RESEARCH

Vitamin D level regulates serum lipids discrepantly in adults with and without dyslipidemia

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Abstract

Vitamin D deficiency is associated with hyperlipidemia, but it remains unclear whether vitamin D supplementation reduces serum lipid levels. The aims of this study were to investigate the associations between increased serum 25-hydroxyvitamin D (25(OH)D) concentrations and lipid levels and identify the characteristics of people with or without lipid reduction associated with increased 25(OH)D levels. The medical records of 118 individuals (53 men; mean age, 54.4 ± 10.6 years) whose serum 25(OH)D levels increased between 2 consecutive measurements were retrospectively reviewed. People with increased 25(OH)D levels (from 22.7 (17.6–29.2) to 32.1 (25.6–36.8) mg/dL; $P < 0.01$) had a significant reduction in serum levels of triglycerides (TGs) (from 111.0 (80–164) to 104.5 (73–142) mg/dL; $P < 0.01$) and total cholesterol (TC) (from 187.5 (155–213) to 181.0 (150–210) mg/dL; $P < 0.05$). The individuals who responded to vitamin D (≥10% reduction in TG or TC levels) exhibited significantly higher baseline TG and TC levels than those who did not. Only patients with hyperlipidemia (not those without hyperlipidemia) at baseline exhibited significantly reduced TG and TC levels at follow-up. However, increasing serum 25(OH)D concentrations were significantly correlated with decreasing lipid levels in individuals with baseline 25(OH)D levels less than 30 ng/mL and in individuals aged 50–65 years (not in patients younger than 50 years or older than 65 years). In conclusion, increasing serum 25(OH)D concentrations may be potentially helpful for the treatment of hyperlipidemia in people with vitamin D deficiency.

Background

Vitamin D, a group of lipid-soluble molecules, is synthesized primarily from 7-dehydrocholesterol in the skin through the action of ultraviolet B radiation. A major physiological role of vitamin D involves the regulation of calcium homeostasis (1). In addition to being associated with poor musculoskeletal health, vitamin D deficiency is associated with obesity, hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome, and cardiovascular diseases (2, 3, 4, 5, 6). Vitamin D deficiency, defined as a serum 25-hydroxyvitamin D (25(OH)D) level less than 30 ng/mL, is a common disorder with an estimated prevalence of approximately 30–80% among adults worldwide (7, 8). Although a serum 25(OH)D level greater than 30 ng/mL is considered to be adequate for improved musculoskeletal health, the optimal serum

level of 25(OH)D for organs other than bone remains debatable. The 2018 Vitamin D Supplementation Guidelines recommended daily supplementation of 400–800 IU vitamin D for bone health, 400–2000 IU vitamin D for pleiotropic benefits, and 30–50 ng/mL serum 25(OH)D levels for overall health benefits (9).

Observational data indicate an inverse correlation between the serum levels of 25(OH)D and those of lipids (10, 11). The aforementioned studies have reported that individuals with low levels of serum 25(OH)D have higher levels of total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C) but lower levels of high-density lipoprotein cholesterol (HDL-C) than those with higher levels of 25(OH)D. Our recent study in an East Asian population revealed that sex and age modulate the positive correlation between vitamin D deficiency and hypertriglyceridemia (12). Furthermore, a recent meta-analysis indicated that vitamin D supplementation substantially reduces the levels of TC, TG, and LDL-C (13). Conversely, another meta-analysis suggested that vitamin D supplementation does not affect the levels of TC, LDL-C, and HDL-C but increases those of TG in adults with metabolic syndrome (14). Moreover, whether patient characteristics can help predict their response to the lipid-lowering effects of vitamin D remains unclear. Therefore, in the present study, we investigated the association between increased concentrations of circulating vitamin D and the levels of serum lipids and aimed to identify the individuals (responders) who could benefit from vitamin D supplementation.

Methods

Participants

We retrospectively reviewed the data of individuals aged >18 years whose serum 25(OH)D levels increased between two consecutive blood tests and who had available biochemistry data, including data on complete blood count (CBC) and the levels of TC, TG, HDL-C, LDL-C, glycated hemoglobin (HbA1c), blood urea nitrogen, creatinine, uric acid, aspartate transaminase, alanine transaminase (ALT), γ-glutamyl transpeptidase (γ-GT), alkaline phosphatase, total bilirubin, and albumin. Inclusion criteria were individuals aged older than 18 years who had two serum 25(OH)D measurements during the period between June 2017 and May 2022 in Wan Fang hospital. Exclusion criteria were individuals who had decreased serum 25(OH)D levels, had no lipid measurement within 12 weeks of each 25(OH)D measurement, and had two 25(OH)D measurements less than 3 months or greater than 3 years apart (Fig. 1). We collected data regarding patient characteristics, such as age, sex, body weight, body height, drug history (e.g., statin, fibric acids, nicotinic acid, and ezetimibe), and medical history (e.g., hypertension, diabetes mellitus, and cancer). Hypertriglyceridemia was defined as a TG level of >150 mg/dL, and hypercholesterolemia was defined as a TC level of >200 mg/dL (15). TC and TG responders were defined as individuals exhibiting decreases of ≥10% in their serum levels of TC and TGs, respectively (16). The present study was approved by
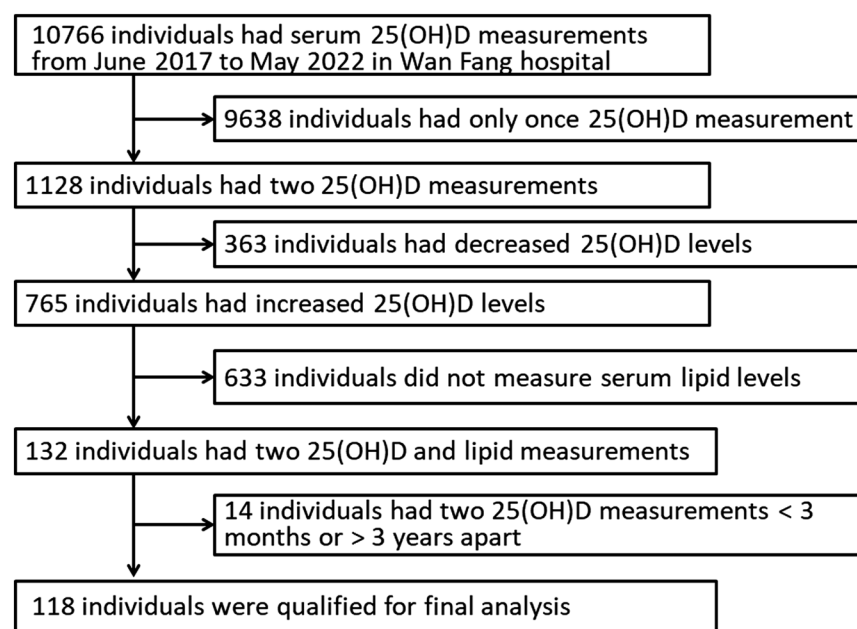

Figure 1
Flow diagram of study individual enrollment process. 25(OH)D, 25-hydroxyvitamin D.

the Institutional Review Board of Taipei Medical University, Taiwan (protocol code: N202205067).

