Effect of Vitamin D3 Supplementation Combined with Exercise Training on Glycemic Control and Bone Health in Patients with Type 2 Diabetes: A Randomized, Placebo-Controlled Trial

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Abstract

Aims

This study aimed to examine the effect of a 12-week vitamin D supplementation and exercise training alone and in combination on glycemic control and bone health in Chinese type 2 diabetes patients.

Methods

Sixty-one type 2 diabetes patients (age, 33–65 years; 72.0% men) with non-insulin dependence were randomized into the 12-week vitamin D group (1000 IU/day), exercise group (60%–80% of maximal heart rate, 1 h/time, 2–3 times/week), vitamin D combined with exercise group, and control group. A 75-g oral glucose tolerance test was used to estimate glycemic control. Dual X-ray absorptiometry was used to examine bone health (bone mass content and bone mass density) and body fat percentage (%).

Results

During the 75-g oral glucose tolerance test, lower glucose and higher insulin levels were found in the vitamin D combined with exercise group, vitamin D group, and exercise group after intervention than before intervention, although the differences were not statistically significant. A significant exercise and vitamin D interaction for the insulinogenic index (P = 0.032) and a borderline interaction for the glucose disposition index (P = 0.051) were observed, while no further independent effect was observed. Compared with non-vitamin D supplementation, vitamin D supplementation significantly alleviated the loss of total bone mass content (95% CI: -29.9–19.4 vs. -74.9–-24.7), trunk bone mass content (95% CI: -24.1–19.5 vs. -56.1–-11.7), and spine bone mass density (95% CI: -0.03–0.03 vs. -0.07–-0.01).

Conclusions

The findings suggest that 12-week combined vitamin D and exercise intervention has a potentially positive effect on glycemic control, and vitamin D supplementation plays an important role in the prevention of bone loss, which was identified in the exercise alone group. Further studies are needed to elucidate the long-term effect of combined vitamin D and exercise intervention in type 2 diabetes patients.

The study was registered in the Chinese Clinical Trial System (No. ChiCTR1800015383).

Introduction

With rapid social and economic developments during the past three decades, China is facing a growing threat from non-communicable chronic diseases (NCDs), and diabetes is considered one of the most common NCDs in China and several other countries [1]. Diabetes prevalence in Chinese adults increased substantially from 0.67% in 1980 to 9.7% in 2008 and 10.9% in 2013 [2, 3]. Studies have demonstrated that intentional weight loss and increased physical activity intervention are associated with high rates of bone

loss in patients with type 2 diabetes [4]. Thus, optimizing type 2 diabetes management without a negative effect on bone mass has become one of the emphases in the treatment of type 2 diabetes.

Accumulating evidence indicates that high 25-hydroxycholecalciferol (25(OH)D) levels are positively associated with areal bone mineral density (BMD). Accordingly, vitamin D supplements are widely recommended and prescribed in the general population to promote bone health [5]. In addition, altered vitamin D homeostasis may play a role in the development of insulin resistance (IR) and type 2 diabetes [6], and low 25(OH)D levels are associated with a high prevalence of type 2 diabetes [7, 8]. Therefore, vitamin D supplementation has been proposed as a potential intervention to lower the incidence of type 2 diabetes [9, 10].

Vitamin D deficiency (25(OH)D < 20 ng/mL) is prevalent in several populations and has become a common public health problem worldwide due to sun protection measures, reduction of outdoor activities, and environmental pollution [5]. Zhang et al. recently showed that in China, 50% of type 2 diabetes patients were vitamin D deficient, which could further deteriorate glucose tolerance status [11]. However, to date, studies on the role of vitamin D supplementation in IR in type 2 diabetes patients have been mainly conducted in non-Asian countries, and the findings are inconsistent [12–17], partly because of marked differences in study duration, participant population, and dosing regimen [9, 10]. Furthermore, the independent effect of vitamin D on glycemic control is possibly limited in type 2 diabetes patients [18]. For example, Krul-Poel et al. found that 6-month vitamin D supplementation had no effect on HbA1c and fasting glucose levels and IR in type 2 diabetes patients [12], and similar results were also observed in German and Chinese type 2 diabetes patients [13, 19]. Therefore, further studies are needed to clarify the role of vitamin D supplementation in type 2 diabetes patients.

Exercise intervention is one of the most effective traditional lifestyle interventions to prevent and treat type 2 diabetes [20]. Recent studies have shown that exercise may be involved in the regulation of vitamin D and increases vitamin D receptor (VDR) expression in skeletal muscle and serum 25(OH)D levels [21–23]. Moreover, in addition to regulating Ca^{2+} levels, vitamin D supplementation can directly upregulate the AMP-activated protein kinase (AMPK)-glucose transporter 4 (GLUT-4) signaling pathway through VDR to promote exercise-associated glucose utilization [24]. These results suggest that vitamin D supplementation combined with exercise intervention might have a synergistic effect on the improvement of glycemic control by activating different glucose utilization pathways. However, few studies have investigated the synergistic effect of vitamin D supplementation and exercise training intervention on glycemic control in type 2 diabetes patients.

This study aimed to examine the effects of 12-week vitamin D supplementation combined with exercise training on glycemic control, as well as bone health in Chinese type 2 diabetes patients. Our findings will provide a comprehensive understanding of combined vitamin D and exercise intervention on glycemic control in Chinese type 2 diabetes patients.

Methods

Experimental design

This 12-week 2 × 2 factorial design, randomized, placebo-controlled trial assessed the impact of combined vitamin D and exercise intervention on glycemic improvement in type 2 diabetes patients with non-insulin dependence in Xi'an, China (34°N latitude). The purpose, procedures, and risks of the study were explained to each participant before inclusion, and all participants provided written informed consent. All of the procedures were reviewed and approved by the Ethics Committee of Xi'an Jiaotong University Health Science Center. The study was conducted in accordance with the Declaration of Helsinki and registered in the Chinese Clinical Trial System (No. ChiCTR1800015383). The complete process is outlined in Fig. 1.

