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No effect of vitamin D administration plus dietary intervention on emerging cardiovascular risk factors in patients with metabolic syndrome

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HIGHLIGHTS

- 74% of participants were VitD deficient possibly due to reduced outdoor activity or VitD sequestration in their fat tissue.
- MetS patients have increased atherogenic sdLDL-C levels and elevated Lp-PLA_2 activity, associated with increased CVD risk.
- MetS subjects also have increased leptin and decreased adiponectin serum levels, related to a chronic low-grade inflammatory state.
- Data indicate a relationship between 25(OH)VitD and these emerging CVD risk factors. However interventional studies show contradictory results.
- In this study VitD supplementation was not associated with significant changes in emerging CVD risk factors.

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ABSTRACT

Background: Patients with metabolic syndrome (MetS) have low serum 25-hydroxyvitamin D (25(OH)VitD) levels. Low 25(OH)VitD has been associated with several emerging cardiovascular disease (CVD) risk factors, while VitD administration may ameliorate them.

Aim: To study the effect of 25(OH)VitD supplementation plus dietary instructions on novel CVD risk factors in MetS patients.

Methods: This is a pre-specified analysis of a previously published study. Patients with MetS (n = 50, 52 ± 10 years) were given dietary instructions and were randomized to receive either 25(OH)VitD, 2.000 IU/day p.o. (Suppl group) or nothing (No-Suppl group). Serum 25(OH)VitD, small dense low-density lipoprotein cholesterol (sdLDL), as well as lipoprotein-associated phospholipase A_2 ($LpPLA_2$) activity, leptin and adiponectin levels were measured at baseline and 3 months later.

Results: In the Suppl group 25(OH)VitD levels increased by 90% [from 16.1 (3.3–35.1) to 30.6 (8.4–67.6) ng/mL, p = 0.001] and by 33.3% [from 9.9 (4.0–39.6) to 13.2 (3.5–36.8) ng/mL, p = NS] in the No-Suppl group. sdLDL serum levels, mean LDL size, $LpPLA_2$ activity, leptin, adiponectin concentration and leptin to adiponectin ratio did not change significantly in both groups.

Conclusion: In this small study the administration of 25(OH)VitD plus dietary intervention in patients with MetS were not associated with any significant change in various emerging CVD risk factors. (NCT01237769 ClinicalTrials.gov).

1. Introduction

During the last decades it has become evident that vitamin D (VitD), essential for bone homeostasis and calcium metabolism, plays also an important role in several other metabolic pathways [1]. VitD deficiency (25(OH)VitD levels < 20 ng/mL) [2] has been related to various chronic musculoskeletal, infectious, autoimmune and malignant diseases [3] as well as to metabolic syndrome (MetS) [4] and cardiovascular diseases (CVD) [5,6]. However, despite the mounting epidemiological evidence of a link between VitD deficiency and increased CVD

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risk [7–10], the results of VitD supplementation trials have been negative [11–19].

MetS is associated with increased risk for CVD and has also been related to various emerging CVD risk factors, such as increased levels of atherogenic small dense low-density lipoprotein cholesterol (sdLDL-C) [20,21], elevated lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity [22], as well as decreased plasma adiponectin and increased leptin levels [23]. Scarce data indicate a possible relationship between 25(OH)VitD serum levels and these emerging CVD risk factors, though not consistently [24–29], while interventional studies have shown contradictory results [30–35]. Of note, there is a pausity of data on VitD supplementation effect in MetS subjects.

In this study, we examined the effect of VitD supplementation plus dietary intervention on various emerging CVD risk factors in MetS subjects.

2. Material and methods

2.1. Study population

This is a pre-specified analysis of a previously published study with a prospective, randomized, open-label, blinded end-point (PROBE) design [36]. Consecutive subjects with MetS visiting the Outpatient Metabolic and Obesity Clinic of the University Hospital of Ioannina, Ioannina, Greece, were included. Patients with diabetes, chronic kidney or liver disease, triglycerides > 500 mg/dL (5.65 mmol/L) and intake of calcium and/or VitD supplements as well as lipid-lowering medications were excluded. Eligible patients were randomly allocated (through a computer-generated sequence of random numbers) by sex and age as baseline factors to either only dietary instructions (n = 25, No-Suppl group) or to receive 2000 IU VitD/day po (Vitamin D3, Lamberts) plus dietary instructions (n = 25, Suppl group) for 3 months. Endocrine Society clinical practice guidelines state that to raise serum 25(OH)VitD to levels above 30 ng/mL, VitD intakes of 1500–2000 IU/day may be required [37]. All patients (n = 50) followed a 12-week dietary intervention programme so as to achieve a 500 kcal reduction in daily energy intake. Compliance with dietary instructions was assessed by completing food diaries and through discussion during follow-up visits, while compliance with study medication was assessed by tablet count at week 12; patients were considered compliant if they took 80–100% of the prescribed tablets. In order to minimise the effect of sunlight on 25(OH)VitD levels, all specimens were collected during March to September, a season during which the duration of sunlight is approximately similar in Greece. The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by hospital ethics committee. Informed consent was obtained from all participants. This study is registered in ClinicalTrials.gov (NCT01237769).