Statistical analysis

Data are expressed as the mean ± standard deviation for normally distributed variables, or median and interquartile range for non-normally distributed variables, or frequency and percentage for categorical variables. Chi-square test (for categorical variables), paired or unpaired *t*-test (for normal distribution), and Wilcoxon signed-rank test or Mann–-Whitney *U* test (for non-normal distribution) were performed to analyze between-group differences. SigmaPlot (version 12; Systat Software, Inc., San Jose, CA, USA) was used for statistical analyses. Logistic regression analysis was performed to evaluate the independent biomarkers associated with TC or TG responders, and the data are expressed as odds ratios (ORs). A *P*-value of <0.05 indicated statistical significance.

Results

General characteristics

We included a total of 118 individuals (53 men; mean age, 54.4 ± 10.6 years) with increased serum 25(OH)D levels during a mean follow-up period of 447 ± 230 days. In total, 34 individuals used statin and 4 used fenofibrate (including two who used both statin and fenofibrate) at consistent doses of these lipid-lowering agents between baseline and follow-up. As shown in Table 1, people with increased 25(OH)D levels (from 22.7 (17.6–29.2) to 32.1 (25.6–36.8) mg/dL; *P* < 0.01) also had a significant reduction in TG levels (from 111.0 (80–164) to 104.5 (73–142) mg/dL; *P* < 0.01) and TC levels (from 187.5 (155–213) to 181.0 (150–210) mg/dL; *P* < 0.05). No significant differences were noted in LDL-C (from 113.5 (95–136) to 109.0 (88–130) mg/dL; *P* = 0.51), HDL-C (from 52.2 ± 13.9 to 54.0 ± 15.4 mg/dL; *P* = 0.82), HbA1c (from 5.7 (5.4–6.1) % to 5.6 (5.3–6.1) %; *P* = 0.93), or BMI (from 24.0 (21.4–27.6) to 24.1 (21.7–26.9) kg/m²; *P* = 0.84) between baseline and follow-up.

Additionally, the 118 individuals were divided into two groups according to the magnitude of increases in 25(OH)D levels, which was greater or less than 10 mg/dL. We found that people with increased 25(OH)D >10 mg/dL had a tendency to have a greater reduction in TG levels than those with increased 25(OH)D <10 mg/dL (TG change: −14 (−49.5 to 1.5) mg/dL vs −5 (−29.5 to 14.5) mg/dL, *P* = 0.089). The decreases in TC levels

Table 1 Biomarkers of cohorts (*n* = 118) at baseline and follow-up: mean ± s.d. for normally distributed variables or median (interquartile range) for non-normally distributed variables.

Biomarkers	Baseline	Follow-up	*P*-value
BMI (kg/m²)	24.0 (21.4–27.6)	24.1 (21.7–26.9)	0.84
25(OH)D (ng/mL)	22.7 (17.6–29.2)	32.1 (25.6–36.8)	<0.01
TG (mg/dL)	111.0 (80–164)	104.5 (73–142)	<0.01
TC (mg/dL)	187.5 (155–213)	181.0 (150–210)	<0.05
LDL-C (mg/dL)	113.5 (95–136)	109.0 (88–130)	0.51
HDL-C (mg/dL)	52.2 ± 13.9	54.0 ± 15.4	0.82
HbA1c (%)	5.7 (5.4–6.1)	5.6 (5.3–6.1)	0.93
BUN (mg/dL)	12.3 ± 5.6	13.2 ± 6.0	0.06
Creatinine (mg/dL)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.51
Albumin (g/dL)	4.4 ± 0.2	4.4 ± 0.2	0.27
AST (U/L)	19 (17–23)	20 (17–23)	0.45
ALT (U/L)	19 (14–29)	21 (15–28)	0.98
Total bilirubin (mg/dL)	0.8 (0.6–1.1)	0.8 (0.6–1.0)	0.53
Alk-p (U/L)	60 (46–65)	55 (45–62)	0.25
γ-GT (U/L)	21 (15–31)	20 (14–28)	<0.05
Uric acid (mg/dL)	5.6 ± 1.2	5.7 ± 1.3	0.89
Hb (g/dL)	14.5 ± 1.2	14.3 ± 1.3	0.11
Hct (%)	42.7 ± 3.3	42.6 ± 3.9	0.35
MCH (pg)	31.1 (29–32)	30.6 (29–32)	0.26
MCV (fL)	90.2 (87–93)	91.1 (88–94)	0.57
WBC (10³/μL)	6.2 (5.2–7.6)	5.8 (4.9–7.0)	<0.01
Platelets (10³/μL)	229.5 ± 60.4	235.8 ± 57.4	0.62

25(OH)D, 25-hydroxyvitamin D; AST, aspartate transaminase; ALT, alanine transaminase; Alk-p, alkaline phosphatase; BUN, blood urea nitrogen; γ-GT, γ-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; Hb, hemoglobin; Hct, hematocrit; LDL-C, low-density lipoprotein cholesterol; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; TGs, triglycerides; TC, total cholesterol; WBC, white blood cell count.

were similar between people with increased 25(OH)D greater and less than 10 mg/dL (TC change: −7 (−18.5 to 12) mg/dL vs −6 (−21.5 to 12.5) mg/dL, *P* = 0.764).

Comparison between the responders and nonresponders to vitamin D

Among the 118 individuals, 55 exhibited decreases of >10% in TG levels (TG responders). TG responders had significantly higher baseline TG levels and lower baseline 25(OH)D levels than did the nonresponders (Table 2). However, at follow-up, both TG responders and nonresponders exhibited similar levels of 25(OH)D. Furthermore, no differences were noted in the baseline levels of TC, LDL-C, HDL-C, or HbA1c between TG responders and nonresponders. However, TG responders exhibited nonsignificantly decreasing levels of HbA1c

while TG nonresponders exhibited nonsignificantly increasing levels of HbA1c; at follow-up, the levels of HbA1c were considerably lower in TG responders than in TG nonresponders. No differences were noted between TG responders and nonresponders in terms of age, sex, BMI, creatinine level, liver function, CBC, lipid-lowering agent use, or the presence of diabetes mellitus, hypertension, or cancer. Additionally, we performed multivariate analysis (including age, sex, body weight, body height, drug and medical history, baseline 25(OH)D, TC, and TG levels) and found that decreased baseline 25(OH)D levels (OR per 1 ng/mL = 0.942, 95% CI, 0.888–1.000, $P = 0.049$) and elevated baseline TG levels (OR per 1 mg/dL = 1.008, 95% CI, 1.001–1.015, $P = 0.02$) were both independent biomarkers to predict TG responders.