<Figure 1 about here>

An investigator who was blinded to this study randomly divided the participants into the following four groups based on a computer-generated random allocation table stratified according to age and sex: vitamin D combined with exercise training group (VEG), vitamin D supplementation group (VDG), exercise group (EG), and placebo control group (CG). To ensure the randomized, double-blind effect, trial designers, testers, and data collectors were blinded to the vitamin D/placebo intake grouping until the intervention trial and data collection were completed. All patients were instructed not to undertake any formal exercise or change their general physical activity levels and dietary habits during the intervention period. Participants were asked to abstain from caffeine, alcohol, tobacco, and strenuous physical activity before the day of blood sample collection. All measurements were assessed at baseline and at the end of the intervention.

Participants

Sixty-one type 2 diabetes patients aged 33–65 years without receiving insulin treatment were enrolled between 2017 and 2018. Patients were eligible for study participation if they met the following inclusion criteria: (a) diagnosed with type 2 diabetes according to the WHO (1999)[25] and had type 2 diabetes for ≤ 10 years, (b) no plan to replace the hypoglycemic agent in the near future, (c) without regular vitamin D and/or calcium supplements in the past year, (d) did not meet the current National Physical Activity guidelines, and (e) without regular exercise habits in the past year.

The following participants were excluded: participants with acute infection; participants experiencing stress or acute complications of diabetes; participants with heart, liver, and kidney insufficiency, osteoporosis and fracture, and metal implants in the body that could affect magnetic resonance imaging and dual-energy X-ray absorptiometry (DXA) measurements; and participants who had used insulin therapy and had a recent history of sunlight exposure.

Interventions

Vitamin D intervention (double-blind)

Patients in the VDG or VEG group received one tablet of vitamin D_3 supplement (1000 IU/day, Nature Made, Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan), and those in the EG or CG group received a placebo tablet every day for 3 months. The tablets of vitamin D_3 supplements and placebos had identical appearance, shape, and color. Placebo tablets contained only starch, cellulose, and magnesium stearate. All supplements were prepared in identical bottles and sent to their homes or hand-delivered monthly. Participants were asked to report remotely their supplements use weekly.

Exercise intervention

Patients in the EG or VEG group performed a 1-h progressively increasing aerobic exercise (cycling, running, or rowing) at 60–80% of maximal heart rate (HR_{max}) 2–3 times a week for 12 weeks. This was supervised by a qualified trainer who is knowledgeable of the study protocol and procedures. A polar monitor was used to monitor heart rate during exercise, and compliance with each protocol was recorded. Participants warmed up during the first 5 min on a treadmill at 50–60% of HR_{max} and subsequently followed the exercise protocol assigned to them, with a 5–10-min recovery exercise at 40–50% of HR_{max}, which comprised walking and stretching exercises.

Primary Outcomes

Glycemic control parameters

A standard 75-g OGTT was performed between 08:30 and 11:00 after a 12-h overnight fast, and venous blood samples were collected in Venoject-II AutoSep tubes at 0, 30, 60, 90, and 120 min to determine plasma glucose and serum insulin levels. Serum samples were used to measure 25(OH)D, fasting glucose (G_0), fasting insulin (I_0), HbA1c, triglyceride, cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, apolipoprotein (Apo)A-1, and ApoB levels. Fasting blood glucose and insulin levels were used to calculate the insulin resistance index (homeostatic model assessment of insulin resistance [HOMA-IR]) as follows: HOMA-IR = $G_0 \times I_0/22.5$.

Insulin sensitivity estimated using the Matsuda index during the OGTT was calculated as follows: 1000/square root of ($[G_0 \times I_0]$) × (mean OGTT glucose concentration × mean OGTT insulin concentration) [26]. The early phase of insulin secretion was estimated using the insulinogenic index (IGI) as follows: $I_{30}-I_0/G_{30}-G_0$ ($\triangle$I30/$\triangle$G30), where I_{30} and G_{30} represent insulin and glucose values at 30 min during the OGTT, respectively [27]. The glucose disposition index (GDI) was calculated based on insulin secretion and insulin resistance as follows: Matsuda index × IGI. The increments in the area under the curves during the

complete 120-min period of the OGTT were calculated using the trapezoid rule to assess the total changes in glucose and insulin levels.

Secondary Outcomes

Body fat and bone mass

Height and body mass were measured with the participants wearing light clothing and barefoot. Body mass index was calculated by dividing the body mass in kilograms by the square of height in meters (kg/m^2). Waist circumference was measured to the nearest 0.1 cm at the umbilical region using an inelastic measuring tape at the end of normal expiration. DXA was used to measure body fat percentage (%) and bone mass (bone mass content [BMC] and BMD) (Hologic QDR-4500, DXA Scanner, Hologic Inc., Waltham, MA, USA) by a recognized technologist.

Sunlight exposure

Participants were instructed to record their outdoor activity time and exposed areas of the skin from 9 am to 5 pm for 7 consecutive days in a week using a questionnaire before and after the intervention. A score to estimate the mean weekly sunlight exposure was calculated, and additional details were published elsewhere [28].

International Physical Activity Questionnaire

Daily physical activity, except for the exercise program, was assessed using the International Physical Activity Questionnaire monthly and expressed as metabolic equivalent minutes per week. This questionnaire refers to activities in the preceding 7 days. Participants were instructed to report the number of days, hours, and minutes spent on vigorous activities, including aerobics, or moderate activities, such as carrying light loads [29].

Statistical Analyses

Power analysis

Based on a previous study examining the association of vitamin D intervention with HOMA-IR [30], the sample size required for each group was estimated to be 12 with a power of 85%, and an effect size of 0.26 was assumed. Therefore, 48 type 2 diabetes patients were required. To account for 20% loss to follow-up, 60 type 2 diabetes patients were recruited. Power calculations were performed using G*Power software version 3.1.9.2 [31].

