

## Association of serum 25-Hydroxy Vitamin D level with lipid, lipoprotein, and apolipoprotein level

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### ABSTRACT

**Introduction** 25-Hydroxy vitamin D (Vit D3) deficiency was found to be associated with vascular dysfunction, arterial stiffening, extent of coronary artery disease and cardiovascular mortality. Previous studies showed positive correlation between serum Vit D3 and HDL-C and negative correlation between Vit D3 and LDL-C. The aim of this study is to investigate more details about the possible association of serum Vit D3 level with lipid, lipoprotein and apolipoprotein level. **Methods** Totally 101 patients were included in this study and Vit D3, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), total triglyceride (TG), non-high-density lipoprotein cholesterol (Non-HDL-C), low-density lipoprotein particle (LDL-P), small dense low-density lipoprotein particle (sLDL-P), small dense low-density lipoprotein cholesterol (sdLDL-C), High-density lipoprotein cholesterol particles (HDL-P), High-density lipoprotein 2-cholesterol (HDL2-C), Apolipoprotein B(ApoB), Apolipoprotein A1 (Apo A1) and Apolipoprotein B/Apolipoprotein A1 ratio (ApoB/A ratio) were tested. **Results** Our results show that patients with Vit D3 deficiency (Vit D3 < 30 ng/ml) have significantly higher level of LDL-C, TG, Non-HDL-C, LDL-P, sLDL-P, sdLDL-C, ApoB and ApoB/A ratio compare with patients have normal Vit D3 level (Vit D3 > 30 ng/ml). Patients with normal Vit D3 level have significantly higher level of HDL-C and HDL2-C. Correlation study shows that Vit D3 level is negative correlated with TC, LDL-C, TG, Non-HDL-C, LDL-P, sLDL-P, sdLDL-C, ApoB and ApoB/A ratio and positive correlated with HDL2-C level. **Conclusion** Our results show that Vit D3 deficiency links to an increased risk for dyslipidemia and that may be the reason that patients with vitamin D deficiency tend to have higher risk of coronary artery disease.

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## 1. Introduction

Vitamin D is one of the fat soluble vitamins responsible for increasing intestinal absorption of calcium, magnesium, phosphate, and multiple other biological effects [1]. The most important forms of vitamin D are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) [2] Although vitamin D can be ingested from diet, the major natural source of the vitamin is synthesis of cholecalciferol in the skin from cholesterol through a chemical reaction that is dependant on sun exposure [3] Vitamin D from the diet, or from skin synthesis, is biologically inactive and must be converted to the active form after hydroxylation by an enzyme in the liver and the kidneys [4] Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol) and then further hydroxylated by the kidneys to form the biologically active form of vitamin D, calcitriol (also known as 1,25-dihydroxycholecalciferol).

Vitamin D has been found to be associated with vascular dysfunction, arterial stiffening, left ventricular hypertrophy, hypertension, hyperlipidemia, and worsening diabetes [5] Previous studies showed positive correlation between serum vitamin D3 and HDL cholesterol level and negative correlation between vitamin D3 and LDL cholesterol level [6] With the development of lipid research, there are more lipid, lipoprotein, and apolipoprotein level were shown to be associated with coronary artery disease(CAD) in the past several years. For example, Apolipoprotein B to Apolipoprotein A1 ratio is considered as a better discriminator of risk of coronary heart disease than is LDL or LDL/HDL ratio. Other lipid parameters such as low-density lipoprotein particle (LDL-P), small dense low-density lipoprotein particle (sLDL-P), small dense low-density lipoprotein cholesterol (sdLDL-C), High-density lipoprotein cholesterol particles (HDL-P) and high-density lipoprotein

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2-cholesterol (HDL2-C) have also been shown to closely associated with CAD [7–12]. It is not clear if Vit D level is also related with these new lipid parameters.

In this study, we investigated more details about the possible association of serum vitamin D3 level with lipoprotein and apolipoprotein level.

## 2. Methods

### 2.1. Subjects

We assessed 101 ambulatory patients treated by cardiovascular clinic from June 2017 to December 2018. This study was approved and monitored by Copernicus Group Institutional Review Boards. This study was in compliance with the Declaration of Helsinki. Informed consent was obtained from all individuals who participated. The study inclusion criteria were patients aged 18 to 80 years. Participants were excluded if they were diagnosed of chronic liver disease, familial hypercholesterolemia, active cancer or pregnant.