As shown in Table 3, among the 118 individuals, 32 exhibited decreases of >10% in TC levels (TC responders). TC responders exhibited substantially higher baseline levels of TC, TGs, BMI, and HbA1c, and lower baseline levels of HDL-C than did TC nonresponders. However, no significant differences were noted between TC responders and nonresponders in terms of baseline and follow-up 25(OH)D levels. TC responders exhibited considerably higher use of lipid-lowering agents and incidence of hypertension than did TC nonresponders. However, we found that only increased baseline TC levels (OR per 1 mg/dL = 1.038, 95% CI, 1.006–1.072, $P = 0.02$) were an independent biomarker to predict TC responders through multivariate analysis (including age, sex, body weight, body height, drug and medical history, baseline 25(OH)D, TC, TGs, HDL-C, HbA1c, ALT, and γ-GT levels).

Different effects of increased vitamin D levels on individuals with or without hypertriglyceridemia

We investigated the effects of baseline TG levels on the correlations between increases in the levels of serum 25(OH)D and changes in the levels of various biomarkers. Individuals with or without hypertriglyceridemia had similar baseline and follow-up data and increases in 25(OH)D levels. These individuals used similar medications for diabetes mellitus, hypertension, cancer, and dyslipidemia. However, at baseline, individuals with hypertriglyceridemia exhibited considerably higher body weight and HbA1c levels but lower HDL-C levels than those without hypertriglyceridemia. However, at follow-up, no significant differences were noted in body weight, HbA1c levels, or HDL-C levels between individuals with hypertriglyceridemia and those

Table 2 Correlations between increases in 25(OH)D levels and biomarkers among TG responders and TG nonresponders: mean ± s.d. for normally distributed variables or median (interquartile range) for non-normally distributed variables.

Serum TG response to 25(OH)D	TG responders ($n = 55$)	TG nonresponders ($n = 63$)	*P*-value
Age (years)	54.4 ± 10.0	54.3 ± 11.2	0.97
Female, *n* (%)	32 (58)	33 (52)	0.52
BMI (kg/m²)	24.8 (21.7–28.4)	23.7 (21.2–27.2)	0.22
Use of lipid-lowering medication, n (%)	16 (29)	20 (31)	0.75
History of DM, *n* (%)	6 (10)	10 (15)	0.43
History of hypertension, *n* (%)	14 (25)	11 (17)	0.28
History of cancer, *n* (%)	4 (7)	2 (3)	0.55
Baseline 25(OH)D (ng/mL)	20.6 (15.4–27.3)	26 (20.6–31.2)	<0.01
Baseline TGs (mg/dL)	141 (90–210)	98 (74–133)	<0.01
Baseline TC (mg/dL)	192.4 ± 36.0	184.2 ± 40.6	0.25
Baseline LDL-C (mg/dL)	118.1 ± 29.9	112.8 ± 29.3	0.37
Baseline HDL-C (mg/dL)	47 (42–60)	52 (43–60)	0.30
Baseline HbA1c (%)	5.7 (5.5–6.1)	5.6 (5.4–6.2)	0.93
Baseline BUN (mg/dL)	11 (9.5–14)	11 (8.8–14)	0.62
Baseline creatinine (mg/dL)	0.8 (0.6–0.9)	0.7 (0.6–0.9)	0.78
Baseline albumin (g/dL)	4.4 ± 0.2	4.4 ± 0.2	0.84
Baseline AST (U/L)	19 (17–21)	19 (18–23)	0.88
Baseline ALT (U/L)	20 (13–33)	18 (14–25)	0.48
Baseline total bilirubin (mg/dL)	0.8 (0.5–0.9)	0.9 (0.6–1.4)	0.06
Baseline Alk-p (U/L)	60 (46–64)	58 (46–67)	0.88
Baseline γ-GT (U/L)	21 (14–38)	22 (15–31)	0.76
Baseline uric acid (mg/dL)	5.5 (4.8–6.5)	5.5 (4.7–6.2)	0.67
Baseline Hb (g/dL)	14.4 ± 1.4	14.6 ± 1.1	0.53
Baseline Hct (%)	42.3 ± 3.6	43.1 ± 2.9	0.29
Baseline MCH (pg)	31.4 (30–32)	31.0 (30–32)	0.86
Baseline MCV (fL)	90 (86–93)	90 (88–92)	0.63
Baseline WBC (10³/μL)	6.5 (5.4–7.9)	6.0 (5.1–7.3)	0.17
Baseline platelets (10³/μL)	237 (199–257)	217 (184–263)	0.49

25(OH)D, 25-hydroxyvitamin D; AST, aspartate transaminase; ALT, alanine transaminase; Alk-p, alkaline phosphatase; BUN, blood urea nitrogen; γ-GT, γ-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; Hb, hemoglobin; Hct, hematocrit; LDL-C, low-density lipoprotein cholesterol; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; TGs, triglycerides; TC, total cholesterol; WBC, white blood cell count.

without hypertriglyceridemia. As shown in Fig. 2, at follow-up, individuals with hypertriglyceridemia exhibited significant decreases in the serum levels of TG (from 209 (164–296) to 181 (125–218) mg/dL; $P < 0.005$), TC (from 197 ± 37.5 to 177 ± 39.0 mg/dL; $P < 0.005$), and LDL-C (from 120 ± 33.4 to 104 ± 32.7 mg/dL; $P < 0.05$).

By contrast, individuals without hypertriglyceridemia exhibited similar changes in the levels of TGs (from 87 (72–111) to 88 (64–116) mg/dL; $P = 0.63$), TC (from 183 (151–211) to 183 (156–212) mg/dL; $P = 0.84$), and LDL-C (from 111 (90–132) to 111 (95–134) mg/dL; $P = 0.46$) at follow-up.