Data analysis

Descriptive statistics were calculated using means (SDs) for continuous variables, n (%) for categorical variables, or 95% CI unless otherwise stated. Differences at baseline were compared using one-way ANOVA for continuous variables and chi-squared tests for categorical variables. Repeated measures ANOVA was used to analyze the effect of vitamin D supplementation on serum 25(OH)D levels. A 2 × 2 factorial design was used to estimate the effects of vitamin D and exercise intervention on metabolic profiles and bone health. A post hoc test with Bonferroni correction was used to identify significant differences among the mean values when a significant main effect or interaction was identified. All data were analyzed based on the intention to treat. Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

Sixty-one eligible participants (44 men and 17 women) underwent initial assessments and subsequent randomization (Fig. 1). During the intervention, one participant in the VDG and another in the VEG dropped out for personal reasons, and all participants in the CG and EG completed the intervention. In addition, one participant in the VDG and another in the CG did not complete DXA measurement, and two participants in the VDG and the other two participants in the CG did not complete the OGTT. Of the 29 participants who were allocated to the exercise groups, 20 participants completed 2–3 times exercise per week, and three completed 20 times exercise during the intervention period.

Baseline characteristics of participants are detailed in Table 1. The study participants had a mean BMI of 25.8 ± 3.6 kg/m^2 and a mean age of 50.0 ± 7.6 years at baseline. There were no significant differences between the four groups in age, men%, BMI, body fat percentage, sun exposure score, physical activity, and glucose profiles at baseline (Table 1). In addition, of the 61 participants, 40 (65.6%) had vitamin D deficiency (25(OH)D levels < 20 ng/mL), and 19 (31.1%) had vitamin D insufficient (25(OH)D levels: 20–30 ng/mL).

Table 1
Subject characteristics at baseline

Variable	Overall	VEG	VDG	EG	CG	P
	n = 61	n = 16	n = 16	n = 14	n = 15	
Age (years)	50.0 ± 7.6	51.3 ± 6.9	50.1 ± 8.3	47.9 ± 8.6	50.7 ± 7.0	0.763
Male (%)	44 (72.0%)	11 (64.7%)	11 (73.3%)	11 (73.3%)	11 (78.6%)	0.855
Height (cm)	167.5 ± 7.5	165.4 ± 7.9	167.7 ± 8.2	169.1 ± 7.7	167.8 ± 6.1	0.581
Weight (kg)	72.7 ± 13.0	68.6 ± 12.7	71.3 ± 12.7	74.7 ± 15.1	76.9 ± 10.9	0.316
BMI (kg/m^2)	25.8 ± 3.6	24.9 ± 3.0	25.3 ± 3.2	26.1 ± 4.8	27.2 ± 3.2	0.279
Body fat (%) [a]	30.1 ± 7.6	31.6 ± 6.0	27.6 ± 8.9	30.9 ± 8.6	30.3 ± 6.6	0.640
Trunk body fat (%) [a]	36.5 ± 7.8	37.4 ± 6.7	33.9 ± 9.3	37.7 ± 8.2	37.3 ± 6.8	0.652
Physical activity (MET-min/week)	3633 ± 3432	3161 ± 2331	4272 ± 4504	4334 ± 4286	2801 ± 1976	0.788
Sun exposure score	14.9 ± 7.5	17.3 ± 8.6	13.1 ± 4.4	16.1 ± 8.8	13.2 ± 7.3	0.561
Diabetes duration (years)	3.6 ± 2.6	3.7 ± 2.9	3.7 ± 2.4	3.1 ± 2.5	3.7 ± 2.6	0.969
HbA1c (%)	7.0 ± 1.5	7.0 ± 1.8	6.8 ± 1.4	6.7 ± 1.1	7.2 ± 1.6	0.799
Fasting blood glucose (mmol/L)	7.4 ± 2.0	6.8 ± 1.4	7.4 ± 1.8	7.8 ± 2.1	7.5 ± 2.6	0.626
Fasting insulin (μU/mL)	12.0 ± 7.1	12.1 ± 8.5	9.6 ± 5.5	11.7 ± 6.1	4.7 ± 7.6	0.452
HOMA-IR	4.0 ± 2.6	3.8 ± 2.9	3.4 ± 2.5	3.9 ± 2.3	4.9 ± 2.6	0.598

Data are mean ± standard deviation or n (%). VEG: vitamin D_3 combined exercise intervention group; VDG: vitamin D_3 intervention group; EG: exercise intervention group; CG: control group; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent; HbA1c, Glycated hemoglobin. Data were analyzed by one-way ANOVA or chi-square test. [a], only 14 samples in control group were included.

Serum 25(oh)d Concentrations And Glycemic Control

After 12-week vitamin D supplementation, serum 25(OH)D levels were increased in the mid and at end of the intervention in the VEG (baseline, 18.1 ± 2.0 ng/mL; mid, 24.7 ± 2.1 ng/mL; end, 27.8 ± 2.4 ng/mL) and VDG (baseline, 18.2 ± 2.4 ng/mL; mid, 22.8 ± 2.1 ng/mL; end, 25.9 ± 2.4 ng/mL). However, no changes in serum 25(OH)D levels were observed in the EG and CG at any time point (Fig. 2).

A significant exercise and vitamin D interaction for the IGI (P = 0.032) and a borderline significant interaction for GDI (P = 0.051) were observed. Post hoc analysis showed that in the non-vitamin D supplementation groups, exercise increased the IGI compared with without exercise, although the difference was not statistically significant (EG: mean = 0.09, 95% CI = -0.00–0.19; CG: mean = -0.02, 95% CI = -0.12–0.06; P = 0.09). In addition, no independent effect on GDI was observed in any group. There was no significant exercise and vitamin D interaction or any main effects for other blood profiles. Notably, exercise significantly decreased triglyceride levels (main effect: mean = -0.14, 95% CI = 0.00–0.59) (Table 2).

