Effectiveness of combined exercise in people with type 2 diabetes and concurrent overweight/obesity: a systematic review and meta-analysis

Xiaoyan Zhao, Qiyanu He, Yongmei Zeng, Li Cheng

ABSTRACT

Objective To synthesise the available scientific evidence on the effects of combined exercise on glycaemic control, weight loss, insulin sensitivity, blood pressure and serum lipids among patients with type 2 diabetes (T2D) and concurrent overweight/obesity.

Design and sample PubMed, EMBASE, Web of Science, the Cochrane library, WANFANG, CNKI, SinoMed, OpenGrey and ClinicalTrials.gov were searched from inception through April 2020 to identify randomised controlled trials (RCTs) that reported the effects of combined exercise in individuals with T2D and concurrent overweight/obesity.

Methods Quality assessment was performed using the Cochrane Collaboration’s risk of bias tool. The mean difference (MD) with its corresponding 95% CI was used to estimate the effect size. Meta-analysis was performed using Review Manager V.5.3.

Results A total of 10 RCTs with 978 participants were included in the meta-analysis. Pooled results demonstrated that combined exercise significantly reduced haemoglobin A1c (MD=−0.16%, 95% CI: −0.28 to −0.05, p=0.006); body mass index (MD=−0.98 kg/m², 95% CI: −1.41 to −0.56, p<0.001); homeostasis model assessment of insulin resistance (MD=−1.19, 95% CI: −1.93 to −0.46, p=0.001); serum insulin (MD=−2.18 μIU/mL, 95% CI: −2.99 to −1.37, p<0.001) and diastolic blood pressure (MD=−3.24 mm Hg, 95% CI: −5.32 to −1.16, p=0.002).

Conclusions Combined exercise exerted significant effects in improving glycaemic control, influencing weight loss and enhancing insulin sensitivity among patients with T2D and concurrent overweight/obesity.

INTRODUCTION

The number of patients with diabetes is increasing globally, with an estimated 463 million adults diagnosed with diabetes. This number is predicted to exceed 700 million by 2045.1 Type 2 diabetes (T2D), characterised by hyperglycaemia resulting from hyposecretion of insulin and/or insulin resistance, accounts for nearly 90% of all types of diabetes.1 Propelling the surge of diabetes is the increasing prevalence of overweight and obesity. Data from the WHO2 show that nearly 2 billion adults are overweight and more than half a billion worldwide are obese. Furthermore, obesity accounts for 50.9%–98.6% of adults with T2D in Europe and 56.1% in Asia.3 Overweight and obesity contribute to the development of cardiovascular disease, cancer, T2D, hypertension, dyslipidaemia and mental health disorders. The coexistence of excess body weight and diabetes further aggravates the quality of life of individuals and imposes a tremendous burden on the healthcare system. Although various exercise options are available for individuals with either T2D or excess weight, individuals with T2D and concurrent overweight/obesity receive little attention. Measures to support individuals to optimise glycaemic control and weight management remain elusive.

Physical activity (defined as all body movement that increases energy use) and exercise (defined as a structured form of physical activity)4 have been recommended as the key components of lifestyle management for patients with T2D and concurrent overweight/obesity. Combined exercise involves aerobic exercise (repeated and continuous movement of large muscle groups when oxygen supply is sufficient) and resistance exercise (a strength-training workout that uses some form of resistance or tension).
performed within the same or separate exercise sessions of a training programme. Compelling evidence shows that aerobic exercise has an active effect on receptor affinity (adipose tissue, skeletal muscle and insulin receptors), thereby inducing insulin sensitivity and glucose homeostasis. Resistance exercise can enhance muscle strength, insulin sensitivity and muscle rehabilitation. Current national and international guidelines recommend that people with diabetes should perform combined exercise, integrating both aerobic (at least 150 min per week of moderate-vigorous aerobic activities) and resistance exercise (two sessions per week at least 60 min). However, in reality, the adoption rate of combined exercise is quite low, and the combined modes have the potential to become excessively burdensome. Moreover, it remains unclear whether the combined exercise modes can exert benefits on glycaemic control and body weight among individuals with T2D and concurrent overweight/obesity. Therefore, the aim of this systematic review and meta-analysis is to synthesise the best available evidence and explore the effectiveness of combined exercise on glycaemic control, weight loss, insulin sensitivity, blood pressure (BP) and serum lipids among patients with T2D and concurrent overweight/obesity.

