Research Article

Effects of eight weeks of resistance training and vitamin D supplementation on insulin resistance, glycemic control, and inflammatory markers in men with type 2 diabetes: A single blind randomized controlled trial

Sepideh Salimi[1], SeyedSepehr Mousavi[1], Asal Mohammadi[1], Mohammad Hadi Pourramezan[*2], Sara Yazdan mehr[1], Anahita Sarrafpour Habibi[1]

Abstract

This study aimed to investigate the effects of eight weeks of resistance training (Ex), vitamin D supplementation (VD), and their combination (VD+Ex) on insulin resistance (HOMA IR), glycemic control (HbA1c, fasting glucose), inflammatory markers (interleukin 6 [IL 6] and C reactive protein [CRP]), and anthropometric measures in men with T2DM. In this single blind randomized controlled trial, 40 men with T2DM (aged 40–55 years) were randomly allocated into four groups (n=10 each): placebo control (PI), vitamin D supplementation (2000 IU/day, VD), resistance training (three sessions/week, 60–70% of 1RM, progressive overload, Ex), and combined VD+Ex. All participants maintained their usual diet, lifestyle, and anti-diabetic medications. Fasting blood samples were collected pre and post intervention to measure serum glucose, insulin, 25 hydroxy vitamin D, IL 6, and CRP. HOMA IR was calculated. Post hoc analysis showed that the Ex group had significantly lower HOMA IR than the placebo group (p=0.002), and the VD+Ex group had significantly lower HOMA IR compared to both placebo (p<0.001) and VD alone (p=0.001). The comparison between VD+Ex and Ex was not statistically significant (p>0.05). No significant difference in HbA1c was observed (p=0.210). For body fat percentage, both Ex (p=0.043) and VD+Ex (p<0.001 vs. placebo;p=0.009 vs. VD) showed significant reductions. IL 6 levels were significantly lower in the Ex and VD+Ex groups compared to placebo and VD groups (p<0.001 for both). No significant changes were found in CRP levels (p=0.078). The combination of resistance training and vitamin D did not provide additional statistically significant benefits over resistance training alone for any outcome, including HOMA IR, body fat percentage, or IL 6.

Key Words: Type 2 diabetes; Resistance training; Vitamin D supplementation; Insulin resistance; Interleukin 6; HOMA IR

1. Department of Physical Education and Sport Sciences, SR.C., Islamic Azad university, Tehran, Iran. 2. Department of Exercise Physiology, Sport Sciences Research Institute, Tehran, Iran.

*Author for correspondence: m.porramezan@ssrc.ac.ir

S S: 009-0002-3460-4120, SS M: 0009-0000-0989-8484, A M: 0009-0006-9527-1410, M HP: 0009-0005-5453-6323, S YM: 0009_0008_1599_9730, A SH: 0009-0007-2854-4252

Received 24 April 2026; Accepted 9 June 2026

Introduction

Type 2 diabetes mellitus (T2DM) has become one of the most pressing global health challenges, with the International Diabetes Federation reporting that over 500 million adults currently live with the condition (Pan et al., 2025). This chronic metabolic disorder is characterized primarily by insulin resistance, which precedes and drives the progressive decline in glycemic control, compounded by a persistent state of low grade systemic inflammation (Wang et al., 2025). In T2DM patients, elevated circulating levels of pro inflammatory cytokines such as interleukin 6 (IL 6) and C reactive protein (CRP) not only worsen insulin sensitivity but also increase the risk of cardiovascular complications. Given that approximately 90% of all diabetes cases are T2DM, and associated healthcare costs exceed $1 trillion annually, there is a critical need for effective, cost efficient non pharmacological interventions (Pan et al., 2025). Lifestyle strategies, particularly exercise training and nutritional supplementation, have therefore become cornerstones in the management of T2DM, offering benefits that complement standard pharmacotherapy (Agede, 2024).

Among these strategies, resistance training (RT) has gained increasing recognition as a powerful intervention for improving metabolic health and reducing inflammation in individuals with T2DM (Wang et al., 2025). Unlike aerobic exercise, which primarily enhances cardiorespiratory fitness, resistance training directly improves skeletal muscle mass, strength, and quality critical determinants of glucose uptake and insulin sensitivity. A recent meta-analysis by Wang and colleagues (2025), which included 43 randomized controlled trials (RCTs) involving 2,012 participants, found that RT significantly reduced insulin resistance (mean difference [MD] in HOMA IR: -1.15), fasting glucose (MD: -6.99 mg/dL), and HbA1c (MD: -0.55%), and also increased muscle mass (MD: 0.89 kg) and improved upper and lower body strength (Wang et al., 2025). Additionally, a network meta analysis by Pan and colleagues (2025) ranked resistance

exercise among the most effective exercise modalities for enhancing insulin sensitivity (SUCRA score: 71.8%) (Pan et al., 2025). With respect to inflammation, a systematic review and meta-analysis by Kadoglou and colleagues (2025) demonstrated that RT significantly reduced circulating CRP levels (weighted mean difference [WMD]: -0.63 mg/L; 95% CI: -1.05 to -0.20; p<0.001), although no significant changes were observed for IL-6 or TNF-α (Kadoglou et al., 2025). Nevertheless, other meta -analyses have concluded that exercise training, including resistance training, effectively reduces IL-6 (SMD: -0.58), TNF α (SMD: -0.62), and CRP (SMD: -0.78), supporting the role of RT in reducing the inflammatory burden of T2DM (Khalafi et al., 2025).