Table 2
Mean differences (95% CI) of blood parameter from the endpoint with each group

variable	VEG	VDG	EG	CG	*P*		
	N = 15	N = 15	N = 14	N = 15	$P_{vitamin\ D}$	$P_{exercise}$	$P_{interaction}$
Δ Apolipoprotein A (g/L)	0.02 (-0.1, 0.15)	0.04 (-0.07, 0.15)	0.01 (-0.06, 0.07)	0.08 (-0.05, 0.21)	0.582	0.349	0.400
Δ Apolipoprotein B (g/L)	0.02 (-0.07, 0.12)	0.03 (-0.03, 0.08)	0.03 (-0.06, 0.12)	0.07 (-0.02, 0.15)	0.232	0.986	0.327
Δ Low density lipoprotein (mmol/L)	-0.09 (-0.43, 0.25)	-0.1 (-0.26, 0.06)	-0.26 (-0.54, 0.01)	-0.1 (-0.27, 0.06)	0.969	0.977	0.203
Δ High density lipoprotein (mmol/L)	0.06 (-0.05, 0.17)	0 (-0.16, 0.17)	0.01 (-0.12, 0.15)	-0.03 (-0.14, 0.07)	0.563	0.455	0.777
Δ Cholesterol (mmol/L)	0.06 (-0.39, 0.51)	0 (-0.29, 0.29)	-0.19 (-0.5, 0.12)	-0.11 (-0.37, 0.14)	0.699	0.691	0.281
Δ Triglyceride (mmol/L)	-0.04 (-0.26, 0.18)	-0.11 (-0.43, 0.2)	-0.24 (-0.66, 0.18)	**0.33 (0.01, 0.65)**	0.698	**0.050**	0.085
Δ HbA1c (%)	-0.8 (-1.6, 0.1)	-0.3 (-1.0, 0.4)	-0.2 (-0.5, 0.2)	-0.3 (-1.0, 0.4)	0.506	0.820	0.229
Δ Fasting blood glucose (mmol/L)	**-0.9 (-1.6, -0.2)**	**-1.1 (-2.0, -0.1)**	-0.6 (-1.3, 0.2)	0.2 (-0.8, 1.1)	0.337	0.884	0.798
Δ Fasting insulin (μU/mL)	-1.8 (-6.1, 2.5)	1.5 (-1.7, 4.6)	0.5 (-3.8, 4.8)	1.0 (-3.0, 5.1)	0.806	0.342	0.594
Δ HOMA-IR	-0.9 (-2.4, 0.5)	-0.2 (-1.3, 0.8)	-0.2 (-1.6, 1.3)	0.8 (-1.5, 3.0)	0.446	0.274	0.751
Δ Matsuda Index [a]	0.34 (-0.48, 1.16)	0.26 (-0.32, 0.83)	0.31 (-0.55, 1.18)	-0.38 (-0.99, 0.24)	0.573	0.159	0.628
Δ Glucose AUC [a]	-78.1 (-225.8, 69.6)	-140.1 (-307.2, 27.0)	-75.9 (-201.7, 49.8)	36.1 (-112.0, 184.2)	0.197	0.716	0.208

Data are mean (95% confidence interval). Δ, changes from the endpoint to the pre; VEG: vitamin D_3 combined exercise intervention group; VDG: vitamin D_3 intervention group; EG: exercise intervention group; CG: control group; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, Glycated hemoglobin. [a], n = 13 in VDG, and n = 13 in CG were included

variable	VEG	VDG	EG	CG	*P*		
	N = 15	N = 15	N = 14	N = 15	$P_{vitamin\ D}$	$P_{exercise}$	$P_{interaction}$
Δ Insulin AUC [a]	515.8 (-1106.7, 2138.2)	1018.1 (-128.1, 2164.3)	1205.9 (-161.9, 2249.9)	-149.1 (-1879.0, 1680.9)	0.724	0.529	0.173
Δ Insulinogenic Index [a]	-0.01 (-0.09, 0.07)	**0.09 (0.00, 0.17)**	0.09 (-0.05, 0.24)	-0.02 (-0.11, 0.06)	0.937	0.801	**0.032**
Δ Disposition Index [a]	0.03 (-0.25, 0.31)	0.28 (-0.19, 0.74)	0.25 (-0.14, 0.64)	-0.16 (-0.43, 0.10)	0.552	0.553	**0.051**

Data are mean (95% confidence interval). Δ, changes from the endpoint to the pre; VEG: vitamin D_3 combined exercise intervention group; VDG: vitamin D_3 intervention group; EG: exercise intervention group; CG: control group; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, Glycated hemoglobin. [a], n = 13 in VDG, and n = 13 in CG were included

During the OGTT, the values of glucose and insulin at the five time points were similar between before and after intervention in the CG, while lower glucose and higher insulin levels were found after intervention than before intervention in the VEG, VDG, and EG, although the difference was not statistically significant (Supplemental Fig. 1). No significant exercise and vitamin D interaction or any main effect of exercise or vitamin D on glucose and insulin during OGTT was observed except for glucose at 30 min ($P_{interaction}$=0.052, data not shown). In the non-exercise training groups, vitamin D supplementation significantly decreased glucose levels 30 min after OGTT compared with without vitamin D supplementation (VDG: mean = -1.6, 95% CI = -2.9–-0.2; CG: mean = 0.3, 95% CI = -1.1–1.6).

Body Fat And Bone Mass

Vitamin D, but not exercise, significantly attenuated the loss of total BMC (vitamin D: mean = -5.3. 95% CI = -29.9–19.4; exercise: mean = -49.8, 95% CI = -74.9–-24.7), trunk BMC (vitamin D: mean = -2.3, 95% CI = -24.1–19.5; exercise: mean = -33.9, 95% CI = -56.1–-11.7), and spine BMD (vitamin D: mean = 0.00, 95% CI = -0.03–0.03; exercise: mean = -0.04, 95% CI = -0.07–-0.01) measured using DXA (Table 3 and Fig. 3). Exercise, but not vitamin D intervention, significantly decreased total body fat% (mean = -1.04, 95% CI = -1.69–-0.39) and trunk body fat% (mean = -1.45, 95% CI = -2.31–-0.59) (Table 3 and Fig. 4). There were no vitamin D and exercise interaction for any body fat and bone mass variables (Table 3). Weight, BMI, total body fat%, trunk body fat%, total BMC, and trunk BMC significantly decreased after intervention compared with before intervention (0 week) in the EG, but not in the other three groups (Table 3).