2.2. Laboratory measurements

All laboratory assays were performed after an overnight fast and were blindly assessed regarding treatment allocation at baseline and 12 weeks after study onset. Serum 25(OH)VitD levels were measured quantitatively by an enzyme immunoassay method using the reagents from DRG Instruments GmbH kit (DRG, Marburg, Germany). The method's analytical sensitivity is 1.28 ng/mL and the intra- and inter assay variation is 13% for each at the level of 18 and 16 ng/mL, respectively.

LDL subclass analysis was performed electrophoretically by use of high-resolution 3% polyacrylamide gel tubes and the Lipoprint LDL System (Quantimetrix, Redondo Beach, CA). After electrophoresis, very low-density lipoprotein (VLDL) remained at the origin [retention factor (R_f) = 0.0], high-density lipoprotein (HDL) migrated to the front (R_f = 1.0). In between, several bands can be detected: MID bands C, B, and A, which correspond mainly to intermediate-density lipoprotein (IDL), as well as up to 7 LDL bands. The LDL-1 and LDL-2 bands correspond to large buoyant LDL particles, whereas bands LDL-3 to LDL-7 correspond to sdLDL particles. The cholesterol mass (in mg/dL) of sdLDL particles, the mean LDL particle size (in nm) and the proportion (%) of the cholesterol mass of sdLDL particles over the total LDL-C mass were determined as we have previously described [21,38].

Lp-PLA_2 activity was measured with the trichloroacetic acid precipitation procedure in plasma using [^{3}H]-PAF (1-*O*-hexadecyl-2-[^{3}H-acetyl]-*sn*-glycero-3-phosphocholine) (10 Ci/mmol; DuPont-New England Nuclear, Boston, MA) as a substrate at a final concentration of 100 μM. The radioactivity was determined in a liquid scintillation counter (Packard Tri-Card 2100). Lp-PLA_2 activity was expressed as nmol PAF degraded per min per mL of plasma [39].

Leptin was determined using the human leptin ELISA kit purchased from BioVendor (Czech Republic) following manufacturer instructions. Coefficient of variation was less than 7%. Each concentration obtained was determined from the standard curve [40]. Plasma levels of total adiponectin were determined using the adiponectin multimeric enzyme immunoassay (ALPCO DIAGNOSTICS, Salem, NH, USA) according to manufacturer's protocol. The intra-assay coefficient of variation (CV) was 5.4% [40].

2.3. Statistical analysis

This was a pilot study and therefore formal power calculations were not performed. The evaluation of the distribution of each variable (Gaussian or not) was done with the Kolmogorov-Smirnoff test. For variables with a Gaussian distribution data are presented as mean ± standard deviation and for those with a non-Gaussian distribution as median (range, min-max). The paired samples t-test or the Wilcoxon Signed Ranks test was used so as to assess the effect of treatment in each group. For comparisons between treatment groups analysis of covariance (ANCOVA) or the Kruskal-Wallis test for non-parametric variables, adjusted for baseline values was applied. The significance was set at $p < 0.01$ due to multiple comparisons (Bonferoni correction). All analyses were performed through the SPSS 18.0 statistical package for Windows (SPSS Inc., 1989–2004, Chicago, IL).

3. Results

The clinical and laboratory characteristics of study participants (n = 50) are shown in Table 1. No significant differences in baseline characteristics were noted between the 2 groups. There were also no differences in dietary intake between the groups at baseline and after the intervention (data not shown).