### 2.2. Blood sampling and laboratory measurements

Fasting blood samples were obtained between 8 and 10 a.m. after an overnight fast. All analyses of biomarkers were performed on the same blood sample. All biochemical parameters including Vit D3, total cholesterol(TC), low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), total triglyceride(TG), non-high-density lipoprotein cholesterol (Non-HDL-C), low-density lipoprotein particle (LDL-P), small dense low-density lipoprotein particle (sLDL-P), small dense low-density lipoprotein cholesterol (sdLDL-C), high-density lipoprotein cholesterol particles (HDL-P), High-density lipoprotein 2-cholesterol (HDL2-C), Apolipoprotein B(ApoB), Apolipoprotein A1 (Apo A1) and Apolipoprotein B/Apolipoprotein A1 ratio (ApoB/A ratio) were measured by True Healthy Diagnostics (Frisco, Texas, USA).

### 2.3. Statistics

SPSS 16 was used for statistical analysis. Data is presented as mean  $\pm$  standard error and  $P < 0.05$  was considered to be statistically significant. Categorical variables are defined as percentages. Student's t-test was used for continuous variables and the  $\chi^2$  test was used for categorical variables. Pearson's correlations were used to quantify associations between two variables. Multivariate linear regression was used to evaluate

**Table 1.** Clinical characteristics of study population.

Variable	Vit D3 <30 ng/ml	Vit D3 >30 ng/ml	P
Gender (men), n(%)	14(43.8%)	32(48.5%)	0.508
Age,years	59.3 $\pm$ 2.9	66.4 $\pm$ 1.9	0.037*
BMI,kg/m <sup>2</sup>	32.6 $\pm$ 1.2	28.3 $\pm$ 0.6	0.001*
HbA1c,%	6.30 $\pm$ 0.21	5.94 $\pm$ 0.08	0.115
UA, mg/dL	6.16 $\pm$ 0.33	5.75 $\pm$ 0.19	0.251
TSH, $\mu$ U/mL	2.88 $\pm$ 0.33	2.41 $\pm$ 0.18	0.216
Hs-CRP, mg/L	18.3 $\pm$ 12.7	6.5 $\pm$ 2.6	0.371
LVEF, %	53.7 $\pm$ 2.8	57.2 $\pm$ 1.5	0.230
Cr, mg/dL	1.04 $\pm$ 0.09	0.98 $\pm$ 0.03	0.440
DM, n(%)	7(20.0)	21(31.8)	0.207
CAD, n(%)	13(38.2)	17(25.8)	0.197
HTN, n (%)	19(52.3)	35(53.0)	0.904
Statin, n (%)	19(55.9)	36(59.0)	0.767

Data are presented as mean  $\pm$  standard error for continuous variables and number(percentage) for categorical variables. \*\*,  $P < 0.01$ , \*,  $P < 0.05$ .

BMI, body mass index; HbA1c, hemoglobin A1c; UA, uric acid; TSH, Thyroid-stimulating hormone; FFA, free fatty acid; hsCRP, high-sensitive C-reactive protein; LVEF, left ventricular ejection fraction; Cr, Serum creatinine; DM, diabetes mellitus; CAD, coronary artery disease; HTN, hypertension.

the association of myocardial damage with biomarkers and other possible contributed clinical factors.

## 3. Results

Baseline characteristics shows that vitamin D3 deficiency (vitamin D3 level <30 ng/ml) patients have significantly younger age and higher BMI than normal vitamin D3 level (Vit D3  $\geq$  30 ng/ml) patients, otherwise, the two groups have very balanced baseline characteristics (Table 1).

Our results show that the patients with vitamin D3 deficiency have statistically significant higher level of LDL-C (111.4  $\pm$  5.3 vs 96.9  $\pm$  3.5,  $P$  value 0.021), TG (163.7  $\pm$  14.3 vs 120.9  $\pm$  7.6,  $P$  value 0.004), Non-HDL-C, (130.5  $\pm$  5.6 vs 112.5  $\pm$  4.2,  $P$  value 0.011), LDL-P (1669.2  $\pm$  79.9 vs 1377.4  $\pm$  57.9,  $P$  value 0.004), sLDL-P (958.7  $\pm$  55.3 vs 761.6  $\pm$  41.5,  $P$  value 0.005), sdLDL-C (34.7  $\pm$  2.4 vs 28.1  $\pm$  1.5,  $P$  value 0.014), ApoB (94.7  $\pm$  3.5 vs 84.4  $\pm$  2.6,  $P$  value 0.020), and ApoB/A ratio (0.73  $\pm$  0.03 vs 0.63  $\pm$  0.02,  $P$  value 0.006) compared with the patients who have normal vitamin D3 level (Table 2).

