*P*
	Below median serum 25(OH)D concentration (<11.1 ng/dl) (*n*=60)	Above median serum 25(OH)D concentration (>11.1 ng/dl) (*n*=60)		
Total cholesterol (% >220 mg/dl)	191.8±31.7* (12)	179.3±30 (7)	185.6±31.4 (9)	0.029
Triglycerides (% >150 mg/dl)	165.5±53.4* (67)*	140±39.1 (32)	152.8±48.3 (49)	0.003
LDL-C (% >130 mg/dl)	112±32* (25)†	100±30.2 (13)	106±31.6 (19)	0.037
HDL-C (% <40 mg/dl)	47.6±9.3* (9)*	53±14 (2)	50.3±12.1 (11)	0.014
PTH (% >79 pg/ml)	54.1±27.8* (nil)	44.6±20 (nil)	49.4±24.6 (nil)	0.035
TG:HDL	3.7±1.7*	2.7±1.0	3.2±1.5	0.000
TC:HDL	4.1±1.1*	3.5±0.8	3.8±1.0	0.001
LDL:HDL	2.4±0.9*	1.9±0.7	2.2±0.8	0.005

*Significant difference between the groups (*P*<0.05), †Marginal difference between the groups (0.05<*P*<0.1). PTH: Parathyroid hormone, HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, TC: Total cholesterol, TG: Triglycerides, 25(OH)D: 25-hydroxyvitamin D_3

Table 3: Correlation of serum 25-hydroxyvitamin D_3 with serum lipids in the study population

Parameters	Total (*n*=120) 25(OH)D
Total cholesterol	−0.202*
Triglycerides	−0.284**
LDL-C	−0.184*
HDL-C	0.250**
TG:HDL	−0.333**
TC:HDL	−0.309**
LDL:HDL	−0.249**

**Correlation is significant at the 0.01 level (two-tailed), *Correlation is significant at the 0.05 level (two-tailed). HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol, TC: Total cholesterol, TG: Triglycerides, 25(OH)D: 25-hydroxyvitamin D_3

The percentage of women with adverse serum TC, TG, LDL-C, and HDL-C were higher in the group with below median serum 25(OH)D concentrations as compared to above median serum 25(OH)D concentration group (TC >220 mg/dl −11.7% vs. 6.7%; TG >150 mg/dl −66.7% vs. 31.7%; LDL-C >130 mg/dl −25% vs. 13.3% and HDL-C <40 mg/dl −18.3% vs. 3.3%).

Table 3 illustrates the correlation between serum 25(OH)D and serum lipid concentrations. Serum 25(OH)D concentrations showed significant inverse correlation with TC ($r = -0.202$, $P = 0.027$), TG ($r = -0.284$, $P = 0.002$), LDL-C ($r = -0.184$, $P = 0.044$) and showed a positive correlation with HDL-C ($r = 0.250$, $P = 0.006$). Serum 25(OH)D concentrations also showed significant inverse correlation with the lipid ratios, i.e., TG/HDL-C ($r = -0.333$, $P = 0.0001$), TC/HDL-C ($r = -0.309$, $P = 0.001$), and LDL-C/HDL-C ($r = -0.249$, $P = 0.006$).

Discussion

We observed a high prevalence of vitamin D deficiency in middle-aged premenopausal Indian women. Our results showed inverse correlation of serum 25(OH)D with serum TC, TG, and LDL-C and a positive correlation with HDL-C. In addition, lipid ratios, i.e., TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C also showed inverse correlation with serum 25(OH)D. Furthermore, when the population was dichotomized according to median

serum 25(OH)D concentrations, women with above median serum 25(OH)D concentration had favorable serum lipid concentrations as compared to the women with below median serum 25(OH)D concentrations; this difference was seen even though there were no differences in lifestyle factors between the two groups which could have independently influenced them.

Similar to the previous studies, our study also showed a high prevalence of Vitamin D deficiency where most of the women had Vitamin D concentrations below 20 ng/ml.[3,4] Factors contributing toward this were very little sunlight exposure of <1 h per day, predominant consumption of vegetarian diet (92%), and complete lack of Vitamin D fortification.

Various association studies have linked Vitamin D with a myriad of extraskeletal effects including dyslipidemia.[19-21] Our results are in line with some of the recent association studies where Vitamin D concentration was inversely correlated with atherogenic lipids (TC, TG, and LDL-C) and showed strong positive correlation with atheroprotective lipids (HDL-C).[22,23] While studies associating relationship of 25(OH)D with LDL-C have provided diverse conclusions, relationship of Vitamin D with HDL-C has been more consistent with most studies reporting positive associations.[3] The physiological basis for these associations is not clear. It has been hypothesized that low serum 25(OH)D concentrations increase serum PTH concentrations which promote calcium influx into the adipocytes. Intracellular calcium enhances lipogenesis in adipocytes which leads to an altered lipid profile.[2] Another potential mechanism could be mediated through increased adiponectin secretion by Vitamin D by increasing expression of adiponectin gene. Adiponectin influences lipid metabolism by enhancing fatty acid oxidation and reducing triglyceride and cholesterol content in liver, skeletal, and cardiac muscles.[3,24,25] Vitamin D has also been found to increase concentrations of apolipoprotein A-1, which is the main protein component in HDL-C.[26]

The negative correlation of the lipid ratios TG/HDL-C, TC/HDL-C, and LDL-C/HDL-C with serum 25(OH)D have also been reported in the previous studies,[3] which further supports association of higher serum 25(OH)D levels with a favorable serum lipid profile.[3,27]

Lipid profile and serum 25(OH)D concentration both can be influenced by anthropometric parameters (BMI and percentage body fat), physical activity and exposure to sunlight (both could be interrelated), and diet. The strength of this study has been that above confounding factors were taken into consideration, and the groups studied were similar in above characteristics. Furthermore, our study consisted of healthy premenopausal women whereas the previous studies were performed on specific groups such as obese and geriatric populations.[6,28]

One of the limitations of the present study is that we did not find a significant difference in the sunlight exposure hours between the two groups which could be because we used a short and simple questionnaire that recorded limited information on sunlight exposure, a detailed questionnaire may have helped to get an accurate data on sunlight exposure. The association of 25(OH)D and lipid profile is strong in our study group; however, this observation does not prove causality. In cross-sectional studies, any association of such nature could be by chance and therefore, a longitudinal interventional trial on a larger cohort would be required to confirm causation. The previous intervention studies have provided conflicting results, and further studies are thus required.[29,30]

Conclusion

To summarize, we have found a very high prevalence of Vitamin D deficiency among premenopausal Indian women. Serum 25(OH)D concentrations showed an inverse correlation with atherogenic lipids (TC, TG, and LDL-C) and a strong positive correlation with atheroprotective, HDL-C. Our study suggests that Vitamin D deficiency can lead to dyslipidemia and potentially increase the risk of CVDs. Further randomized controlled trials are required in this population to confirm causation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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