At baseline 74% of the participants were VitD deficient (25(OH) VitD < 20 ng/mL). Three months after intervention, a similar small weight reduction (1–2 kg) was achieved in both groups (Table 2). In the Suppl group, 25(OH)VitD increased significantly by 90% [from 16.1 (3.3–35.1) to 30.6 (8.4–67.6) ng/mL, p = 0.001] and in the No-Suppl group by 33.3% [from 9.9 (4.0–39.6) to 13.2 (3.5–36.8) ng/mL, p = NS]. At the follow-up visit 3 months later, no significant changes in serum sdLDL levels, sdLDL proportion, mean LDL size and LpPLA_2 activity, as well as in leptin and adiponectin levels and leptin to adiponectin ratio were noted in both groups (Table 2). No difference in changes of these parameters was noticed between groups.

4. Discussion

In this study we showed that VitD supplementation plus dietary instructions was not associated with any meaningful change of several emerging CVD risk factors in patients with MetS as compared with dietary instructions alone.

MetS is a constellation of known CVD risk factors (abdominal obesity, atherogenic dyslipidemia, disturbed carbohydrate metabolism and elevated blood pressure) [41], that has also been associated with

Table 1
Baseline characteristics of study participants.

	No-Suppl	Suppl	p
N (males/females)	25 (10/15)	25 (15/10)	NS
Age (years)	52 ± 15	53 ± 7.0	NS
Smoking, %	24	16	NS
Body Weight (kg)	89.0 ± 13.4	89.3 ± 16.6	NS
BMI (kg/m^2)	33.4 ± 6.0	31.2 ± 5.3	NS
WC (cm)	110.0 ± 9.0	107.7 ± 12.7	NS
SBP (mm Hg)	137 ± 13	135 ± 14	NS
DBP (mm Hg)	87.0 ± 9.0	86.0 ± 8.0	NS
25(OH)VitD (ng/mL)	9.9 (4.0–39.6)	16.1 (3.3–35.1)	NS
TCHOL (mg/dL)	225 ± 33	230 ± 46	NS
TGs (mg/dL)	153 (84–273)	155 (112–248)	NS
HDL-C (mg/dL)	51 ± 8.0	47 ± 9.0	NS
LDL-C (mg/dL)	143 ± 25	148 ± 46	NS
sdLDL-cholesterol (mg/dL)	7.0 (0.0–22.0)	9.0 (0.0–40.0)	NS
sdLDL proportion (%)	3.8 ± 2.8	5.7 ± 5.2	NS
Mean LDL size (nm)	266.5 ± 3.9	264.8 ± 6.3	NS
LpPLA$_2$ activity (nmol/mL/min)	57.4 ± 13.3	56.4 ± 15	NS
Leptin (ng/mL)	17.9 (3.9–93.7)	11.2 (3.0–106.3)	NS
Adiponectin (μg/mL)	8.1 ± 3.3	8.2 ± 3.6	NS
Leptin: Adiponectin Ratio	2.4 (0.4–75)	1.8 (0.3–76.2)	NS

BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, TCHOL: total cholesterol, TGs: triglycerides, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, 25(OH)Vit D: 25-hydroxy vitamin D, sdLDL: small dense low-density lipoprotein, LpPLA$_2$: lipoprotein-associated phospholipase A$_2$.
NS: non significant.

various emerging CVD risk factors. In particular, patients with MetS have increased atherogenic sdLDL-C levels [21,42], and elevated lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) activity [22], both of which have been associated with increased CVD risk [43,44]. Also, MetS subjects have increased leptin and decreased adiponectin serum levels [23]. These features are associated with a chronic low-grade inflammatory state, since leptin up-regulates pro-inflammatory cytokines, while adiponectin has anti-inflammatory properties [23]. In this context, the leptin/adiponectin ratio has been related to central obesity and other metabolic risk factors [45].

Patients with MetS have decreased 25(OH)VitD levels [46], a finding confirmed in this study (74% of participants had VitD deficiency at baseline). This is possibly attributed to obesity and associated co-morbidities which could reduce outdoor physical activity and sun exposure, leading to reduced 25(OH)VitD skin synthesis, or to VitD sequestration in their excessive fat tissue [47].

Low 25(OH)VitD serum levels have been linked with poor CVD outcomes based on strong evidence from observational studies [7–10]. In particular, VitD deficiency has been associated with increased all-cause mortality [48–50] and increased CVD risk, including cardiovascular mortality [7,49], greater carotid intima-medial thickness [51], peripheral arterial disease [52], myocardial infarction [53], coronary heart disease [54,55], stroke [56–58] and heart failure [59]. However, results from randomized controlled trials on the effect of VitD supplementation on CVD risk have been negative [13–19]. Recently, in the VITAL trial supplementation with 2000 IU/day VitD3 in 25,871 subjects did not result in a lower incidence of CVD events compared with placebo [12]. Also, in ViDA trial the rate of CVD events was not lower among participants who received monthly administration of high-dose

Table 2
Anthropometric and metabolic parameters at baseline and 3 months after treatment.