The patients with normal vitamin D3 level have statistically significant higher level of HDL-C (51.0  $\pm$  2.1 vs 45.0  $\pm$  1.6,  $P$  value 0.024) and HDL2-C (14.1  $\pm$  1.1 vs 10.1  $\pm$  1.0,  $P$  value 0.010) compared with the patients with vitamin D3 deficiency (Table 2).

Pearson correlation analysis shows that vitamin D3 level is negatively correlated with LDL-C ( $r = -0.259$ ,  $P$  value 0.011), TG ( $r = -0.350$ ,  $P$  value 0.001), Non-HDL-C ( $r = -0.298$ ,  $P$  value 0.004), LDL-P ( $r = -0.324$ ,  $P$  value 0.001), sLDL-P ( $r = -0.317$ ,  $P$  value 0.002), sdLDL-C ( $r = -0.354$ ,  $P$  value 0.000),

**Table 2.** Association of Vit D3 level with lipid, lipoprotein and apolipoprotein level.

Lipid parameter	Vit D3		P value	Pearson correlation	P value
	<30 ng/ml	≥30 ng/ml			
TC	175.6 ± 6.3	163.3 ± 5.2	0.147	-0.250	0.015*
LDL-C	111.4 ± 5.3	96.9 ± 3.5	0.021*	-0.259	0.011*
HDL-C	45.0 ± 1.6	51.0 ± 2.1	0.024*	0.132	0.203
TG	163.7 ± 14.3	120.9 ± 7.6	0.004**	-0.350	0.001**
Non-HDL-C	130.5 ± 5.6	112.5 ± 4.2	0.011*	-0.298	0.004**
LDL-P	1669.2 ± 79.9	1377.4 ± 57.9	0.004**	-0.324	0.001**
sLDL-P	958.7 ± 55.3	761.6 ± 41.5	0.005**	-0.317	0.002**
sdLDL-C	34.7 ± 2.4	28.1 ± 1.5	0.014*	-0.354	0.000**
HDL-P	35.1 ± 0.9	34.8 ± 0.9	0.851	-0.090	0.393
HDL2-C	10.1 ± 1.0	14.1 ± 1.1	0.010*	0.354	0.005**
ApoB	94.7 ± 3.5	84.4 ± 2.6	0.020*	-0.294	0.004**
Apo A1	130.±3.6	135.4 ± 3.3	0.354	0.039	0.708
Apo B/A ratio	0.73 ± 0.03	0.63 ± 0.02	0.006**	-0.291	0.005**

Data are presented as mean ± standard error, \*\*, P < 0.01, \*, P < 0.05.

Vit D3, 25-Hydroxy vitamin D; LDL-C, low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; TG, total triglyceride; Non-HDL-C, non-high-density lipoprotein cholesterol; LDL-P, low-density lipoprotein particle; sLDL-P, Small dense low-density lipoprotein particle; sdLDL-C, small dense low-density lipoprotein cholesterol; HDL-P, High-density lipoprotein cholesterol particles; HDL2-C, High-density lipoprotein 2-cholesterol; ApoB, Apolipoprotein B; Apo A1, Apolipoprotein A1; ApoB/A ratio, Apolipoprotein B/Apolipoprotein A1 ratio.

ApoB ( $r = -0.294$ , P value 0.004), and ApoB/A ratio ( $r = -0.291$ , P value 0.005). It also showed that vitamin D3 level is positively correlated with HDL2-C level ( $r = 0.354$ , P value 0.005) (Table 2).

#### 4. Discussion

Vitamin D is a steroid hormone that executes its biological function by bindings to and activating its cognate receptor vitamin D receptor (VDR). Upon ligand binding, VDR forms a heterodimer with retinoic X receptor (RXR) to induce transcription of its target genes [13]. VDR is widely expressed in nearly 30 different tissues, which explains the wide range of biological function of vitamin D. Besides the well-studied musculoskeletal consequences of vitamin D deficiency (VDD) such as rickets, osteopenia, osteoporosis, fragility bone fracture and muscle weakness, the condition is also increasingly recognized to be associated with an array of non-skeletal pathologies including cardiovascular diseases (CVD) such as coronary artery disease (CAD), cerebrovascular accident (CVA), congestive heart failure (CHF) etc [14,15]. On the basis of Hill's criteria for causality, Wayland PG et al concluded that VDD is casually associated with increased risk for CVD [16]. Both animal and human studies have revealed that VDD is associated with increased renin-angiotensin system activity [17]. Vitamin D level was found inversely associated with blood pressure [18]. VDD is associated with increased production of reactive oxygen species and development of insulin resistance [19] vitamin D might also directly affect a variety of endothelial cell functions to regulate cardiovascular health [20]