Table 3
Mean differences (95% CI) of body composition from the endpoint with each group

Variable	VEG	VDG	EG	CG	*P*		
	N = 15	N = 14	N = 14	N = 14	$P_{vitamin\ D}$	$P_{exercise}$	$P_{interaction}$
Δ Weight (kg) [a]	-0.3 (-1.3, 0.7)	-0.1 (-1.6, 1.4)	**-1.1 (-1.9, -0.2)**	-0.3 (-1.3, 0.8)	0.516	0.386	0.341
Δ BMI (kg/m^2) [a]	0.8 (-1.0, 2.5)	0.0 (-0.6, 0.6)	**-0.3 (-0.7, -0.0)**	-0.1 (-0.6, 0.3)	0.245	0.522	0.211
Δ Total body fat (%)	-1.0 (-2.1, 0.2)	0.3 (-1.0, 1.7)	**-1.1 (-2.0, -0.2)**	-0.4 (-1.1, 0.4)	0.262	**0.032**	0.428
Δ Total body muscle (g)	529 (-194, 1252)	10 (-640, 661)	414 (-404, 1232)	113 (-485, 711)	0.758	0.134	0.505
Δ Total BMD (g/cm2)	-0.01 (-0.02, 0.01)	-0.00 (-0.01, 0.00)	-0.00 (-0.01,0.01)	-0.01 (-0.01, 0.01)	0.796	0.597	0.539
Δ Total BMC (g)	-16 (-41, 9)	9 (-37, 55)	**-73 (-118, -27)**	-29 (-71, 13)	**0.014**	0.062	0.485
Δ Trunk body fat (%)	-1.1 (-2.6, 0.5)	0.4 (-1.3, 2.1)	**-1.8 (-2.9, -0.7)**	-0.4 (-1.5, 0.8)	0.156	**0.023**	0.856
Δ Trunk muscles (g)	43 (-682, 68)	169 (-515, 852)	426 (-41, 892)	115 (-452, 682)	0.523	0.442	0.479
Δ Trunk BMD (g/cm^2)	-0.01(-0.01, 0.00)	-0.00 (-0.01, 0.01)	-0.03 (-0.08, 0.01)	0.01 (-0.02, 0.04)	0.523	0.087	0.160
Δ Trunk BMC (g)	-16 (-38, 5)	16 (-19, 52)	**-50 (-94, -6)**	-14 (-51, 22)	**0.046**	0.600	0.912
Δ Spine BMD (g/cm^2)	0.02 (-0.01, 0.04)	-0.01 (-0.03, 0.00)	-0.05 (-0.11, 0.02)	-0.03 (-0.07, 0.02)	**0.046**	0.826	0.234

Data are mean (95% confidence interval). [a], n = 15 in VDG, and n = 15 in CG were included. Δ, changes from the endpoint to the pre; VEG: vitamin D_3 combined exercise group; VDG: vitamin D_3 group; EG: exercise group; CG: control group; BMI, body mass index. BMD, bone mineral density; BMC, bone mineral content.

Physical Activity And Sun Exposure Score Changes

There were no group differences in the changes (after-before) in weekly physical activity (Mean ± SD) (VEG, 1500.1 ± 4475.3; VDG, -310.8 ± 4888.9; EG, -241.9 ± 4160.1; CG, 509.8 ± 1541.9; P = 0.754) and sun exposure score (mean ± SD) (VEG, -0.13 ± 11.9; VDG, 5.7 ± 11.4; EG, 4.6 ± 11.4; CG, 5.6 ± 16.6; P = 0.667) (data not shown).

Discussion

This RCT found that in type 2 diabetes patients, vitamin D combined with exercise intervention had a potentially beneficial effect on glycemic control, although the effect was not statistically significant. Exercise significantly decreased total and trunk body fat percentage, and vitamin D supplementation significantly reduced bone loss.

In addition to the traditional role in maintaining bone health, higher serum 25(OH)D levels have been found to be associated with a low risk of developing type 2 diabetes [7–10]. However, to date, the findings in previous studies are inconsistent [12–17], and these studies have mainly been conducted in non-Asian populations. Additionally, accumulating evidence indicates that vitamin D supplementation combined with exercise intervention may have a synergistic effect on the improvement of type 2 diabetes via different glucose utilization pathways [21–24]. However, few studies have investigated the synergistic effect of vitamin D supplementation and exercise training intervention on metabolic profiles in type 2 diabetes patients.

Glycemic control is an important metabolic aspect in the improvement and control of type 2 diabetes and has been identified as a risk factor for the development of diabetic complications [32]. Although there were no vitamin D and exercise main effects or combined effects on fasting blood glucose, insulin, or HbA1c levels or HOMA-IR, a reduction in glucose levels in the VEG and VDG and an increase in the insulinogenic index in the VDG were observed in this study. However, the effects were not statistically significant, probably due to the relatively small sample size and the relatively short follow-up period. Our results are consistent with those in a study conducted in 42 type 2 diabetes elderly women [33] but inconsistent with those in a study conducted in type 2 diabetes model rats, in which rats were fed with alfacalcidol instead of vitamin D [34]. Further studies with larger samples and prolonged follow-up periods are warranted to corroborate the current findings.

Exercise is recommended for both prevention and treatment of type 2 diabetes [20]. Consistent with previous findings [35], we found the main effects of exercise on the reduction of body fat and blood triglyceride, but not on glucose profiles. In addition, previous studies showed that improved glucose profile, for example HbA1c levels, were not achieved by aerobic or exercise training alone but were observed in the combination of aerobic and resistance training in type 2 diabetes patients [36, 37]. In the present study, exercise training was mainly aerobic training, which probably led to a limited effect on glucose profiles. Moreover, HbA1c is a measure of how well blood glucose has been controlled over a

period of about 3 months [38] thus, long-term interventions may be needed to improve HbA1c levels in type 2 diabetes patients with non-insulin dependence.