MATERIALS AND METHODS
This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Inclusion and exclusion criteria: Eligibility was defined according to the PICO (patient, intervention, comparison, outcome) framework. Type of participants: (1) T2D patients aged ≥18 years; (2) overweight or obesity indicated by body mass index (BMI) (BMI≥25 kg/m² for Caucasians or BMI≥23 kg/m² for Asian subjects). Type of intervention and comparison: (1) Included an intervention group performing the combined form of exercise, which included both aerobic (e.g., jogging, running, cycling, brisk walking) and resistance (e.g., push-ups, abdominal crunch, chest press, leg press, squats, knee extensions) exercise with predefined intensity, frequency and duration; (2) exercise intervention time ≥3 weeks; and (3) potential comparison groups included any format of exercise intervention, general health counselling or usual care.

Outcomes: Primary outcomes included haemoglobin Alc (Hba1c) and BMI at the data collection timepoint. Secondary outcomes included serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) or psycho-behavioural outcomes such as exercise performance, muscle strength or performance, exercise adherence, exercise self-efficacy, emotional well-being, anxiety, depression and objective measures (e.g., pedometers or accelerometers).

Type of studies: RCTs.

Exclusion criteria: Studies were excluded if (1) participants were diagnosed with type 1 diabetes or gestational diabetes; (2) participants suffered from severe complications that impeded exercise engagement, such as acute infection, diabetic foot, diabetes ketoacidosis, severe hepatorenal insufficiency, diabetic retinopathy or obstacles to limb movement; (3) vague description of exercise intervention in terms of time and type and (4) full texts were not available.

Search strategy and literature selection: The literature retrieval was performed in PubMed, Embase, Web of Science, the Cochrane library, WANFANG, CNKI and SinoMed from inception through April 2020 for published studies; OpenGrey and ClinicalTrials.gov were also searched for unpublished studies. The reference lists of eligible publications were also retrieved to identify additional eligible studies. Keywords with the combination of medical subject heading terms were used in the search strategy: aerobic, exercise, training, isometric exercise, physical activity, physical exercise, resistance, strength training, strength exercise, weight lifting, weight bearing, combined exercise, diabetes, DM, T2D, NIDDM, overweight, obese, obesity, BMI, body weight and adiposity (online supplemental file). After removing duplicate records, two reviewers independently selected potential articles by assessing titles and abstracts. Then, full texts were further screened to identify study eligibility; at this stage, the two reviewers checked whether the participants were human subjects with T2D and concurrent overweight/obesity instead of animal model studies or people without T2D and concurrent overweight/obesity, and they eliminated articles that had no desired results shown in the inclusion criteria. Any disagreements or discrepancies regarding the selection of potential studies were resolved through discussion, and a third reviewer was consulted in case of any disagreement.