The potential of vitamin D supplementation as an adjunct therapy for T2DM is also well recognized, given the widespread prevalence of vitamin D deficiency among these patients and the presence of vitamin D receptors on pancreatic β cells and immune cells (Zhang et al., 2025). Nevertheless, evidence regarding the efficacy of vitamin D supplementation alone on glycemic control and inflammation has been mixed. An updated meta-analysis by Chen and colleagues (2024) of 39 RCTs (2,982 participants) concluded that vitamin D supplementation significantly reduces fasting glucose (WMD:-0.49 mmol/L), HbA1c (WMD:-0.30%), HOMA IR (WMD:-0.39), and fasting insulin (WMD:-1.31 μIU/mL), with more pronounced effects observed in deficient, overweight, or poorly controlled (HbA1c ≥8%) patients (Chen et al., 2024). However, a more recent systematic review and network meta-analysis found that while low dose vitamin D (<1,000 IU/day) significantly improved HbA1c, moderate doses (1,000 2,000 IU/day) reduced fasting insulin, and higher doses (2,000 4,000 IU/day) improved both HbA1c and insulin, raising the possibility that dosage and patient characteristics are crucial determinants of efficacy. More recently, studies combining vitamin D supplementation with exercise have emerged as a potentially synergistic approach. A meta-analysis by Pour Ahmadi and colleagues (2025) reported that vitamin D combined with exercise significantly reduced fasting blood glucose (WMD:-16.59 mg/dL), fasting insulin (WMD:-1.54 μIU/mL), HbA1c (WMD:-0.97%), and HOMA IR (WMD:-0.98) compared to control groups, with effects greater than either intervention alone (Ahmadi et al., 2025). These findings support the biological plausibility that exercise, by increasing vitamin D receptor expression and local activation of vitamin D in skeletal muscle, may enhance the insulin sensitizing and anti-inflammatory actions of vitamin D supplementation. Nonetheless, few studies have specifically examined the interact-ion between resistance training (a potent anabolic stimulus) and vitamin D supplementation in a four group parallel design RCT that includes a placebo control. Therefore, this single blind, randomized controlled trial was designed to investigate the effects of eight weeks of resistance training, vitamin D supplementation (2000 IU/day), and their combination on insulin resistance (HOMA IR), glycemic control, inflammatory markers (IL 6 and CRP), and body composition in men with T2DM aged 40 55 years. We hypothesized that combined resistance training plus vitamin D would produce superior outcomes compared with either intervention alone or placebo, reflecting a synergistic interaction between the two strategies.

Materials and Methods

Subjects

Study population consisted of men with type 2 diabetes mellitus, aged between 40 and 55 years. From among the eligible individuals who expressed willingness to participate, a total of 40 participants were selected as the final study sample. A single blind randomized sampling method was employed for participant selection. Initially, a convenience sampling approach was used to recruit accessible and volunteer patients with type 2 diabetes. Subsequently, all eligible individuals were randomly assigned to the different study groups, ensuring unbiased allocation.

Study procedure

To recruit participants, informational announcements were posted at the Tehran Diabetes Association, inviting eligible individuals to voluntarily take part in the study. All potential participants received a thorough explanation of the study procedures, including the potential benefits and possible risks associated with the intervention. Following this, 40 eligible individuals who agreed to the study conditions were randomly selected, and written informed consent was obtained from each participant. Confirmation of study eligibility was based on two separate fasting blood glucose (FBG) measurements, with an average FBG level greater than 125 mg/dL, in addition to a physician's formal diagnosis of type 2 diabetes. After confirmation, participants were randomly allocated into four groups, each consisting of 10 participants: (1) Control (placebo) group, (2) Resistance Training (Ex) group, (3) Vitamin D supplementation (VD) group, and (4) Combined Resistance Training plus Vitamin D (VD+Ex) group. Randomization was performed using a computer generated random number sequence (www.randomization.com). Allocation was concealed using sequentially numbered, opaque, sealed envelopes that were opened only after baseline assessments by a researcher not involved in the intervention. The study was single blind: the outcome assessor and the statistician were blinded to group allo-