Weight loss during type 2 diabetes management may lead to a high rate of bone loss, which would increase the risk of future fractures in type 2 diabetes patients [4, 39]. In the present study, body weight, BMI, and body fat%, in addition to total and trunk BMC, were significantly decreased in the exercise alone group, but those results were not observed in the other three groups, suggesting that exercise training alone may increase fracture risk in type 2 diabetes patients accompanied with weight loss. Vitamin D is well known for its beneficial effect in maintaining bone health and reducing the risk of osteoporosis [5]. Consistently, we found that vitamin D supplementation could efficiently maintain total BMC, trunk BMC, and spine BMD. Thus, a combination of vitamin D and exercise intervention in type 2 diabetes management may help mitigate the adverse effects of exercise training on bone health.

China is facing a rising epidemic of NCDs, with no sign of abating. Prevention of NCDs, including diabetes, by promoting healthy eating and lifestyles has become a national public policy priority [2, 40]. In October 2016, China issued the “Healthy China 2030,” thereby bringing the NCDs issue into a sharper and more concrete focus [41]. The findings in this study of vitamin D supplementation and exercise training in Chinese type 2 diabetes patients could provide a comprehensive understanding of the development of therapeutic strategies for type 2 diabetes.

The strengths of this study include the 2 × 2 factorial RCT design, high participant retention and adherence to the intervention, and objective and high-accuracy assessment of glycemic control, body fat, and bone mass. Our study provides a novel finding that combined vitamin D and exercise training could not only mitigate potential adverse effects during type 2 diabetes management but also have possible benefits in glycemic control. Some limitations of this study should be noted. First, the study duration was relatively short, although it has been demonstrated that body fat and blood metabolic profile changes can be detected during 12 weeks [42]. Second, this study did not comprehensively assess dietary intake, although participants were instructed not to alter their diet; these factors could have affected the results. Thus, future studies should attempt to thoroughly control the diet. Third, the intensity and frequency of exercise training in our study were supervised, and the sample size was relatively small. However, the pre-power analysis showed that the sample size in our study would provide a more than 85% chance to demonstrate the effect.

Conclusions

To the best of our knowledge, no study has investigated the combined effects of vitamin D supplementation and exercise training on glycemic control and bone health in type 2 diabetes patients. We found that 12 weeks of vitamin D supplementation and exercise training had a potentially positive effect on glycemic control. Circulating 25(OH)D levels substantially increased after vitamin D supplementation, and this increase might play an important role in maintaining the bone mass, which was reduced in the exercise alone group. The present findings shed light on the potential applications of

vitamin D supplementation combined with exercise training in type 2 diabetes patients. Further studies are required to investigate the long-term effect of a combined vitamin D and exercise intervention on glycemic control and explore its potential mechanisms in type 2 diabetes patients.

Declarations

Ethics approval and consent to participate

The purpose, procedures, and risks of the study were explained to each participant before inclusion, and all participants provided written informed consent. All of the procedures were reviewed and approved by the Ethics Committee of Xi'an Jiaotong University Health Science Center. The study was conducted in accordance with the Declaration of Helsinki and registered in the Chinese Clinical Trial System (No. ChiCTR1800015383).

Consent for publication

Not applicable.

Availability of data and materials

The data are not publicly available due to research ethical reasons and the corresponding author can provide further information on a reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

X.S. drafted the manuscript. M.D., X. H., Y. M. contributed to data acquisition and/or analysis. S.Z. and W.X. contributed to the interpretation of data. X.S., Y.W., and W.C. contributed to the conception and design of the study. All authors critically revised the manuscript and gave final approval. Y. W. and W. C. are the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility of the data and the accuracy of the data analysis.