Data extraction: Two reviewers independently extracted details of the included studies using a structured data extraction form, including the study design, sample size, exercise intervention details, data collection time points, participant characteristics and outcomes (table 1). Any disagreements or discrepancies regarding data extraction were resolved through discussion, and a third reviewer was consulted in case of any disagreement.
## Table 1 Characteristics of the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Sample size (EX/CON)</th>
<th>Exercise format</th>
<th>Intervention type</th>
<th>Combined exercise intervention</th>
<th>Time points of data collection (week)</th>
<th>Participant characteristics</th>
<th>Dropout rate (%)</th>
<th>Outcomes</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amini Lari et al 2017</td>
<td>2017</td>
<td>Iran</td>
<td>30</td>
<td>Centre-based and group-based: each exercise session consisted of three phases: warm up, the main stage, and a cool-down period</td>
<td>AE: cycle ergometer RE: leg extension, prone leg curl, abdominal crunch</td>
<td>AE: 50%–55% of HR&lt;sub&gt;max&lt;/sub&gt; RE: 50%–55% 1RM</td>
<td>40–70 12</td>
<td>NR</td>
<td>0.12</td>
<td>EX 29.2±2.6 CON 29.2±2.8</td>
<td>= 2</td>
</tr>
<tr>
<td>Balducci et al 2010a</td>
<td>2010</td>
<td>Italy</td>
<td>606</td>
<td>Centre-based and group-based: in metabolic fitness centre</td>
<td>AE: treadmill, step, elliptical, cycle ergometer RE: four resistance exercises (eg, chest press, lateral pull down, leg press, trunk flexion for the abdomen) and three stretching position standard care</td>
<td>AE: 50%–60% VO&lt;sub&gt;2max&lt;/sub&gt; RE: 80% 1RM</td>
<td>75 49</td>
<td>Standard care counseling and diet management</td>
<td>0.48</td>
<td>EX 58.8±8.6 CON 59.8±8.5</td>
<td>0 (3–10)</td>
</tr>
<tr>
<td>Balducci et al 2010b</td>
<td>2010</td>
<td>Italy</td>
<td>42</td>
<td>Centre-based and group-based: NR</td>
<td>AE: treadmill, cycle ergometer RE: bilateral leg press, lateral pull down, knee press, trunk flexion for the abdomen and the stretching position</td>
<td>AE: 70%–80% VO&lt;sub&gt;2max&lt;/sub&gt; RE: 80% 1RM</td>
<td>60 48</td>
<td>Dietary prescriptions</td>
<td>4.8</td>
<td>EX 60.6±9.3 CON 61.1±7.1</td>
<td>0.12 20.0</td>
</tr>
<tr>
<td>Banitalebi et al 2019</td>
<td>2019</td>
<td>Iran</td>
<td>35</td>
<td>Centre-based and group-based: in a hospital gym</td>
<td>AE: treadmill, cycle ergometer RE: bilateral leg press, lateral pull down, knee press, trunk flexion for the abdomen and the stretching position</td>
<td>AE: 60%–70% of HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>50 10</td>
<td>Usual medical care and diabetes recommendations for self-management</td>
<td>0.78</td>
<td>EX 56.4±3.4 CON 57.8±3.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Bjorgaas et al 2005</td>
<td>2005</td>
<td>Norway</td>
<td>29</td>
<td>Centre-based and group-based: each exercise session consisted of three phases: warm up, the main stage, a cool-down, and a stretching period</td>
<td>AE: light jogging, core conditioning exercises, low-resistance stretching and strengthening exercises</td>
<td>AE: 50%–70% of HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>90 12</td>
<td>Diet information: primary gain, clinical nutrition</td>
<td>0.12</td>
<td>EX 57.9±2.8 CON 58.7±2.8</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Sample size (EX/CON)</th>
<th>Exercise format</th>
<th>Supervision/ facilitator</th>
<th>Exercise type</th>
<th>Intensity</th>
<th>Frequency (days/week)</th>
<th>Duration/session (min)</th>
<th>Intervention time (weeks)</th>
<th>Control</th>
<th>Time points of data collection (weeks)</th>
<th>Participant characteristics</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansen et al 2017</td>
<td>Zealand and Denmark</td>
<td>58 (6/52)</td>
<td>Group-based; the geographical location of the participants' home address</td>
<td>Yes/ physiotherapist and trainer</td>
<td>AE: power walking, cycling, jogging, uphill or on stairs; RE: aerobics; FGP: posture or chair (right), seat; back and shoulders standard care; same as control group</td>
<td>AE: 60%–90% HRmax; RE: 10–12 RM</td>
<td>5–6</td>
<td>30–60</td>
<td>48</td>
<td>Standard care; medical counselling, education in type 2 diabetes and lifestyle advice by the study nurse at baseline and every 3 months for 12 months</td>
<td>0, 48</td>
<td>EX: 52.6±8.1; CON: 56.6±8.1</td>
<td>31.4±4.9; CON: 32.5±5.0</td>
</tr>
<tr>
<td>Leehey et al 2016</td>
<td>USA</td>
<td>36 (18/18)</td>
<td>12 weeks of centre-based exercise followed by 40 weeks of home-based exercise</td>
<td>Yes/trainer</td>
<td>AE: treadmill, elliptical trainer and cycle ergometer; RE: using elastic bands, hand-held weights or weight machine; Diet management: same as control group</td>
<td>AE: interval RE: progressive</td>
<td>Centre-based: 3-6 Home-based exercise: 3-6</td>
<td>52</td>
<td>Diet management: nutritional counseling; session at baseline with 9 follow-up telephone calls</td>
<td>0.12, 2</td>
<td>EX: 65.4±8.7; CON: 66.6±7.5</td>
<td>36.4±4.8</td>
<td>37.4±4.2</td>
</tr>
<tr>
<td>Lucotti et al 2011</td>
<td>Italy</td>
<td>50 (30/20)</td>
<td>Centre-based and group-based: in a hospital</td>
<td>Yes/physician</td>
<td>AE: row ergometer and bicycle ergometer; RE: arm curls, military press, push-ups, upright rowing, back extensions, squats, lunges, heel raises and bent knee sit-ups; Diet management: same as control group</td>
<td>AE: 70% HRmax; RE: 40%–50% of 1 RM</td>
<td>5</td>
<td>3</td>
<td>45</td>
<td>AE plus diet; management: 30%–50% HRmax 5 days per week, 30 min/session; Diet management: hypocaloric diet, administered under daily supervision of a dietician</td>
<td>0.3</td>
<td>EX: 65.4±1.5; CON: 56.6±3.9</td>
<td>39.8±4.5</td>
</tr>
<tr>
<td>Otten et al 2017</td>
<td>Sweden</td>
<td>32 (19/13)</td>
<td>Centre-based: in a Sports Medicine unit</td>
<td>Yes/therapist</td>
<td>AE: cross-trainer; cycle ergometer; cycle ergometer; RE: leg presses, leg curls, hip raises, seated rows; dumbbell rows, d-dip der, lunge, back extensions, burpees, sprints and wall ball shots; Palaeolithic diet: same as control group</td>
<td>AE: 40%–100% HRmax; RE: 70%</td>
<td>3</td>
<td>60</td>
<td>12</td>
<td>Palaeolithic diet, education about the diet and education about lifestyle advice by a trained dietitian at baseline and once a month</td>
<td>0.12</td>
<td>EX: 31.7; CON: 31.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>
Quality assessment
The risk of bias of included studies was assessed using the Cochrane Collaboration’s Risk of Bias assessment tool. The quality of studies was judged to have low, unclear, or high risk of bias.