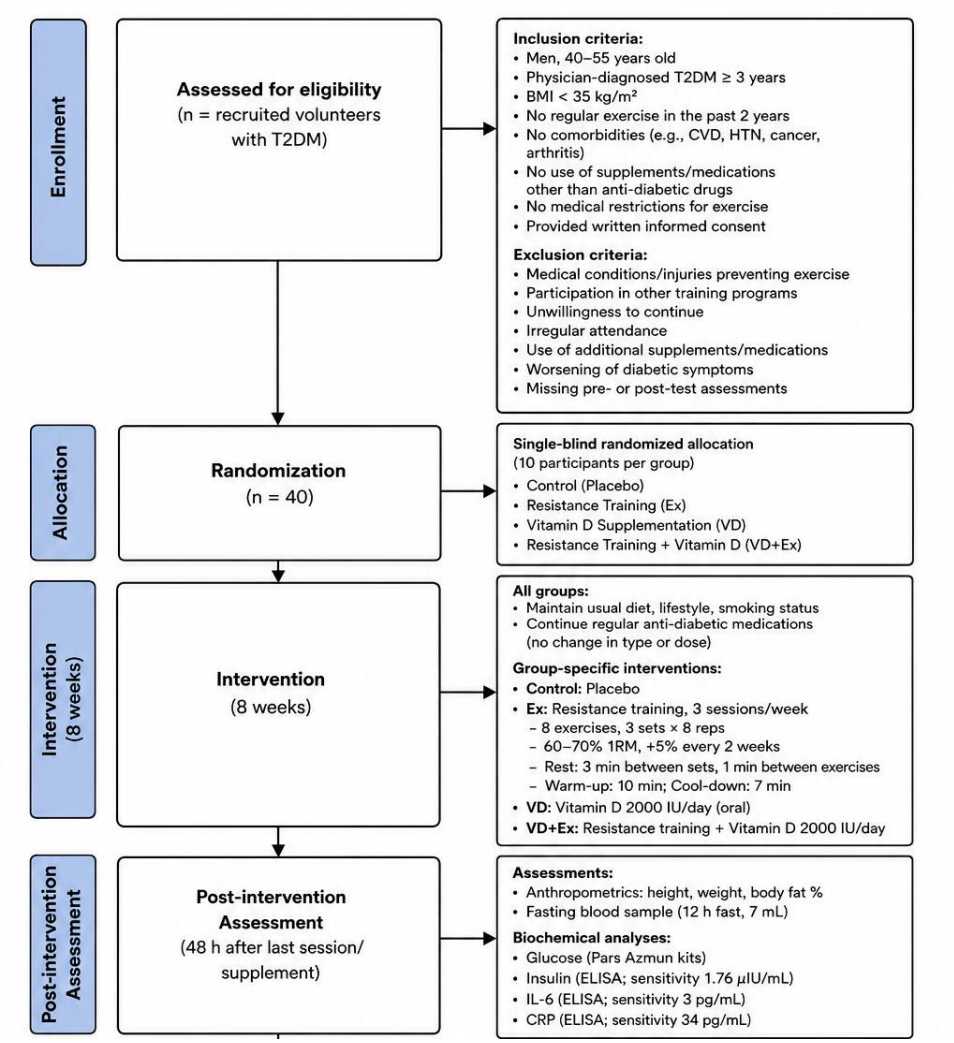

Figure 1. Flowchart of the study design. T2DM, type 2 diabetes mellitus; PI, placebo; VD, vitamin D supplementation (2000 IU/day); Ex, resistance training (3 sessions/week, 60–70% of 1RM); VD+Ex, combined intervention.

-cation. Participants could not be blinded to the resistance training intervention due to its nature, but they were blinded to vitamin D vs. placebo assignment (identical capsules). The placebo group received identical appearing capsules containing microcrystalline cellulose, administered at the same daily schedule (one capsule per day). Capsules were prepared by a third party pharmacy and were indistinguishable from vitamin D capsules in appearance, taste, and packaging. No adverse events were recorded during the study. Specifically, no participant reported musculoskeletal injury related to resistance training or gastrointestinal symptoms/hypercalcemia related to vitamin D supplementation.

All participants were instructed to maintain their usual dietary and nutritional habits, as well as their smoking status, throughout the intervention period. It is important to note that all participants were already taking standard diabetes controlling medications, including metformin, glyburide, or sulfonylureas. They were explicitly asked not to alter the type or dosage of these medications during the study unless advised to do so by their treating physician. For the pre-test blood sampling, participants were required to fast overnight for 12 hours and then report to the laboratory. A 7 ml blood sample was drawn from the antecubital vein to measure the study variables. Anthropometric measurements, including height and weight, were also recorded using a stadiometer and a digital scale, respectively. Several days after the baseline blood draw and assessments, the eight week intervention period commenced, which included resistance training, vitamin D supplementation, or both, depending on the group assignment (Figure 1).

Sample size and power calculation

No a priori sample size calculation was performed due to the exploratory nature of the study. A post hoc power analysis was conducted for the primary outcome (HOMA-IR) using the observed effect size between the Ex and VD+Ex groups. With α =0.05 and n=10 per group, the achieved power was approximately 0.52, indicating that the study was underpowered to detect this difference as statistically significant. Therefore, non-significant comparisons between active intervention groups should be interpreted with caution due to the risk of Type II error.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) age between 40 and 55 years; (b) physician confirmed diagnosis of type 2 diabetes; (c) at least three years since the initial diagnosis; (d) no use of medications or supplements other than anti diabetic drugs; (e) absence of any injuries or medical conditions that would prevent participation in exercise; (f) no regular exercise program during the past two years; (g) absence of comorbidities such as hypertension, cardiovascular disease, cancer, or arthritis; (h) signed informed consent; (i) no medical restrictions for physical activity; (j) body mass index (BMI) below 35 kg/m²; and (k) voluntary agreement to participate under the conditions specified by the researcher.

Participants were excluded from the study if any of the following occurred: (a) unwillingness to continue the program; (b) development of medical contraindications for continuing the intervention; (c) irregular attendance in the training sessions; (d) simultaneous participation in other training programs; (e) injury caused by the training protocol; (f) use of additional medications or supplements during the study period; (g) worsening of diabetic symptoms; or (h) failure to attend either the pre-test or post-test blood sampling sessions.

Resistance training protocol

The resistance training program lasted for eight weeks, with three sessions performed per week. Each session consisted of eight different exercises, each performed for three sets of eight repetitions. The exercises included: leg press, leg extension, leg curl, chest press, lat pulldown, incline chest press, biceps curl, and triceps extension. The training intensity was set at 60–70% of one repetition maximum (1RM), and this intensity was increased by 5% every two weeks. Rest intervals were set at 3 minutes between sets and 1 minute between exercises (Kadoglou et al., 2012). Each training session was preceded by a warm up phase, which included 10 minutes of cycling, static stretching, and light weight exercises. Each session was concluded with a cool down phase consisting of 7 minutes of light jogging and static stretching.

Vitamin D supplementation

Participants assigned to the vitamin D group (VD) and the combined resistance training plus vitamin D group (VD+Ex) received a daily oral dose of 2000 IU of vitamin D (Al-Daghri et al., 2012). This dosage was selected based on previous research indicating that daily doses ranging from 800 IU to 2400 IU are considered both safe and effective for individuals with type 2 diabetes (Kim et al., 2014).