Different effects of increased vitamin D levels on individuals with or without hypercholesterolemia

We investigated the effects of baseline TC levels on the correlations between increases in serum 25(OH)D levels and changes in serum biomarker levels. No significant differences were found between individuals with hypercholesterolemia and those without it in terms of 25(OH)D levels at baseline or follow-up or the increases in 25(OH)D levels. The patients with or without hypercholesterolemia used similar medications for diabetes mellitus, hypertension, cancer, and dyslipidemia and exhibited similar HbA1c levels or body weight at baseline and follow-up. However, at baseline, individuals with hypercholesterolemia exhibited significantly higher levels of TC, TGs, and LDL-C than did those without hypercholesterolemia. As shown in Fig. 3, patients with hypercholesterolemia exhibited significant decreases in the serum levels of TGs (from 139 (88–222) to 120 (74–190) mg/dL; $P < 0.01$), TC (from 220 (210–239) to 202 (172–228) mg/dL; $P < 0.005$) and LDL-C (from 142 ± 23.8 to 122 ± 35.9 mg/dL; $P < 0.005$) at follow-up. By contrast, at follow-up, individuals without hypercholesterolemia exhibited significant increases in the serum levels of LDL-C (from 99.9 ± 21.0 to 105.5 ± 25.9 mg/dL; $P < 0.05$); no significant changes in the serum levels of TG, TC or HDL-C.

Baseline 25(OH)D levels, sex, and age modulate the effects of vitamin D on lipids

We assessed the influence of baseline 25(OH)D levels on the effects of vitamin D on lipids. Individuals with baseline 25(OH)D levels greater or less than 30 ng/mL both exhibited significantly elevated 25(OH)D during the follow-up (from 34.7 (31.7–39.5) to 39.5 (34.7–46.9) mg/dL; $P < 0.01$ and 20.9 (16.9–26.0) to 29.8 (23.7–34.6) mg/dL; $P < 0.01$, respectively). As shown in Fig. 4A, at follow-up, individuals with baseline 25(OH)D levels less than 30 ng/mL exhibited significant decreases in the levels of TGs (from 211 (86–177) to 106 (77–143) mg/dL; $P < 0.005$). However, individuals with baseline 25(OH)D levels greater or less than 30 ng/mL exhibited similar changes in TC levels at follow-up (Fig. 4A).

Table 3 Correlations between 25(OH)D levels and biomarkers among TC responders and nonresponders: mean ± s.d. for normally distributed variables or median (interquartile range) for non-normally distributed variables.

Serum TC response to 25(OH)D	TC responders ($n = 32$)	TC nonresponders ($n = 86$)	P-value
Age (years)	55.5 ± 10.0	53.9 ± 10.8	0.47
Female, n (%)	14 (43)	51 (59)	0.13
BMI (kg/m^2)	24.9 (23.9–27.8)	22.9 (21.0–27.3)	<0.05
Use of lipid-lowering medication, n (%)	17 (53)	19 (22)	<0.01
History of DM, n (%)	6 (18)	10 (11)	0.31
History of hypertension, n (%)	11 (34)	14 (16)	<0.05
History of cancer, n (%)	2 (6)	4 (4)	0.90
Baseline 25(OH)D (ng/mL)	25.1 (17.8–30.2)	22.3 (17.6–28.3)	0.57
Baseline TGs (mg/dL)	157 (109–219)	99 (75–150)	<0.01
Baseline TC (mg/dL)	203.0 ± 40.0	182.5 ± 36.7	<0.01
Baseline LDL-C (mg/dL)	123.7 ± 35.2	112.4 ± 28.6	0.09
Baseline HDL-C (mg/dL)	44 (39–53)	52 (44–63)	<0.01
Baseline HbA1c (%)	5.8 (5.7–6.3)	5.6 (5.4–6.0)	<0.05
Baseline BUN (mg/dL)	13 (10–15)	11 (8.5–14)	0.07
Baseline creatinine (mg/dL)	0.8 (0.7–1.0)	0.7 (0.6–0.9)	0.08
Baseline albumin (g/dL)	4.4 ± 0.2	4.4 ± 0.2	0.78
Baseline AST (U/L)	20 (17–25)	28 (17–23)	0.54
Baseline ALT (U/L)	21 (15–31)	17 (13–27.5)	0.07
Baseline total bilirubin (mg/dL)	0.9 (0.6–1.1)	0.8 (0.6–1.1)	0.91
Baseline Alk-p (U/L)	60 (44–66)	55 (47–65)	0.82
Baseline γ-GT (U/L)	30 (21–42)	19 (14–30)	<0.01
Baseline uric acid (mg/dL)	6.1 (5.2–6.5)	5.4 (4.5–6.3)	0.14
Baseline Hb (g/dL)	14.7 ± 1.4	14.4 ± 1.2	0.34
Baseline Hct (%)	43.2 ± 3.6	43.0 ± 3.2	0.40
Baseline MCH (pg)	31 (30–32)	31 (30–32)	0.73
Baseline MCV (fL)	92 (88–93)	90 (88–93)	0.84
Baseline WBC (10^3/μL)	6.5 (5.8–7.9)	6.0 (5.1–7.5)	<0.05
Baseline platelets (10^3/μL)	232 (198–262)	227 (188–257)	0.67

25(OH)D, 25-hydroxyvitamin D; AST, aspartate transaminase; ALT, alanine transaminase; Alk-p, alkaline phosphatase; BUN, blood urea nitrogen; γ-GT, γ-glutamyl transpeptidase; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; Hb, hemoglobin; Hct, hematocrit; LDL-C, low-density lipoprotein cholesterol; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; TGs, triglycerides; TC, total cholesterol; WBC, white blood cell count.

We further evaluated the influence of age and sex on the effects of vitamin D on serum lipids. Both genders exhibited decreased TG levels at follow-up with increased 25(OH)D levels (Fig. 4B). Moreover, middle-aged adults (aged 50–65 years) had reduced levels of TGs (from 110 (83–196) to 105 (70–159) mg/dL; $P < 0.005$) and TC (from 194 (168–227) to 180 (149–213) mg/dL; $P < 0.05$; Fig. 4C).

Discussion

Patients with hyperlipidemia exhibited lipid reduction associated with increased serum 25(OH)D levels