Data analysis
All analyses were performed using RevMan V.5.3 (Cochrane Collaboration, http://ims.cochrane.org/revman). Heterogeneity was assessed using Cochran’s Q test and the I²-test. A random-effects model was applied to calculate the pooled results if I² ≥50%; otherwise, a fixed-effects model was used. Subgroup analysis on primary outcomes stratified by exercise frequency was conducted. The mean difference (MD) with its corresponding 95% CI was used to calculate the effect size. A two-sided p<0.05 was considered to indicate statistical significance.

Patient and public involvement
No patient involved.

RESULTS

Search outcome
A total of 10,580 records were identified. After duplicate deletion, 8,383 articles were screened for titles and abstracts, and 50 articles were further screened for full text. Finally, 10 studies were deemed eligible and included in this meta-analysis (figure 1).

An overview of the characteristics of included studies is summarised in table 1. Across the included studies, the sample size ranged from 20 to 606; the intervention duration ranged from 3 to 52 weeks; the mean (SD) age of participants was similar across the included studies (range: 53.6 (9.1)–66.6...
Quality of the included studies

Figure 2 shows the quality assessment of the included studies: six studies were judged to have a low risk of bias, while the remaining four studies showed uncertain risk of bias. The following were main sources of bias: lack of blinding of participants and personnel, absence of random sequence generation and allocation concealment and incomplete outcome data. In summary, the quality of the included studies was considered as having moderate risk of bias.

Pooled results

Glycemic control (HbA1c)

Nine studies provided data about the effect of combined exercise on HbA1c. The pooled results showed the combined intervention significantly reduced the HbA1c level of patients, favouring the intervention group, as compared with the control group (MD=−0.16%, 95% CI: −0.28 to −0.05, p=0.006) (figure 3).