Anthropometric measurements

Anthropometric assessments, including body weight, height, and body fat percentage, were conducted according to a standardized protocol. All measurements were taken while participants were wearing light clothing and were barefoot. Body fat percentage was determined using a BOCA X1 body composition analyzer. Participants were instructed to strictly follow all pre-test conditions required for accurate body composition analysis.

Blood sampling and measurements

For post intervention blood sampling, participants were instructed to visit the laboratory 48 hours after their last resistance training session or vitamin D supplementation. Blood samples were collected by a licensed physician and immediately transferred into Falcon tubes. After centrifugation at 3000 rpm for 15 minutes, the serum was separated and stored at –80°C until subsequent analysis.

Glucose levels were measured using commercial kits supplied by Pars Azmun Company. Serum insulin concentrations were assessed using an enzyme linked immunosorbent assay (ELISA) kit (DE2935, Demeditec, Germany), which had a sensitivity of 1.76 µIU/ml. Levels of interleukin 6 (IL 6) and C reactive protein (CRP) were also determined using ELISA kits from RayBiotech (catalog numbers: ELH IL6 1 for IL 6 with a sensitivity of 3 pg/ml; and ELH CRP 1 for CRP with a sensitivity of 34 pg/ml, respectively).

Statistical analysis

All statistical analyses were performed using SPSS software, version 24 (IBM Corp., Armonk, NY, USA). Initially, the distribution of the data was assessed for normality. Because the Shapiro–Wilk test confirmed that the data followed a normal distribution ($p>0.05$ for all variables in all groups), a parametric approach was adopted. As a sensitivity analysis, natural log transformed HOMA IR values were also analyzed using ANCOVA, and the Kruskal–Wallis test was applied to pre post differences; both confirmed the primary findings. When significant differences were detected among the groups, Bonferroni post hoc tests were performed to identify the specific pairwise group differences. The threshold for statistical significance was set at $p<0.05$; any p value below this level was considered statistically significant.

Results

Table 1 presents the mean ± standard deviation (SD) values of all measured variables at both pre-test and post-test stages across the four study groups: placebo (PI), vitamin D supplementation (VD), resistance training (Ex), and combined resistance training plus vitamin D (VD+Ex). The variables include age, height, insulin (mU/ml), glucose (mg/dl), HOMA-IR (as a

measure of insulin resistance), HbA1c, serum 25-hydroxy vitamin D (ng/ml), body fat percentage (%), body mass index (BMI, kg/m²), and body weight (kg). To assess baseline comparability, one way analysis of variance (ANOVA) was performed on pre-test values across the four groups. No significant differences were found for any variable, including HOMA IR, age, BMI, body fat percentage, fasting glucose, insulin, HbA1c, and 25 hydroxy vitamin D, confirming that the groups were comparable at baseline.

To assess the effect of interventions on outcome variables while controlling for baseline values, an analysis of covariance (ANCOVA) was conducted for each dependent variable. Between-group comparisons were followed by Bonferroni-adjusted post-hoc tests where appropriate.

The ANCOVA for HOMA IR revealed a statistically significant difference between the groups. Bonferroni post hoc comparisons indicated that the resistance training group (Ex) had a significantly lower post intervention HOMA IR compared to the placebo group (p=0.002). Furthermore, the combined resistance training plus vitamin D group (VD+Ex) demonstrated significantly reduced HOMA IR levels relative to both the placebo group (p < 0.001) and the vitamin D only group (p=0.001). The difference between the VD+Ex and Ex groups was not statistically significant (p>0.05). No other pairwise comparisons reached statistical significance.

For HbA1c levels, the ANCOVA showed no statistically significant difference among the four groups after adjusting for baseline values (p=0.210). Thus, neither vitamin D supplementation, resistance training, nor their combination significantly altered HbA1c compared to placebo. Analysis of body fat percentage indicated a significant overall group effect. Post hoc testing revealed that the resistance training group (Ex) experienced a significantly greater reduction in body fat percentage compared to the placebo group (p=0.043). Similarly, the combined VD+Ex group showed significant decreases in body fat percentage when compared with both the placebo group (p< 0.001) and the vitamin D only group (p=0.009). The difference between the Ex and VD+Ex groups was not statistically significant. As shown in Table 1, additional variables including fasting insulin, fasting glucose, BMI, and body weight exhibited changes from pre to post intervention; however, the corresponding ANCOVA results were either non-significant or followed patterns consistent with the primary outcomes described above.

Table 1. Baseline (pre-test) and post-intervention (post-test) values (mean ± SD) of all measured variables across the four study groups: placebo (PI), vitamin D supplementation (VD), resistance training (Ex), and combined resistance training plus vitamin D (VD+Ex).