Vitamin D deficiency is associated with atherogenic serum lipid profiles (higher levels of TGs, TC, and LDL-C but lower levels of HDL-C), which are known risk factors for cardiovascular disease (4, 17). However, an individual's change in serum 25(OH)D levels following vitamin D supplementation may be diverse. It remains unclear for the effective dosage of vitamin D supplementation that may affect serum lipids. Because of the differences in the doses, frequencies, and durations of vitamin D supplementation and end-line vitamin D levels between the intervention groups of previous interventional trials, these trials have collectively failed to generate convincing evidence for the therapeutic efficacy of vitamin D on hyperlipidemia (13, 14, 18, 19). Thus, we aimed to investigate the associations between increased serum vitamin D concentrations and lipid levels. In a large retrospective cohort study comprising a total of 8592 patients with vitamin D deficiency (baseline mean 25(OH)D levels, 14.3 ng/mL), an increase in the levels of 25(OH)D to 41.6 ng/mL was not associated with an improvement in the levels of serum lipids. However, the baseline TG

and TC levels of the study cohort were <150 and <200 mg/dL, respectively (20). Similarly, in a Norwegian double-blind, randomized, placebo-controlled trial including a total of 251 healthy adults aged 18–50 years with low vitamin D levels, 16-week vitamin D3 supplementation (where serum 25(OH)D levels were increased from 11.6 to 19.6 ng/mL) exerted no effects on lipid profiles (serum TG levels remained approximately 132.8 mg/dL and serum TC levels remained approximately 189.4 mg/dL) (21). Another randomized controlled trial including a total of 511 individuals with prediabetes revealed that vitamin D3 supplementation at a weekly dose of 20000 IU for 5 years (serum 25(OH)D levels were increased from 24 to 46 ng/mL) exerted no effects on serum TGs levels (remained approximately 115.1 mg/dL) (22). The lipid-lowering effects of vitamin D were not observed in the aforementioned study possibly because most participants had no hyperlipidemia at baseline. To the best of our knowledge, the present study is the first to report that increases in 25(OH)D levels may be correlated with decreases in serum TG and TC levels in individuals with hyperlipidemia but not in those without hyperlipidemia. Our results also showed that increasing serum 25(OH)D concentrations might be dose dependently correlated with decreasing levels of serum TGs. These findings suggest the therapeutic potential of vitamin D for hyperlipidemia.
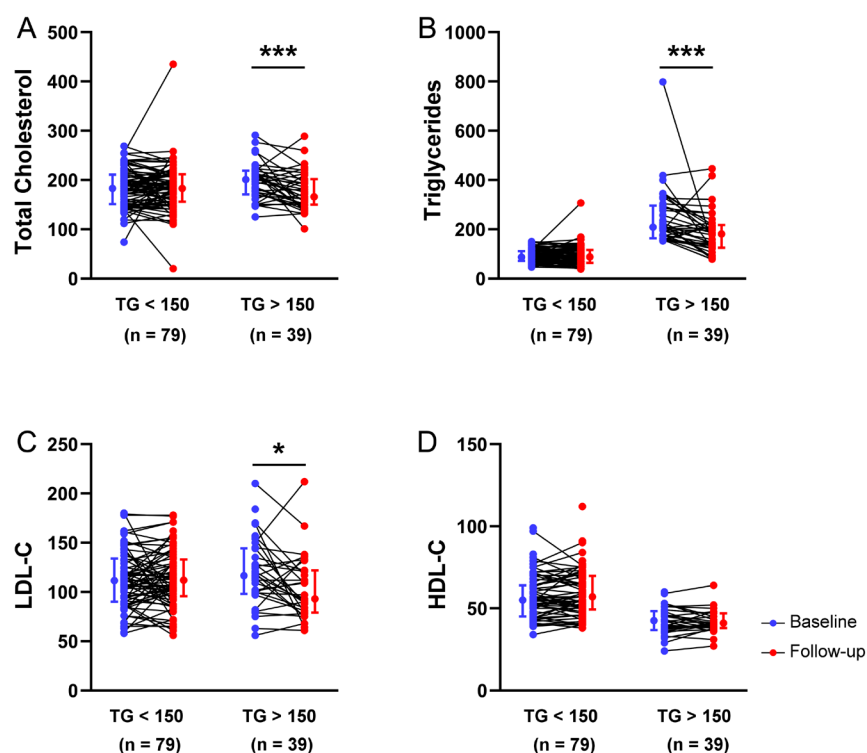

Figure 2

Changes in serum lipid levels with increasing levels of 25-hydroxyvitamin D (25(OH)D) differed between individuals with or without hypertriglyceridemia. Baseline and follow-up levels of (A) total cholesterol, (B) triglycerides, (C) low-density lipoprotein cholesterol (LDL-C), and (D) high-density lipoprotein cholesterol (HDL-C) in individuals with triglyceride levels higher or lower than 150 mg/dL. *P < 0.05 and ***P < 0.005. n, number of subjects.
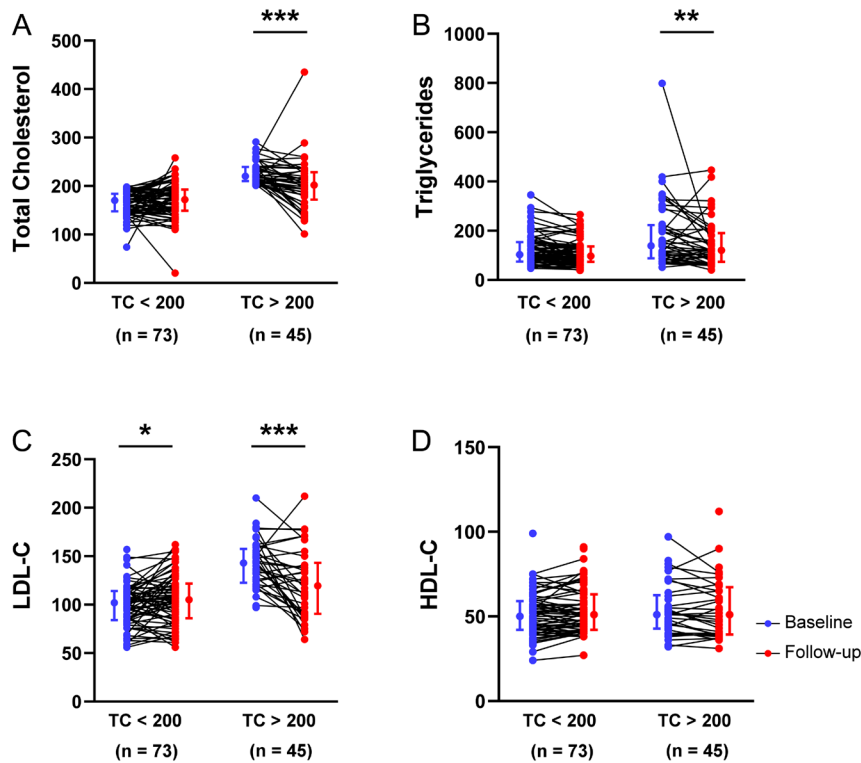
Figure 3