Weight loss (BMI)

Eight studies reported changes in BMI. The pooled results showed that combined exercise significantly reduced BMI in the intervention group as opposed to the control group (MD=−0.98 kg/m², 95% CI: −1.41 to −0.56, p<0.001) (figure 3).

Insulin sensitivity (HOMA-IR, serum insulin)

Four of the 10 studies examined the effectiveness of combined exercise on the HOMA-IR index. The pooled result revealed a significant reduction in the HOMA-IR index favouring the intervention group (MD=−1.19, 95% CI: −1.93 to −0.46, p=0.001) (figure 4).

Figure 2  Quality assessment of the included studies. (A) As percentages across all included studies in risk of bias graph; (B) bias risk of the included studies. ‘+’ indicates Low risk of bias; ‘?’ represents unclear risk of bias; ‘−’ indicates high risk of bias.
Six studies examined serum insulin. The difference in mean of serum insulin significantly favoured the intervention group (MD=−2.18 μIU/mL, 95% CI: −2.99 to −1.37, p<0.001) (figure 4).

Blood pressure (SBP and DBP)
Eight of the 10 studies measured SBP and seven studies measured DBP. The pooled results showed no difference in SBP between the intervention and control groups (MD=−2.33 mm Hg, 95% CI: −6.01 to 1.35, p=0.21), whereas there was a significant reduction in DBP favouring the intervention group (MD=−3.24 mm Hg, 95% CI: −5.32 to −1.16, p=0.002) (figure 5).

Serum lipids (TG, TC, HDL-C and LDL-C)
Seven studies measured the effectiveness of combined exercise on lipid profiles. The pooled results demonstrated that combined exercise had no significant effect on TG, TC, HDL-C and LDL-C levels (TG: MD=−7.57 mg/dL, 95% CI: −16.42 to 1.28, p=0.09; TC: MD=−8.29 mg/dL, 95% CI: −22.18 to 5.60, p=0.24; HDL-C: MD=−0.72 to 6.10, p=0.12; LDL-C: MD=0.14 mg/dL, 95% CI: −19.87 to 20.14, p=0.99) (figure 6).

Subgroup analysis (exercise frequency)
The results showed that combined exercise with frequency<3 days/week significantly lowered the HbA1c.
Zhao X, et al. BMJ Open 2021; 0:e046252. doi:10.1136/bmjopen-2020-046252

DISCUSSION

The results from this meta-analysis showed that combined exercise was associated with a significant decline in HbA1c, BMI, HOMA-IR index, serum insulin and DBP, indicating the important role of combined exercise in improving glycaemic control and weight control and enhancing insulin sensitivity among patients with T2D and concurrent overweight/obesity. However, the results showed that combined exercise had no effect on serum lipids.

Our results showed that combined exercise had a significant effect on HbA1c among adults with T2D and concurrent overweight/obesity. It is important to mention that a 1% absolute reduction in HbA1c is associated with a 21% reduction in the risk of any end point or death related to diabetes.24 Previous meta-analyses of exercise in diabetic patients with or without overweight/obesity have found a positive effect on glycaemic control. Hou25 assessed the effect of combined exercise compared with aerobic exercise among patients with T2D. Their results showed a significant reduction of HbA1c by 0.31%, which was comparable with our finding that combined exercise decreased HbA1c by 0.16%. The meta-analysis by Zou26 identified 13 eligible studies investigating the effect of exercise on patients with T2D and obesity, and the result showed that exercise had no effect on HbA1c in the 3 months intervention subgroup, whereas exercise

Figure 6 Comparison of triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) between intervention group and control group in patients with T2D and concurrent overweight/obesity. (A) Forest plot of TG; (B) forest plot of TC; (C) forest plot of HDL-C; (D) forest plot of LDL-C. Units of TG, TC, HDL-C and LDL-C are ‘mg/dL’.