Variable	PI	VD	Ex	VD+Ex
Age (years)	46.6 ± 3.54	48.5 ± 3.70	47.8 ± 3.72	45.7 ± 4.23
Height (cm)	171.6 ± 2.6	174.8 ± 5.85	172.9 ± 4.3	171.8 ± 4.28
Insulin (mU/ml)				
Pre-test	9.26 ± 13.4	8.58 ± 11.16	10.19 ± 7.77	9.68 ± 14.44
Post-test	8.91 ± 13.38	8.26 ± 10.14	8.92 ± 7.36	8.36 ± 12.14
Glucose (mg/dl)				
Pre-test	178.6 ± 4.26	167.15 ± 4.92	185.7 ± 7.21	171.19 ± 4.44
Post-test	175.9 ± 6.24	161.14 ± 4.25	169.15 ± 5.23	149.12 ± 2.14
HOMA-IR				
Pre-test	4.04 ± 0.60	3.55 ± 0.66	4.67 ± 0.99	4.08 ± 0.73
Post-test	3.83 ± 0.61	3.28 ± 0.57	3.72 ± 0.77	3.07 ± 0.45
HbA1c (%)				
Pre-test	8.24 ± 1.39	7.76 ± 1.75	7.43 ± 1.22	7.91 ± 1.09
Post-test	8.37 ± 1.46	7.68 ± 1.63	7.32 ± 1.10	7.84 ± 0.95
25-Hydroxy Vitamin D (ng/ml)				
Pre-test	22.9 ± 6.9	27.8 ± 13.5	24.3 ± 11.6	22.7 ± 8.3
Post-test	19.6 ± 3.7	43.1 ± 18.0	23.9 ± 13.7	38.5 ± 15.8
Body Fat Percentage (%)				
Pre-test	31.9 ± 2.8	29.48 ± 2.14	30.45 ± 2.64	32.84 ± 2.0
Post-test	30.88 ± 1.77	28.97 ± 2.06	29.34 ± 2.80	30.79 ± 2.1
BMI (kg/m²)				
Pre-test	28.22 ± 1.21	27.90 ± 1.72	28.10 ± 1.37	28.49 ± 1.68
Post-test	28.15 ± 1.20	27.74 ± 1.47	27.76 ± 1.34	28.13 ± 1.58
Body Weight (kg)				
Pre-test	82.92 ± 7.47	84.51 ± 7.73	85.64 ± 3.65	85.16 ± 5.11
Post-test	82.70 ± 6.60	84.77 ± 7.73	84.60 ± 3.54	84.90 ± 4.89

SD: standard deviation; HOMA-IR: homeostatic model assessment of insulin resistance; HbA1c: glycated hemoglobin; BMI: body mass index.

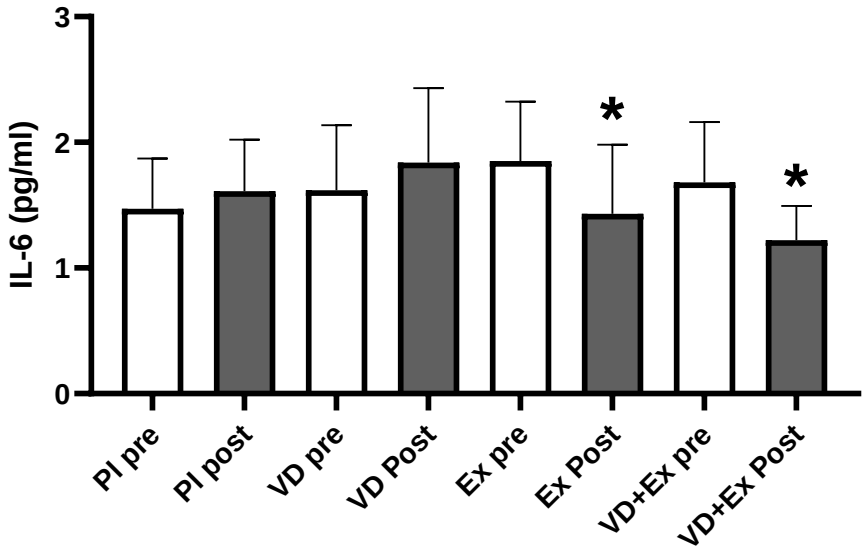

Figure 2. Effects of vitamin D (VD), exercise training (Ex), and their combination (VD+Ex) on serum IL-6 levels (pg/mL). Data are presented as mean ± SD. PI: placebo group. Pre: baseline measurement; Post: post intervention measurement. *Note: The figure shows eight bars – pre and post for each of the four groups. Based on your description, IL 6 decreased notably in the Ex and VD+Ex groups post intervention. ANCOVA with Bonferroni post hoc test was used for statistical analysis. ***p<0.001, **p<0.01 compared to the respective placebo or vitamin D group.

The ANCOVA revealed a significant main effect of group on IL-6 levels ($p < 0.001$). Bonferroni-adjusted post-hoc comparisons showed that IL-6 levels were significantly lower in the exercise training (Ex) group compared with both the placebo (PI) group ($p =0.002$) and the vitamin D (VD) group ($p < 0.001$). Similarly, the combined exercise training plus vitamin D (VD+Ex) group exhibited significantly reduced IL-6 levels relative to the placebo group ($p<0.001$) and the vitamin D group ($p<0.001$) (Figure 2).

Analysis of covariance (ANCOVA) was performed to compare CRP levels across the experimental groups after adjusting for baseline values. The results revealed no statistically significant difference in CRP levels between any of the groups ($p=0.078$). Thus, the null hypothesis could not be rejected, indicating that neither vitamin D supplementation, exercise training, nor their combination had a measurable effect on circulating CRP levels compared to placebo under the present experimental conditions (Figure 3).

Discussion

The primary findings of this single-blind randomized controlled trial demonstrate that eight weeks of resistance training (RT), either alone or combined with vitamin D supplementation (2000 IU/day), significantly improved insulin resistance (HOMA-IR), reduced body fat percentage, and lowered serum IL-6 levels in men with type 2 diabetes (T2DM). Conversely, vitamin D monotherapy failed to produce any significant metabolic or anti-inflammatory effects compared to placebo. Notably, the combin-ed intervention (VD+Ex) resulted in a numerically greater reduction in HOMA-IR (post-intervention mean 3.07 vs. 3.72 in Ex group) compared to resistance training alone, suggesting a potential additive effect that warrants further investigation. No significant changes were observed for HbA1c, CRP, fasting glucose, fasting insulin, BMI, or body weight. These findings suggest that RT is a potent non pharmacological strategy for improving insulin sensitivity and reducing inflammation in T2DM, while adding vitamin D supplementation may confer marginal additional benefit for HOMA IR without augmenting the anti-inflammatory or body composition effects beyond RT alone. Although the Shapiro–Wilk test indicated normal distribution, the relatively large standard deviations for insulin and HOMA IR, likely reflecting the heterogeneous nature of type 2 diabetes, warrant cautious interpretation. Sensitivity analyses using log transformed data and non-parametric tests, however, supported the robustness of our results.