Changes in serum lipid level with increasing levels of 25-hydroxyvitamin D (25(OH)D) varied between individuals with or without hypercholesterolemia. Baseline and follow-up levels of (A) total cholesterol, (B) triglycerides, (C) low-density lipoprotein cholesterol (LDL-C), and (D) high-density lipoprotein cholesterol (HDL-C) in individuals with total cholesterol levels higher or lower than 200 mg/dL. *P < 0.05, **P < 0.01 and ***P < 0.005. *n*, number of subjects.
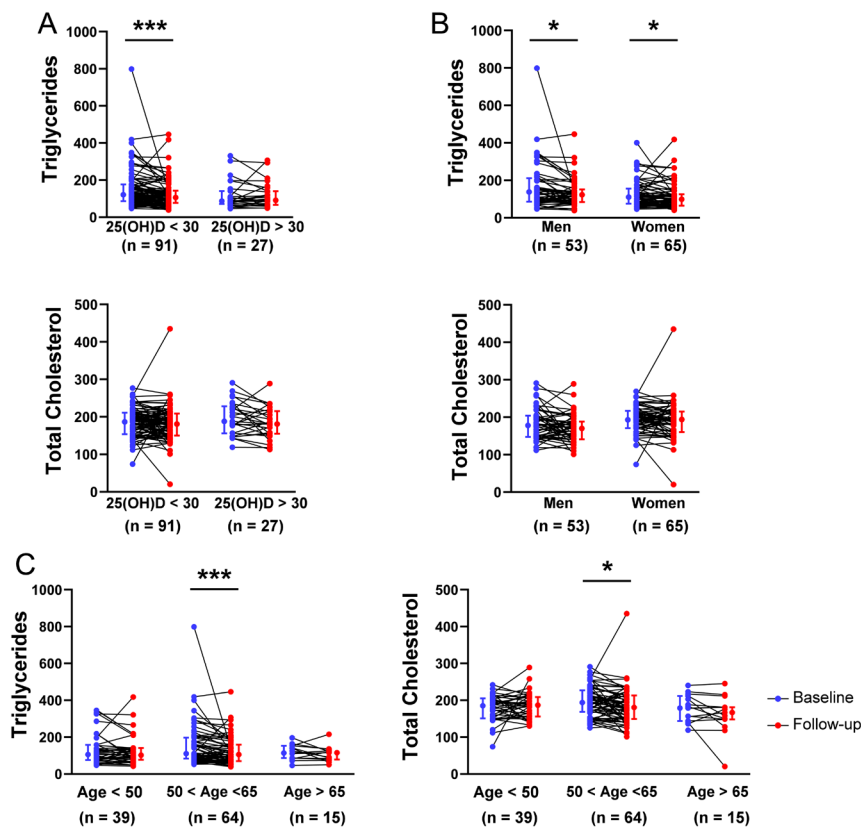
Figure 4

Changes in total cholesterol and triglyceride levels with increasing levels of serum 25-hydroxyvitamin D (25(OH)D) were modulated by baseline 25(OH)D levels, sex, and age. Baseline and follow-up levels of total cholesterol and triglycerides in (A) individuals with baseline 25(OH)D levels greater or less than 30 ng/mL, (B) men and women, and (C) individuals aged <50 years, aged 50–65 years, and >65 years. *P < 0.05 and ***P < 0.005. *n*, number of subjects.

Baseline vitamin D status may affect the association between increased serum 25(OH)D and lipid levels

A recent meta-analysis of 41 randomized controlled trials including a total of 3434 participants showed that vitamin D supplementation appeared to have a beneficial effect on reducing serum lipids. The improvements in TC and TG levels are more prominent in individuals with baseline vitamin D deficiency (13). In 2017, the International Lipid Expert Panel suggested that vitamin D supplementation combined with statin represents an effective management strategy for hypercholesterolemia, particularly in individuals with low levels of vitamin D (23). Thus, the reason underlying the conflicting findings of clinical trials regarding the effects of vitamin D on serum lipids is probably due to the fact that the study cohorts might not have had vitamin D deficiency. Our study also revealed that increased serum 25(OH)D levels weresignificantly associated with decreased serum TG levels in only individuals with baseline 25(OH)D levels of <30 ng/mL but not in those with baseline 25(OH)D levels of >30 ng/mL. We demonstrated that TG responders had significantly lower baseline 25(OH)D levels than did TG nonresponders, and baseline vitamin D levels were an independent predictor for TG response. Therefore, vitamin D supplementation may be considered as an adjunct therapy in patients with hypertriglyceridemia and concomitant vitamin D deficiency in clinical practice.

Age and sex modulate the association between increased serum 25(OH)D and lipid levels

Vitamin D receptor polymorphism is reportedly associated with a risk of dyslipidemia in the Han Chinese population (24), and this association is influenced by patient sex (25). A cross-sectional study comprising a total of 4021 middle-aged and older participants indicated that vitamin D deficiency was positively associated with the prevalence of hyperlipidemia, and this association was stronger in men than in women (26). Similarly, our previous study revealed the positive association between vitamin D deficiency and hypertriglyceridemia was significant in men but not in women (12). However, this study demonstrated that increases in the levels of 25(OH)D were correlated with decreases in the TG levels in both the genders. We also found that only middle-aged adults (not in individuals aged <50 or >65 years) exhibited significant decreases in the levels of TC and TGs in association with increased serum 25(OH)D levels. These findings suggest that age and sex might modulate the association between vitamin D and hyperlipidemia.

Potential mechanisms of vitamin D on lipids

Several possible mechanisms may explain how vitamin D affects lipid metabolism. Adipose tissue is the main site for vitamin D storage (27), and obesity was associated with a high prevalence of vitamin D deficiency (28). Gangloff *et al.* found that decreased adiposity volume was correlated with increased serum 25(OH)D concentrations (29). It has been demonstrated that vitamin D receptor and vitamin D metabolizing enzymes (25-hydroxylase and 1α-hydroxylase) were expressed in human adipocytes, suggesting vitamin D modulates adipose tissue biology (30, 31). Vitamin D upregulates the expression of genes involved in fatty acid oxidation and mitochondrial biogenesis in adipose tissue (32). In addition to fat tissues, muscle was also considered as another functional storage area for 25(OH)D (33, 34), and exercise may have direct effects on serum 25(OH)D levels. Observational studies have found a positive relationship between 25(OH)D levels and physical activity regardless of sun exposure (35, 36). Sun *et al.* demonstrated that serum 25(OH)D levels were increased after intense exercise and short-term endurance training, without changes in total body fat or visceral fat (37, 38). Vitamin D also enhances intestinal calcium absorption, leading to serum TGs reduction via the suppression of hepatic TGs formation and secretion (39). Excessive parathyroid hormone inhibits plasma lipoprotein lipase activity, resulting in decreased lipid removal from the circulation and consequently hyperlipidemia (40). Accordingly, vitamin D may reduce serum lipids through inhibiting parathyroid hormone secretion. Moreover, vitamin D deficiency was shown to increase the risk of insulin resistance, which is linked to an elevation of serum TG levels (27). The therapeutic potential of vitamin D in alleviating insulin resistance may contribute to its lipid-lowering effects.