	Baseline	3 Months	p vs baseline	Change, %	p vs No Suppl
Weight (kg)					
No Suppl	89.0 ± 13.4	87.0 ± 12.4	0.005	- 2.2	
Suppl	89.3 ± 16.6	88.0 ± 17.1	0.02	- 1.4	NS
BMI (kg/m^2)					
No Suppl	33.4 ± 6.0	32.4 ± 5.3	0.008	- 2.9	
Suppl	31.2 ± 5.3	30.9 ± 5.0	0.03	- 0.9	NS
WC (cm)					
No Suppl	110.0 ± 9.0	107.6 ± 9.6	0.002	- 2.2	
Suppl	107.7 ± 12.7	106.3 ± 13.8	0.07	- 1.3	NS
25(OH)VitD (ng/mL)					
No Suppl	9.9 (4.0–39.6)	13.2 (3.5–36.8)	NS	+33.3	
Suppl	16.1 (3.3–35.1)	30.6 (8.4–67.6)	0.001	+90.0	0.002
sdLDL-cholesterol (mg/dL)					
No Suppl	7.0 (0.0–22)	5.0 (2.0–25)	NS	- 28.6	
Suppl	9.0 (0.0–40)	4.0 (0.0–46)	NS	- 55.5	NS
sdLDL proportion (%)					
No Suppl	3.8 ± 2.8	3.3 ± 2.3	NS	- 13.2	
Suppl	5.7 ± 5.2	4.5 ± 4.4	NS	- 21.0	NS
Mean LDL size (nm)					
No Suppl	266.5 ± 3.9	267.0 ± 3.5	NS	+0.2	
Suppl	264.8 ± 6.3	266.6 ± 5.2	NS	+0.7	NS
LpPLA$_2$ activity (nmol/mL/min)					
No Suppl	57.4 ± 13.3	52.7 ± 12.4	NS	- 8.1	
Suppl	56.4 ± 15.0	55.7 ± 13.5	NS	- 1.2	NS
Leptin (ng/mL)					
No Suppl	17.9 (39.0–93.7)	14.6 (3.0–66.2)	NS	- 18.4	
Suppl	11.2 (3.0–106.3)	10.3 (2.8–43.8)	NS	- 8.0	NS
Adiponectin (μg/mL)					
No Suppl	8.1 ± 3.3	8.3 ± 3.1	NS	+2.4	
Suppl	8.2 ± 3.6	8.1 ± 3.9	NS	- 1.2	NS
Leptin: Adiponectin Ratio					
No Suppl	2.4 (0.4–75)	1.7 (0.4–76.2)	NS	- 29.2	
Suppl	1.8 (0.3–76.2)	1.4 (0.3–52.6)	NS	- 22.2	NS

Suppl: supplementation, BMI: body mass index, WC: waist circumference, 25(OH)Vit D: 25-hydroxy vitamin D, sdLDL: small dense low-density lipoprotein, LpPLA$_2$: lipoprotein-associated phospholipase A$_2$.
NS: non significant.

VitD than placebo [11].

VitD deficiency has been associated with MetS characteristics in most [5,60–62], but not all studies [63–66]. The possible relationship between 25(OH)VitD and emerging CVD risk factors is also controversial. We have previously shown that in MetS patients, low 25(OH)VitD levels were associated with increased sdLDL-C levels [24], as confirmed by a recent study [20]. However, 25(OH)VitD was not related either to mean LDL size or to $LpPLA_2$ activity [24]. In the present study, treatment with VitD (2000 IU/day for 3 months) was not associated with any change of sdLDL-C levels, mean LDL size or $LpPLA_2$ activity. As previously published, VitD treatment was neither associated with any change in triglycerides, HDL-C and LDL-C [36]. On the contrary, a small recent study in patients with obstructive sleep apnoea and increased body mass index (BMI = 30.4 kg/m^2) who received 4000 IU/day VitD or placebo per os for 15 weeks showed significant decreases in both LDL-C and $LpPLA_2$ [25]. The mechanism through which VitD could influence lipid profile is not clear. Previous data has suggested that VitD could reduce synthesis and secretion of hepatic triglycerides, by increasing intestinal calcium absorption [67], or by regulating PTH levels [68]. Since the higher the triglyceride levels, the smaller the LDL size [21], VitD deficiency could theoretically contribute to increased sdLDL-C concentrations in an indirect manner, i.e. by increasing triglycerides levels. Moreover, VitD could contribute to serum LDL-C reduction by decreasing fat absorption, particularly saturated fatty acids [69].