From a mechanistic perspective, RT improves insulin sensitivity primarily through enhanced skeletal muscle glucose uptake. Each bout of contraction stimulates the translocation of GLUT4 to the sarcolemma via AMP activated protein kinase (AMPK) and Ca^{2+}/calmodulin dependent protein kinase (CaMK) pathways, independent of insulin signaling (Wang et al., 2025). Chronic RT upregulates total GLUT4 expression, increases muscle mass (providing a larger glucose reservoir), and improves insulin signaling at the level of IRS 1 and PI3K/Akt. In parallel, RT exerts anti-inflammatory effects by reducing visceral and intermuscular adipose tissue, which is a major source of pro-inflammatory cyto-

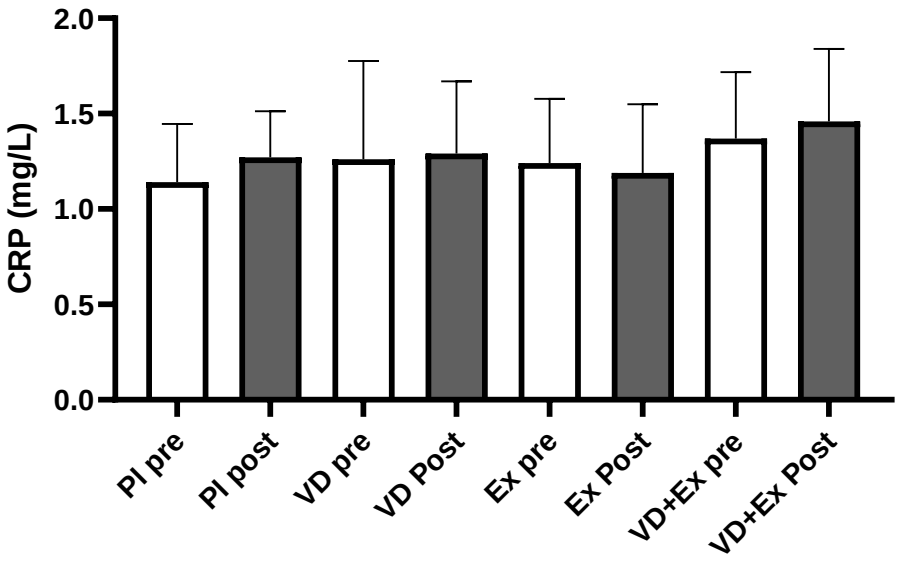

Figure 3. C-reactive protein (CRP) levels (mg/L) before (pre) and after (post) intervention in the placebo (PI), vitamin D (VD), exercise training (Ex), and combined vitamin D plus exercise training (VD+Ex) groups. Data are presented as mean ± SD. PI: placebo; VD: vitamin D; Ex: exercise training; VD+Ex: vitamin D + exercise training. Statistical analysis: analysis of covariance (ANCOVA) followed by appropriate post-hoc tests. No significant between-group differences were detected ($p = 0.078$).

-kines. Notably, a 2025 meta-analysis (Wang et al., 43 RCTs, n = 2012) reported that RT reduced HOMA IR (MD: –1.15; 95% CI), fasting glucose (MD:–6.99 mg/dL), HbA1c (MD: –0.55%), and increased muscle mass (MD: 0.89 kg) (Wang et al., 2025). Furthermore, RT significantly reduced CRP (SMD: –0.80; 95% CI:–1.05,–0.20; p<0.001). However, despite our observed reduction in IL 6, Wang's analysis found no significant changes for IL 6 or TNF α. This aligns with Kadoglou et al. (2025), who reported that RT reduces CRP (WMD: –0.63 mg/L; 95% CI: –1.05,–0.20;p<0.001) and increases adiponectin (WMD:–0.94 µg/mL), but does not significantly affect IL 6 (Kadoglou et al., 2025). In contrast, our study detected a significant reduction in IL 6 (but not CRP) in both Ex and VD+Ex groups, which may be explained by differences in baseline inflammatory status, training volume, participant age, or the specific IL 6 ELISA kits used.

The lack of change in CRP in our study is consistent with some evidence but contradictory to other large meta-analyses. A 2025 network meta-analysis (Khalafi et al., 60 studies, n=3339) found that exercise training effectively reduced IL 6 (SMD: –0.58), TNF-α (SMD: –0.62), and CRP (SMD:–0.78). However, when breaking down by exercise modality, RT alone did not change any inflammatory markers compared to controls; only combined aerobic plus resistance training (AT+RT) reduced IL 6, TNF-α, and CRP (Khalafi et al., 2025). Our RT protocol (three weekly sessions, 60 70% of 1RM, progressive overload) may have been insufficient to achieve the CRP lowering effect seen with AT+RT. Moreover, the observation that IL 6 was reduced while CRP was not may be due to the acute phase nature of CRP, which is more strongly influenced by aerobic exercise and weight loss. In our study, body fat percentage decreased significantly (by ~1.1–2.0%), but this magnitude of change may have been insufficient to lower CRP, which is closely tied to adiposity. Future studies should consider longer intervention periods (≥12 weeks) and combination training modalities to better capture CRP reductions.