Study limitations

The present study has some limitations. This retrospective observational study had a small sample size. Although we adjusted for potential confounding factors, such as lipid-lowering agents, body weight, and serum glucose levels, the data regarding vitamin D

supplementation, vitamin D dietary intake, physical activity, and sun exposure were lacking. We could not control patient exposure, outcome assessment, and record accuracy, which limit the strength of our findings in this retrospective observational study. Accordingly, our study is not able to answer all burden of illness research questions due to insufficient clinical data detail being recorded. Therefore, to clarify the therapeutic potential of vitamin D for hyperlipidemia, large-scale randomized trials on vitamin D supplementation must be designed to investigate the changes in the serum lipid levels of well-defined populations.

Conclusions

Increased serum 25(OH)D levels were associated with decreased serum TC and TG levels, particularly in hyperlipidemic patients with vitamin D deficiency. Thus, increasing circulating 25(OH)D concentrations may be considered as an adjunct therapy in the management of hyperlipidemia.

References

1 Mason RS, Sequeira VB & Gordon-Thomson C. Vitamin D: the light side of sunshine. *European Journal of Clinical Nutrition* 2011 **65** 986–993. (https://doi.org/10.1038/ejcn.2011.105)

2 Savastano S, Barrea L, Savanelli MC, Nappi F, Di Somma C, Orio F & Colao A. Low vitamin D status and obesity: role of nutritionist. *Reviews in Endocrine and Metabolic Disorders* 2017 **18** 215–225. (https://doi.org/10.1007/s11154-017-9410-7)

3 Oberoi D, Mehrotra V & Rawat A. "Vitamin D" as a profile marker for cardiovascular diseases. *Annals of Cardiac Anaesthesia* 2019 **22** 47–50. (https://doi.org/10.4103/aca.ACA_66_18)

4 Martins D, Wolf M, Pan D, Zadshir A, Tareen N, Thadhani R, Felsenfeld A, Levine B, Mehrotra R & Norris K. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. *Archives of Internal Medicine* 2007 **167** 1159–1165. (https://doi.org/10.1001/archinte.167.11.1159)

5 Leu M & Giovannucci E. Vitamin D: epidemiology of cardiovascular risks and events. *Best Practice and Research. Clinical Endocrinology and Metabolism* 2011 **25** 633–646. (https://doi.org/10.1016/j.beem.2011.04.001)

6 Dudenkov DV, Mara KC, Maxson JA & Thacher TD. Serum 25-hydroxyvitamin D values and risk of incident cardiovascular disease: a population-based retrospective cohort study. *Journal of Steroid Biochemistry and Molecular Biology* 2021 **213** 105953. (https://doi.org/10.1016/j.jsbmb.2021.105953)

7 Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, Martucci G, Pilz S & Malle O. Vitamin D deficiency 2.0: an update on the current status worldwide. *European Journal of Clinical Nutrition* 2020 **74** 1498–1513. (https://doi.org/10.1038/s41430-020-0558-y)

8 Palacios C & Gonzalez L. Is vitamin D deficiency a major global public health problem? *Journal of Steroid Biochemistry and Molecular Biology* 2014 **144** 138–145. (https://doi.org/10.1016/j.jsbmb.2013.11.003)

9 Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, Povoroznyuk V, Balatska N, Barbosa AP, Karonova T, *et al.* Vitamin D supplementation guidelines. *Journal of Steroid Biochemistry and Molecular Biology* 2018 **175** 125–135. (https://doi.org/10.1016/j.jsbmb.2017.01.021)

10 Jorde R, Figenschau Y, Hutchinson M, Emaus N & Grimnes G. High serum 25-hydroxyvitamin D concentrations are associated with a favorable serum lipid profile. *European Journal of Clinical Nutrition* 2010 **64** 1457–1464. (https://doi.org/10.1038/ejcn.2010.176)

11 Wang Y, Si S, Liu J, Wang Z, Jia H, Feng K, Sun L & Song SJ. The associations of serum lipids with vitamin D status. *PLoS One* 2016 **11** e0165157. (https://doi.org/10.1371/journal.pone.0165157)

12 Cheng YL, Lee TW, Lee TI, Kao YH, Wu CY & Chen YJ. Sex and age differences modulate association of vitamin D with serum triglyceride levels. *Journal of Personalized Medicine* 2022 **12**. (https://doi.org/10.3390/jpm12030440)

13 Dibaba DT. Effect of vitamin D supplementation on serum lipid profiles: a systematic review and meta-analysis. *Nutrition Reviews* 2019 **77** 890–902. (https://doi.org/10.1093/nutrit/nuz037)

14 AlAnouti F, Abboud M, Papandreou D, Mahboub N, Haidar S & Rizk R. Effects of vitamin D supplementation on lipid profile in adults with the metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Nutrients* 2020 **12**. (https://doi.org/10.3390/nu12113352)

15 Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. *Journal of the American College of Cardiology* 2019 **73,** 3168–3209. (https://doi.org/10.1016/j.jacc.2018.11.002)

16 Trompet S, Postmus I, Slagboom PE, Heijmans BT, Smit RA, Maier AB, Buckley BM, Sattar N, Stott DJ, Ford I, *et al.* Non-response to (statin) therapy: the importance of distinguishing non-responders from non-adherers in pharmacogenetic studies. *European Journal of Clinical*

Pharmacology 2016 **72** 431–437. (https://doi.org/10.1007/s00228-015-1994-9)

17 Lupton JR, Faridi KF, Martin SS, Sharma S, Kulkarni K, Jones SR & Michos ED. Deficient serum 25-hydroxyvitamin D is associated with an atherogenic lipid profile: the Very Large Database of Lipids (VLDL-3) study. *Journal of Clinical Lipidology* 2016 **10** 72–81.e1. (https://doi.org/10.1016/j.jacl.2015.09.006)

18 Mirhosseini N, Rainsbury J & Kimball SM. Vitamin D supplementation, Serum 25(OH)D concentrations, and cardiovascular disease risk factors: a systematic review and meta-analysis. *Frontiers in Cardiovascular Medicine* 2018 **5** 87. (https://doi.org/10.3389/fcvm.2018.00087)

19 Schwetz V, Scharnagl H, Trummer C, Stojakovic T, Pandis M, Grübler MR, Verheyen N, Gaksch M, Zittermann A, Aberer F, *et al.* Vitamin D supplementation and lipoprotein metabolism: a randomized controlled trial. *Journal of Clinical Lipidology* 2018 **12** 588–596.e4. (https://doi.org/10.1016/j.jacl.2018.03.079)

20 Ponda MP, Huang X, Odeh MA, Breslow JL & Kaufman HW. Vitamin D may not improve lipid levels: a serial clinical laboratory data study. *Circulation* 2012 **126** 270–277. (https://doi.org/10.1161/CIRCULATIONAHA.111.077875)