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Figures

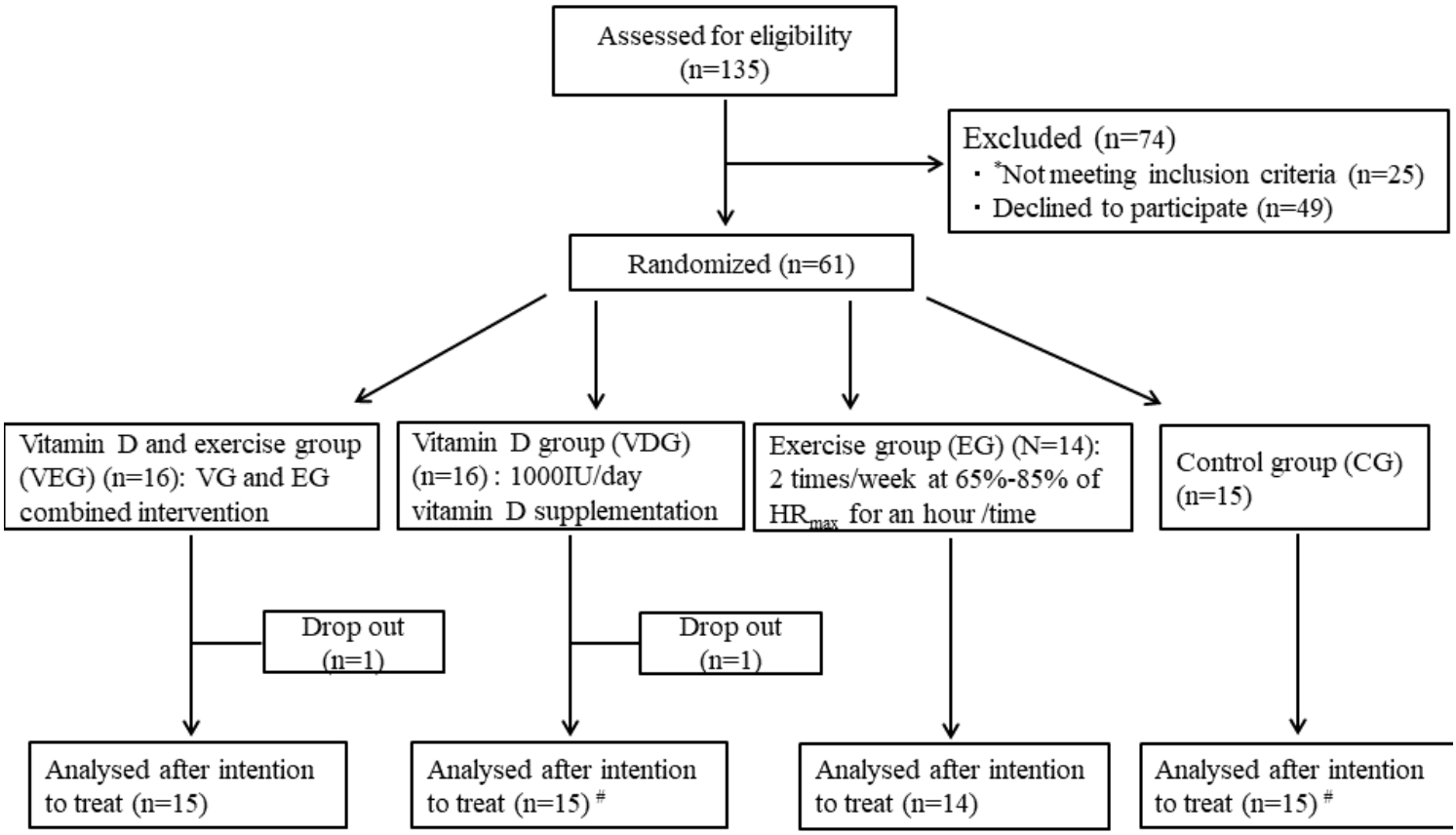

Figure 1

Flow diagram of participants *Most patients did not meet the inclusion criteria because of insulin therapy. #one participant in each VDG and CG for DXA measurement, and two participants in each VDG and CG for the OGTT did not complete. MHR, maximum heart rate.

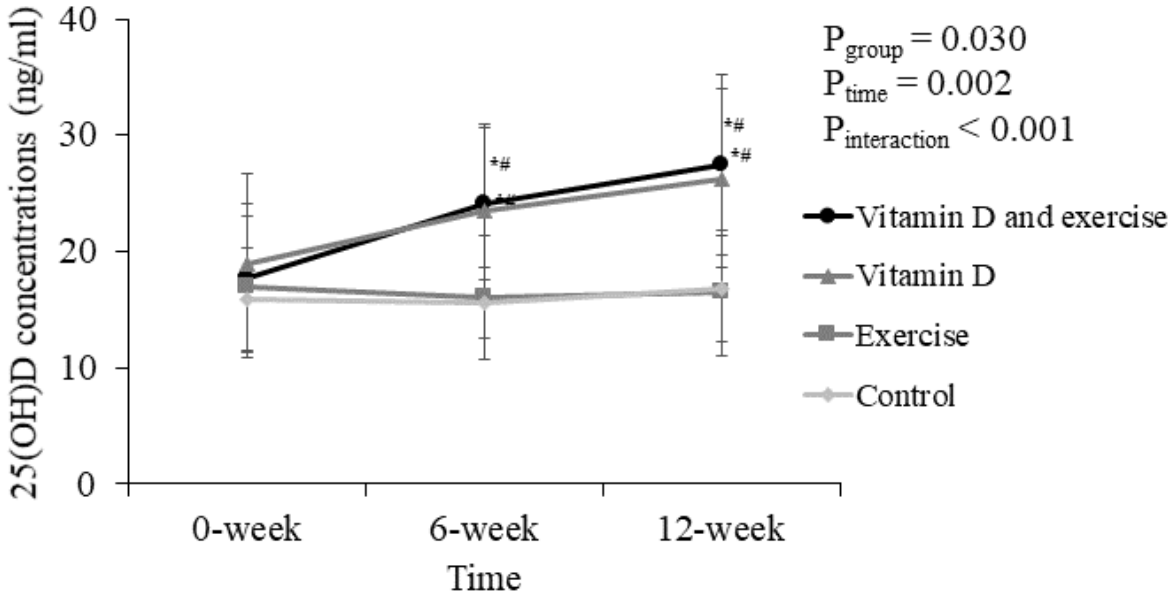

Figure 2

Effect of vitamin D supplementation and exercise training on serum 25(OH)D concentrations in 59 type 2 diabetes Values are expressed as means±standard deviation. Two way repeated-measures ANOVA was used to determine the effect of vitamin D and exercise on the serum 25(OH)D changes. *, P<0.05 vs the baseline within group; #, P<0.05 vs exercise or control group at the same time point.