A recent systematic review and meta-analysis concluded that the inverse association between 25(OH)VitD and serum leptin levels found in most observational studies, was not confirmed in interventional studies [30]. In particular, 25(OH)VitD concentration correlated negatively with leptin levels in pre-diabetic subjects [70], in type 2 diabetic patients [26], in obese women [71], in women with breast cancer [72] and in chronic kidney disease patients [73]. This association is possibly explained by accumulation of the fat-soluble VitD in adipocytes that subsequently prompts leptin secretion [74]. Another hypothesis is that low $1,25(OH)_2$VitD could reduce calcium serum levels and induce secondary hyperparathyroidism, which in turn stimulates lipogenesis and leads to increased leptin secretion by adipocytes [75]. Interventional studies showed conflicting results. Some studies showed that VitD supplementation led to increases in serum leptin levels [74,76] and one showed that it decreased leptin concentration [33]. A meta-analysis of randomized controlled trials concluded that VitD supplementation did not affect leptin levels [32] and so did a secondary analysis of the D-Health trial [31], similar to our results.

Regarding the association of 25(OH)VitD with adiponectin levels, previous studies have shown equivocal findings. Some showed a positive correlation between 25(OH)VitD and adiponectin [26,27] while another did not confirm this relation [28]. Interventional studies generally provided little evidence of an effect of VitD supplementation on adiponectin levels [31,32,77], while one showed an increase in adiponectin levels [33] and another only a marginal raise [34]. In the present study we found no effect of VitD supplementation on adiponectin concentration after treatment.

Only a few studies have investigated the relationship between 25(OH)VitD levels and the leptin to adiponectin ratio. Observational studies reported an inverse relation of 25(OH)VitD and leptin to adiponectin ratio in type 2 diabetic patients [26] and in women with polycystic ovary syndrome [29]. Interventional studies showed that VitD supplementation reduced the leptin to adiponectin ratio [34,35,78], but this was not confirmed in the present study. The inconsistencies between these different studies may be due to the fact that adipokine levels are affected by genetic factors, degree of tissue adiposity, maturity of adipocytes, age at diagnosis and severity of associated conditions [79].

Overall, a discrepancy exists between findings from observational and interventional studies regarding the association between VitD levels and CVD risk factors and outcomes, and at this time a causal relationship between low 25(OH)VitD levels and CVD cannot be supported. Conflicting data among studies may be related to differences in a) studied populations and number of participants, b) baseline VitD status, c) dose, route and duration of treatment, and d) study design.

4.1. Study limitations

This study has certain limitations. It is mainly a pre-specified analysis of a previously published pilot study with a small number of participants. Therefore, safe conclusions cannot be reached. Supplementation dose (2000 IU/day) and duration (3 months) may be inadequate to see an effect on the examined emerging CVD risk factors. According to previous suggestions, concentrations of at least 35–60 ng/mL would be necessary to treat VitD deficiency [80], while in our active treatment group mean VitD levels were 30.6 ng/mL.

5. Conclusion

In this small study we found that VitD supplementation (2000 IU/day for 3 months) plus dietary intervention were not associated with significant changes in various emerging CVD risk factors (sdLDL serum levels, mean LDL size, $LpPLA_2$ activity, leptin, adiponectin and leptin to adiponectin ratio) compared with dietary intervention alone in MetS subjects. These results should be confirmed in larger studies.

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Conflicts of interest

None.

Author statement to the relevant CRediT roles

- Stefania E. Makariou MD: Data curation, Writing - original draft
- Moses Elisaf MD: Conceptualization, Funding acquisition, Project administration
- Anna Challa PhD: Formal analysis, Supervision, review & editing
- Constantinos C. Tellis PhD: Formal analysis
- Alexandros D. Tselepis MD, PhD: Supervision, Validation, review & editing
- Evangelos N. Liberopoulos MD: Conceptualization, Methodology, Supervision, review & editing

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