Regarding vitamin D supplementation alone, our finding that monotherapy did not improve HOMA IR, HbA1c, or IL 6 aligns with several recent high quality meta-analyses. A 2025 meta-analysis by Gong et al. (10 RCTs, n=3460) found that although vitamin D significantly increased serum 25(OH)D levels (SMD: 4.01; 95% CI: 2.43 to 5.59; p < 0.001), it exerted no discernible effect on HbA1c (SMD: 0.08; 95% CI: –0.25 to 0.37; p<0.001) or HOMA IR (SMD: 5.95; 95% CI: –2.87 to 14.77; p<0.001) (Gong & Chen, 2025). Similarly, a 2025 meta-analysis by Madhubala and Harish (18 RCTs, ≈2000 participants) reported that vitamin D supplementation significantly improved HbA1c (MD: –0.42%), fasting blood glucose (MD:–9.5 mg/dL), HOMA IR (MD: –0.98), and CRP (MD:–0.46 mg/L), but the effects were modest and highly dependent on baseline vitamin D status and geographic region. In our study, mean baseline 25(OH) D levels were 22–27 ng/mL (insufficient but not severely deficient), which may explain the lack of metabolic benefits. Moreover, the intervention duration (8 weeks) was relatively short compared to the 12–24 weeks required to detect changes in HbA1c and CRP. A 2026 meta-analysis of 39 RCTs concluded that vitamin D sup- plementation

yields modest improvements in glycemic control only in vitamin D deficient (baseline 25(OH) D<20 ng/mL) or poorly controlled (HbA1c ≥ 8%) patients, and effects may diminish over time (Probosari et al., 2025). These findings align with our observation that vitamin D alone was ineffective in our study.

The combination of RT plus vitamin D in our study showed a numerical improvement in HOMA IR compared to RT alone (post intervention HOMA IR 3.07 vs. 3.72), suggesting a potential additive effect that did not reach statistical significance (likely due to small sample size, n=10 per group). This finding is supported by a 2025 meta-analysis by Pour Ahmadi et al. (15 RCTs), which reported that vitamin D plus exercise significantly reduced HOMA IR (WMD: –0.98; 95% CI: –1.54 to –0.42; p=0.001), fasting blood glucose (WMD:–16.59 mg/dL), and HbA1c (WMD: –0.97%) compared to control (Ahmadi et al., 2025). Furthermore, a 2026 systematic review by Liu et al. (8 databases) found that combining exercise with vitamin D supplementation may overcome the limitations of single interventions, yielding significant synergistic effects in managing T2DM (Liu et al., 2026). The potential mechanism for this synergy is that exercise upregulates vitamin D receptor (VDR) expression and HIF-1α hydroxylase activity in skeletal muscle, thereby enhancing local activation of vitamin D and amplifying its insulin sensitizing actions. However, in our study, this synergy was not robust enough to produce additional benefits for IL 6 or body fat percentage beyond RT alone. This may be due to the relatively low dose of vitamin D (2000 IU/day) and the short intervention duration. Future studies should consider higher doses (≥4000 IU/day), longer intervention periods (≥16 weeks), and stratification by baseline vitamin D status to better elucidate potential synergistic effects.

Several limitations should be acknowledged. First, no a priori sample size calculation was performed, and the small sample size (n=10 per group) limited statistical power. Post hoc power analysis for the primary outcome (HOMA IR) between the Ex and VD+Ex groups yielded only 0.52, indicating that the study was underpowered to detect moderate differences between active interventions. Consequently, the non-significant comparison between Ex and VD+Ex for HOMA IR may represent a Type II error, and the observed numerical trend should not be interpreted as evidence of an additive effect. Second, we did not systematically monitor adherence to anti diabetic medications (e.g., pill counts or diaries), and unreported changes in medication could have influenced the outcomes. Third, although we used sealed envelopes for allocation concealment, we did not independently verify that the sequence was fully concealed from the researcher recruiting participants, which may introduce selection bias. Fourth, we did not formally assess whether participants remained blinded to supplement assignment (e.g., by asking them to guess their allocation). Fifth, the large variability in baseline insulin levels, despite normal distribution per Shapiro–Wilk test, reflects the heterogeneity of T2DM and may have influenced the non-significant findings for HbA1c and CRP. Sixth, the intervention duration of eight weeks was relatively short to detect changes in HbA1c and CRP, which typically require longer follow up. Seventh, the study was underpowered to detect moderate differences between active intervention groups (e.g., VD+Ex vs. Ex). The post hoc power for the HOMA IR comparison between these two groups was only 0.52; therefore, the absence of a statistically significant difference should not be interpreted as evidence of equivalence. Eighth, the exact p value for the VD+Ex vs. Ex comparison was not calculated in the original analysis, but the non-significant result is clear from the absence of a reported p value (p>0.05).

Conclusion

Eight weeks of resistance training, performed three times per week at 60 70% of 1RM, significantly improved insulin resistance (HOMA IR), reduced body fat percentage, and lowered serum IL 6 levels in men with type 2 diabetes. Vitamin D supplementation alone (2000 IU/day) did not produce any significant metabolic or anti-inflammatory effects. The combination of resistance training plus vitamin D did not provide statistically significant additional benefits over resistance training alone for any outcome. These findings support the prescription of resistance training as a primary non pharmacological strategy to enhance insulin sensitivity and reduce inflammation in middle aged men with T2DM. Adding vitamin D supplementation cannot be recommended based on the present data; however, larger and longer term studies are needed to clarify whether a synergistic effect might emerge with higher doses or in vitamin D deficient populations.

What is already known on this subject?

Type 2 diabetes involves insulin resistance and chronic inflammation, with high IL-6 and CRP predicting worse outcomes. Resistance training improves glycemic control and insulin sensitivity, but its effect on inflammatory markers is inconsistent.

What this study adds?