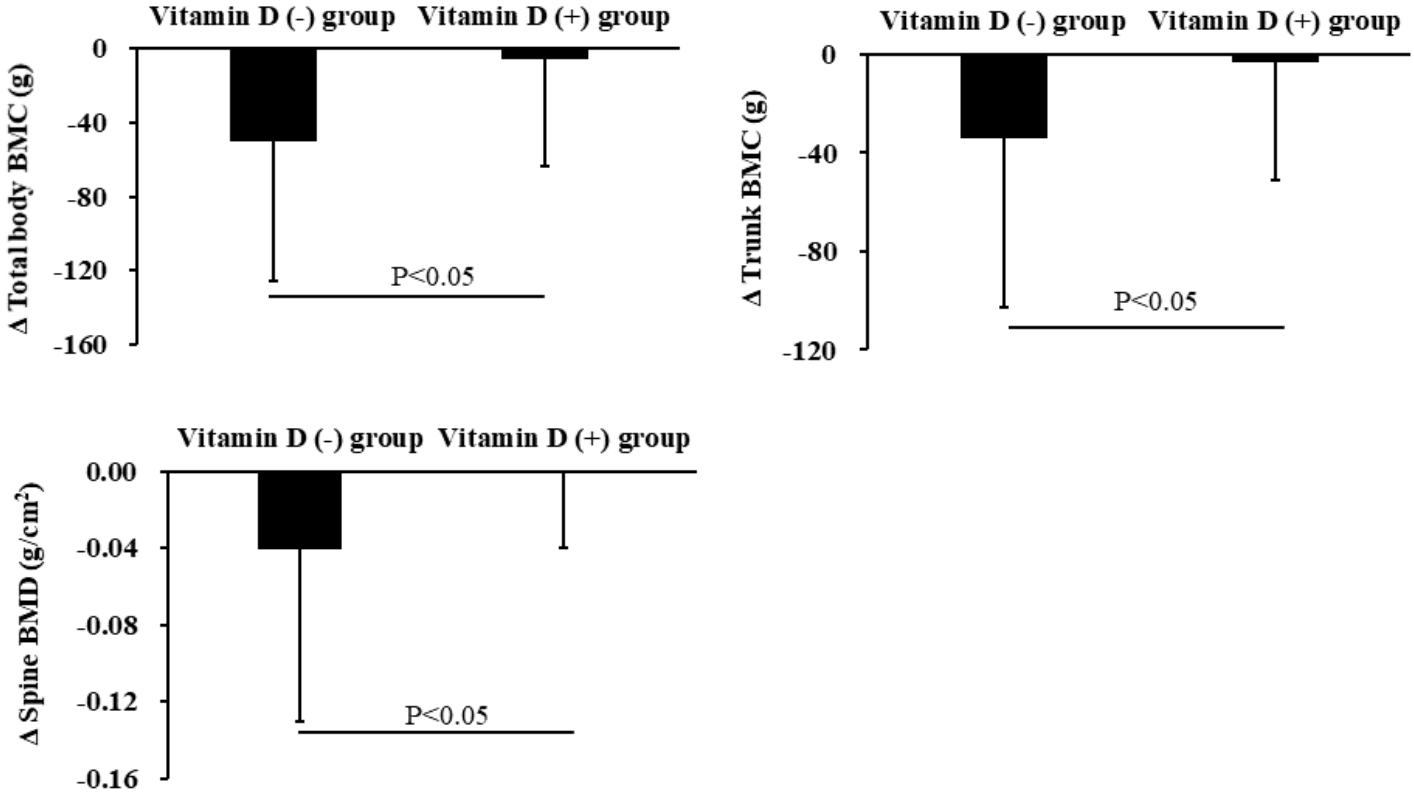

Figure 3

Effect of vitamin D supplementation on total body BMC (a), trunk BMC (b), and Spine BMD according to vitamin D treatment group* Values are expressed as mean changes±standard deviation from the baseline. *vitamin D (-), n= 28; vitamin D (+), n= 29. BMC, bone mineral content; BMD, bone mineral density.

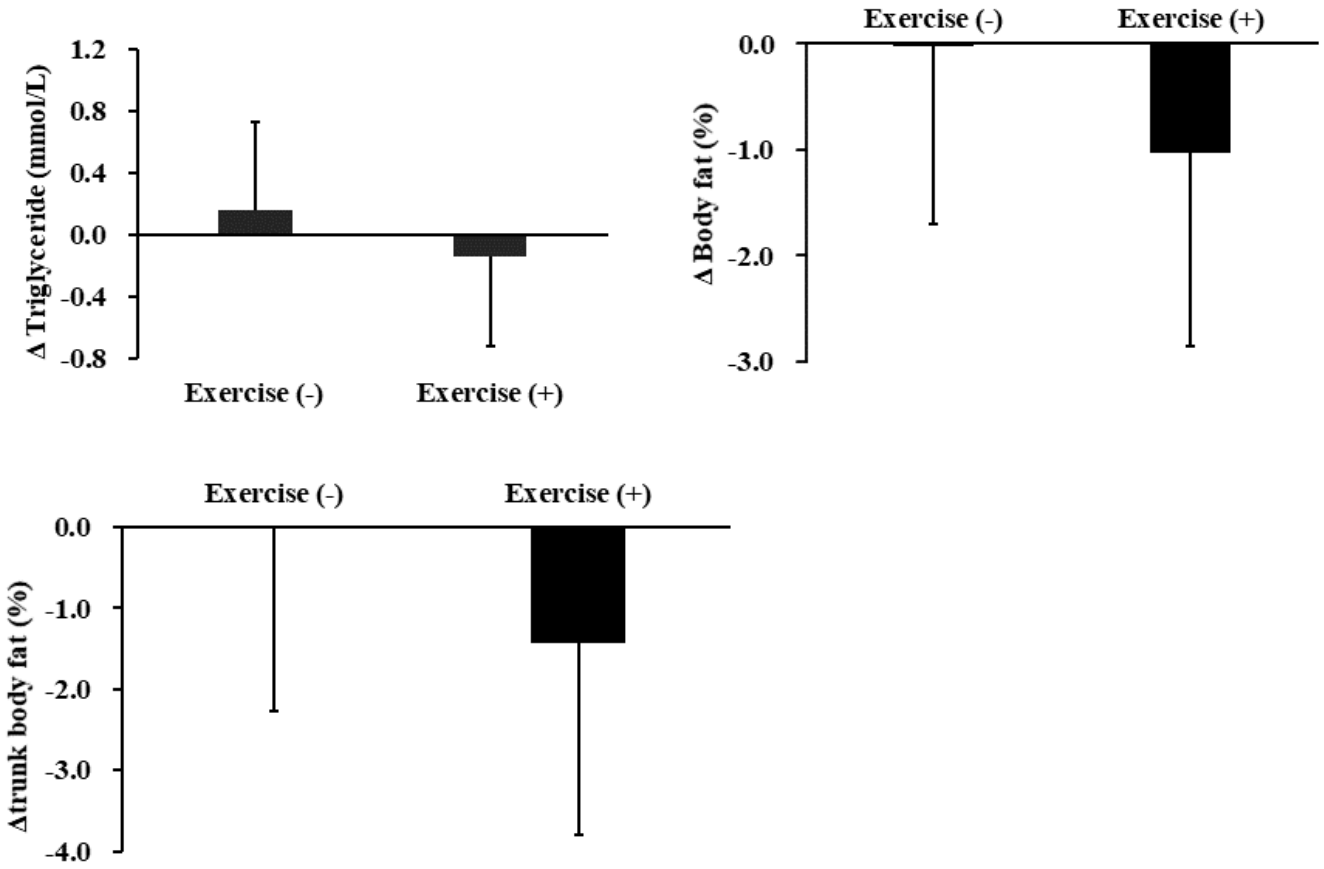

Figure 4

Effect of exercise training on triglyceride (a), body fat% (b) and trunk body fat % (c) according to exercise intervention group* Values are expressed as mean changes±standard deviation from the baseline. *vitamin D (-), n= 28; vitamin D (+), n= 29.

Supplementary Files

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- SuppFigures.pptx