21 Madar AA, Knutsen KV, Stene LC, Brekke M, Meyer HE & Lagerløv P. Effect of vitamin D3 supplementation on glycated hemoglobin (HbA1c), fructosamine, serum lipids, and body mass index: a randomized, double-blinded, placebo-controlled trial among healthy immigrants living in Norway. *BMJ Open Diabetes Research and Care* 2014 **2** e000026. (https://doi.org/10.1136/bmjdrc-2014-000026)

22 Jorde R, Sollid ST, Svartberg J, Schirmer H, Joakimsen RM, Njølstad I, Fuskevåg OM, Figenschau Y & Hutchinson MY. Vitamin D 20,000 IU per week for five years does not prevent progression from prediabetes to diabetes. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 1647–1655. (https://doi.org/10.1210/jc.2015-4013)

23 Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Fras Z, Katsiki N, Langlois M, Latkovskis G, *et al.* Lipid lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Archives of Medical Science* 2017 **13** 965–1005. (https://doi.org/10.5114/aoms.2017.69326)

24 Jia J, Tang Y, Shen C, Zhang N, Ding H & Zhan Y. Vitamin D receptor polymorphism rs2228570 is significantly associated with risk of dyslipidemia and serum LDL levels in Chinese Han population. *Lipids in Health and Disease* 2018 **17** 193. (https://doi.org/10.1186/s12944-018-0819-0)

25 Chen YM, Xu P, Wang ZT, Zhu YM, Gong CM, Huang CH, Liu XL & Zhou JC. Polymorphisms of the vitamin D receptor gene and sex-differential associations with lipid profiles in Chinese Han adults. *Biomedical and Environmental Sciences* 2022 **35** 115–125. (https://doi.org/10.3967/bes2022.016)

26 Huang F, Liu Q, Zhang Q, Wan Z, Hu L, Xu R, Cheng A, Lv Y & Wang L. Sex-specific association between serum vitamin D status and lipid profiles: a cross-sectional study of a middle-aged and elderly Chinese population. *Journal of Nutritional Science and Vitaminology (Tokyo)* 2020 **66** 105–113. (https://doi.org/10.3177/jnsv.66.105)

27 Park CY & Han SN. The role of vitamin D in adipose tissue biology: adipocyte differentiation, energy metabolism, and inflammation. *Journal of Lipid and Atherosclerosis* 2021 **10** 130–144. (https://doi.org/10.12997/jla.2021.10.2.130)

28 Wortsman J, Matsuoka LY, Chen TC, Lu Z & Holick MF. Decreased bioavailability of vitamin D in obesity. *American Journal of Clinical Nutrition* 2000 **72** 690–693. (https://doi.org/10.1093/ajcn/72.3.690)

29 Gangloff A, Bergeron J, Pelletier-Beaumont E, Nazare JA, Smith J, Borel AL, Lemieux I, Tremblay A, Poirier P, Alméras N, *et al.* Effect of adipose tissue volume loss on circulating 25-hydroxyvitamin D levels: results from a 1-year lifestyle intervention in viscerally obese men. *International Journal of Obesity* 2015 **39** 1638–1643. (https://doi.org/10.1038/ijo.2015.118)

30 Ding C, Gao D, Wilding J, Trayhurn P & Bing C. Vitamin D signalling in adipose tissue. *British Journal of Nutrition* 2012 **108** 1915–1923. (https://doi.org/10.1017/S0007114512003285)

31 Di Nisio A, De Toni L, Sabovic I, Rocca MS, De Filippis V, Opocher G, Azzena B, Vettor R, Plebani M & Foresta C. Impaired release of vitamin D in dysfunctional adipose tissue: new cues on vitamin D supplementation in obesity. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 2564–2574. (https://doi.org/10.1210/jc.2016-3591)

32 Marcotorchino J, Tourniaire F, Astier J, Karkeni E, Canault M, Amiot MJ, Bendahan D, Bernard M, Martin JC, Giannesini B, *et al.* Vitamin D protects against diet-induced obesity by enhancing fatty acid oxidation. *Journal of Nutritional Biochemistry* 2014 **25** 1077–1083. (https://doi.org/10.1016/j.jnutbio.2014.05.010)

33 Abboud M, Puglisi DA, Davies BN, Rybchyn M, Whitehead NP, Brock KE, Cole L, Gordon-Thomson C, Fraser DR & Mason RS. Evidence for a specific uptake and retention mechanism for 25-hydroxyvitamin D (25OHD) in skeletal muscle cells. *Endocrinology* 2013 **154** 3022–3030. (https://doi.org/10.1210/en.2012-2245)

34 Mason RS, Rybchyn MS, Abboud M, Brennan-Speranza TC & Fraser DR. The role of skeletal muscle in maintaining vitamin D status in winter. *Current Developments in Nutrition* 2019 **3** nzz087. (https://doi.org/10.1093/cdn/nzz087)

35 Scragg R & Camargo CA, Jr. Frequency of leisure-time physical activity and serum 25-hydroxyvitamin D levels in the US population: results from the Third National Health and Nutrition Examination Survey. *American Journal of Epidemiology* 2008 **168** 577–591. (https://doi.org/10.1093/aje/kwn163)

36 Close GL, Russell J, Cobley JN, Owens DJ, Wilson G, Gregson W, Fraser WD & Morton JP. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. *Journal of Sports Sciences* 2013 **31** 344–353. (https://doi.org/10.1080/02640414.2012.733822)

37 Sun X, Cao ZB, Taniguchi H, Tanisawa K & Higuchi M. Effect of an acute bout of endurance exercise on Serum 25(OH)D concentrations in young adults. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 3937–3944. (https://doi.org/10.1210/jc.2017-00146)

38 Sun X, Cao ZB, Tanisawa K, Taniguchi H, Kubo T & Higuchi M. Effects of chronic endurance exercise training on serum 25(OH)D concentrations in elderly Japanese men. *Endocrine* 2018 **59** 330–337. (https://doi.org/10.1007/s12020-017-1478-z)

39 Cho HJ, Kang HC, Choi SA, Ju YC, Lee HS & Park HJ. The possible role of Ca2+ on the activation of microsomal triglyceride transfer protein in rat hepatocytes. *Biological and Pharmaceutical Bulletin* 2005 **28** 1418–1423. (https://doi.org/10.1248/bpb.28.1418)

40 Akmal M, Kasim SE, Soliman AR & Massry SG. Excess parathyroid hormone adversely affects lipid metabolism in chronic renal failure. *Kidney International* 1990 **37** 854–858. (https://doi.org/10.1038/ki.1990.58)