This four-arm RCT in middle-aged men with T2DM compared resistance training, vitamin D (2000 IU/day), their combination, and placebo. Eight weeks of training (but not vitamin D) significantly reduced HOMA-IR and IL-6; the combination showed a numerically greater HOMA-IR reduction, suggesting a possible additive effect. Neither intervention altered HbA1c or CRP in this short period, indicating longer trials are needed.

Organ Cross-Talk Tips:

- Elevated IL-6 and CRP in T2DM reflect chronic inflammatory cross-talk between adipose tissue, the liver, and the vasculature, which drives systemic insulin resistance and cardiovascular risk.

Acknowledgements

None.

Funding

None.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest in the present research.

Ethical approval All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Informed consent Performed.

Author contributions

Conceptualization: S.S., Methodology: S.S.M., Software: A.M., Validation: M.H.P.,; Formal analysis: S.Y.M.,; Investigation: A.Sh.,; Resources: M.H.P.,; Data curation: M.H.P.,; Writing - original draft: M.H.P.,; Writing–review & editing A.M.,; Visualization: S.S.,; Supervision: M.H.P.; Project administration: M.H.P.; Funding acquisition: M.H.P.

References

Agede, O. (2024). Pharmacotherapy of Type 2 Diabetes Mellitus (T2DM) in Clinical Practice: a comprehensive review of the treatment options. Nigerian Stethoscope, 6(2), 8-18. URL: https://www.nigerianstethoscope.org/index.php/NigSTETH/article/view/142

Ahmadi, M. J. P., Sharifi, M., Shokri, S., Mehranpour, G., & Eslampanah, F. (2025). Effects of vitamin D and exercise on glycemic control and circulating 25 (OH) D in adults with metabolic disorders: A systematic review and meta-analysis with GRADE assessment. doi: https://doi.org/10.21203/rs.3.rs-8122833/v1

Al-Daghri, N. M., Alkharfy, K. M., Al-Othman, A., El-Kholie, E., Moharram, O., Alokail, M. S., . . . Chrousos, G. P. (2012). Vitamin D supplementation as an adjuvant therapy for patients with T2DM: an 18-month prospective interventional study. Cardiovascular diabetology, 11(1), 85. doi: https://doi.org/10.1186/1475-2840-11-85

Chen, W., Liu, L., & Hu, F. (2024). Efficacy of vitamin D supplementation on glycaemic control in type 2 diabetes: an updated systematic review and meta-analysis of randomized controlled trials. Diabetes, Obesity and Metabolism, 26(12), 5713-5726. doi: https://doi.org/10.1111/dom.15941

Gong, S., & Chen, L. (2025). Assessing the potency of vitamin D augmentation on saccharometric indices in type 2 diabetes: a meta-analysis. Frontiers in nutrition, 12, 1677686. doi: https://doi.org/10.3389/fnut.2025.1677686

Kadoglou, N. P., Fotiadis, G., Athanasiadou, Z., Vitta, I., Lampropoulos, S., & Vrabas, I. S. (2012). The effects of resistance training on ApoB/ApoA-I ratio, Lp (a) and inflammatory markers in patients with type 2 diabetes. Endocrine, 42(3), 561-569. doi: https://doi.org/10.1007/s12020-012-9650-y

Kadoglou, N. P., Georgiou, C., Balaskas, N., Panayiotou, C., Vardas, M., Mitsis, A., & Antonopoulos, C. N. (2025). The Anti-Inflammatory Effects of Resistance Training in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Biomolecules, 15(10), 1417. doi: 10.3390/biom15101417

Khalafi, M., Habibi Maleki, A., Symonds, M. E., Azali Alamdari, K., Ehsanifar, M., & Rosenkranz, S. K. (2025). Comparative Efficacy of Different Exercise Modes on Inflammatory Markers in Patients With Type 2 Diabetes Mellitus: A Systematic Review With Pairwise and Network Meta-Analyses. Obesity Reviews, 26(10), e13954. doi: https://doi.org/10.1111/obr.13954

Kim, H.-J., Kang, C.-K., Park, H., & Lee, M.-G. (2014). Effects of vitamin D supplementation and circuit training on indices of obesity and insulin resistance in T2D and vitamin D deficient elderly women. Journal of Exercise Nutrition & Biochemistry, 18(3), 249. doi: 10.5717/jenb.2014.18.3.249

Liu, R., Dong, C., Li, R., Wang, Q., Sun, A., & Huang, Z. (2026). Effects of Exercise Combined With Vitamin D Interventions on Glucose-Lipid Metabolism and Obesity in Individuals With Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Nutrition reviews, nuag010. doi: https://doi.org/10.1093/nutrit/nuag010

Pan, Y., Wang, P., Yue, C., & Liu, C. (2025). Effect of nine different exercise interventions on insulin sensitivity in diabetic patients: a systematic review and mesh meta-analysis. Frontiers in Endocrinology, 16, 1409474. doi: https://doi.org/10.3389/fendo.2025.1409474

Probosari, E., Subagio, H. W., Rachmawati, B., Muis, S. F., Tjandra, K. C., Adiningsih, D., & Winarni, T. I. (2025). The Impact of Vitamin D Supplementation on Fasting Plasma Glucose, Insulin Sensitivity, and Inflammation in Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Nutrients, 17(15), 2489.

Wang, J., Fan, S., & Wang, J. (2025). Resistance training enhances metabolic and muscular health and reduces systemic inflammation in middle-aged and older adults with type 2 diabetes: a meta-analysis. Diabetes research and clinical practice, 112941. doi: https://doi.org/10.1016/j.diabres.2025.112941

Zhang, X., Wang, H., Gao, X., & Zhao, Y. (2025). Effects of oral vitamin D supplementation on vitamin D levels and glycemic parameters in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. Biomedical and environmental sciences, 38(6), 716-726. doi: https://doi.org/10.3967/bes2025.066