Multiple previous studies showed that vitamin D deficiency was associated with unfavorable lipid profile. For example, vitamin D deficiency was

shown to be associated with higher LDL-C[A], TG [21,22] and Apo B [23] level while higher vitamin D level was shown to be associated with higher favorable lipid profile, such as HDL [24,25] and Apo A [25]. ApoB/A ratio and LDL subtypes such as sLDL-P and sdLDL-C have been shown to be positively associated with risk and severity of CAD and are better than the conventional LDL and other lipids as a risk marker [7-11,26]. In this study, we were able to identify that patients with vitamin D3 deficiency have higher levels of sLDL-P, sdLDL-C and ApoB/A ratio which may contribute to accelerated atherosclerosis and risk of coronary artery disease. Our study also indicates that vitamin D level is positively associated HDL2-C level. To the best of our knowledge, no other study has shown such a relationship of vitamin D level with sLDL-P, sdLDL-C, ApoB/A ratio and HDL2-C. The possible mechanism between the association of vitamin D and lipid is not very clear. Vitamin D is structurally related to cholesterol and photosynthesis of cholecalciferol is achieved by irradiation of cutaneous 7-dehydrocholesterol, which is a precursor of cholesterol [5]. Previous study also showed that incubation with calcitriol increases lipoprotein lipase expression and activity in cultured adipocytes [27] Moreover, Shirts et al showed that A 25OH vitamin D receptor binding site modifying APOA5 promoter polymorphism is associated with lower HDL-C in 25OHD-deficient individuals [28].

Numerous studies have also suggested an association between vitamin D level and cardiovascular risk factors and cardiovascular diseases [14] In a meta-analysis with 19 prospective studies and 65,994 participants, Wang et al. demonstrated a general linear, inverse association between circulating vitamin D level and risk of cardiovascular diseases [29]. In a prospective analysis of a large electronic medical record database, Anderson et al. found that vitamin

D levels were highly associated with coronary artery disease, myocardial infarction, heart failure, and stroke [15]. Several studies conducting meta-analyses including from 40,000 to over 100,000 participants also found associations between vitamin D and CAD/MI [29]. However, there are also studies with inconclusive findings. For example, a study by Dziedzic et al. failed to demonstrate a correlation between vitamin D and the stage of coronary atherosclerosis. In this case, it may have been due to heterogeneity of the overall study population because a potential relationship was observed in subgroup analyses, including an analysis on diabetic status [30]. In a subsequent study in non-diabetic cardiac patients, the authors found a significant inverse correlation between 25(OH)D level and Coronary Artery Surgery Study Score (CASSS) [31].

In contrast to observational studies and meta-analyses that consistently showed a significant association between low vit D levels and cardiovascular risk factors and adverse outcomes [14,32–34], results of studies to prove a beneficial effect of vit D supplementation on cardiovascular disease and risk factors including lipid panel have been inconsistent. Multiple RCTs have found no significant improvement in lipid panel with supplementation of vit D. In addition, several meta-analyses have concluded that current evidence does not support a beneficial effect of vit D supplementation on cardiovascular risk factors including lipid panel. However, Mirhosseini [35,36] et al point out that the quality of several of the RCTs included in those meta-analysis are of poor design and are either not powered, lack sufficient follow-up duration or supplement with too low doses of vit D to be able to provide robust conclusions. Several studies also failed to report baseline and/or follow up vit D levels to be able to link a change in vit D levels to observed outcomes. They stress the importance of adequate duration of vit D supplementation since the long half-life of 25 (OH)D requires at least a follow up of 3 months to establish and maintain a steady state concentration. In their meta-analysis, Mirhosseini et al applied strict inclusion criteria regarding follow-up duration, reporting of change in vit D level with supplementation, and use of a control group in an effort to exclude poor quality data. They included 38 papers which reported on the effect of vit D supplementation on lipid profiles and found that the pooled effect size showed a significant reduction in triglycerides, reduction in total cholesterol, and LDL and increase in HDL. Their findings are closely comparable to the meta-analysis of Jafari et al [37], who also reported significant reductions in serum total cholesterol, triglyceride, and LDL levels in patients with type 2 diabetes mellitus following vitamin D supplementation. Overall, evidence supports an

association between low level of vitamin D and cardiovascular diseases. This led to interests to investigate potential cardiovascular protective effects of vitamin D supplementation. However, these studies provided uncertain results.

In summary, our results show that Vit D3 deficiency links to an increased risk for dyslipidemia, especially associated with higher levels of some LDL subtypes (such as sLDL-P, sdLDL-C) and Apolipoprotein B/Apolipoprotein A1 ratio, which may contribute to accelerated atherosclerosis and higher risk of coronary artery disease

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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