(MD=−0.31%, 95% CI: −0.50 to −0.13, p<0.001) and BMI (MD=−1.03 kg/m², 95% CI: −1.49 to −0.57, p<0.001), while combined exercise with frequency≥3 days/week had no effect on HbA1c (MD=−0.3%, 95% CI: −0.65 to −0.05, p=0.021) and BMI (MD=0.18 kg/m², 95% CI: −1.34 to 1.71, p=0.81) (table 2).
significantly reduced HbA1c by 0.25%, 0.93% and 0.26% when intervention duration were 4 months, 6 months and 12 months, respectively. This may indicate the effect of exercise in patients with T2D and obesity tends to be steady and persistent. The pooled effect of combined exercise in patients with T2D and concurrent overweight/obesity, however, seems to be much lower than that reported in the first adequately powered randomised controlled trial (RCT)\(^{27}\) that examined the effects of aerobic, resistance and combined exercise in people with T2D. Sigal and colleagues\(^ {27}\) found a pronounced reduction (0.9%) in HbA1c with combined exercise. Such discrepancy might be attributed to the long exercise duration (210–270 min/week) of the combined exercise programme, in which participants performed intensive aerobic training programme (75–135 min/week) as well as resistance training programme (135 min/week).\(^ {28}\)

Our results showed that combined exercise exerted a significant effect on insulin sensitivity on patients with T2D and concurrent overweight/obesity, which was in line with the results of Thaane,\(^ {29}\) wherein exercise appeared to improve insulin sensitivity among adults with T2D and concurrent overweight/obesity. Way\(^ {30}\) also found that regular exercise had a significant benefit in insulin sensitivity in adults with T2D. They concluded this by synthesising the outcomes of clamps, insulin infusion sensitivity tests, insulin tolerance test and oral glucose tolerance test. The results of Way\(^ {30}\) indicated that the durability of training-induced improvement in insulin sensitivity could persist beyond 72 hours after the last exercise session. However, potential heterogeneity was introduced by diverse measurement techniques for insulin sensitivity.

It is generally more difficult for patients with diabetes to lose weight and/or maintain weight loss than non-diabetic individuals. Our results showed that combined exercise achieved a statistically and clinically significant decrease in BMI among adults with T2D and concurrent overweight/obesity. Previous reviews also showed the effect of combined exercise on weight loss by using other obesity indicators. The review by Hou\(^ {25}\) showed that combined exercise significantly reduced subcutaneous and visceral adipose tissue, and the results of Pan\(^ {31}\) showed that combined exercise safely accentuated reduction in body weight. Whereas the results of Thaane\(^ {29}\) suggested that short-term exercise training exerted no significant effect on body weight, BMI and body fat.

Cardiovascular disease was one of the leading reasons for frequent medical consultation and rehospitalisation for adults with T2D and concurrent overweight/obesity.\(^ {32}\) BP and serum lipids are vital risk factors for cardiovascular disease, and the importance of managing and maintaining BP and cholesterol levels has been emphasised by the American Diabetic Association (ADA) guideline.\(^ {33}\) Evidence has shown the benefits of simultaneous control of HbA1c, BP and lipid levels. Our study found that combined exercise had no effect on SBP and serum lipids, which was contradictory to the findings of Albalawi\(^ {34}\) and Bersaoui,\(^ {35}\) who reported that combined exercise was significantly reduced HbA1c by 0.25%, 0.93% and 0.26%

<table>
<thead>
<tr>
<th>Subgroup analysis on primary outcomes</th>
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<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>Included study (n)</td>
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<tr>
<td>Sample size (EX)</td>
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<tr>
<td>Sample size (CON)</td>
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<tr>
<td>Mean difference (95% CI)</td>
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<tr>
<td>P value I²</td>
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<tr>
<td><strong>HbA1c</strong></td>
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<td>Included study (n)</td>
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<tr>
<td>Sample size (EX)</td>
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<tr>
<td>Sample size (CON)</td>
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<tr>
<td>Mean difference (95% CI)</td>
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<td>P value I²</td>
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**Table 2**

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Exercise frequency (days/week)</th>
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<tbody>
<tr>
<td>≤3</td>
<td>EX: 3 321 306 −0.31 (−0.50 to 0.13) &lt;0.001 0% 2 310 295 0.03 (−0.45 to 0.51) 0.90 0% 4</td>
</tr>
<tr>
<td>≥3</td>
<td>EX: &lt;3 310 57 −1.03 (−1.49 to −0.57) &lt;0.001 0% 2 310 295 −0.18 (−1.34 to 1.71) 0.81 0% 4</td>
</tr>
</tbody>
</table>

EX, exercise group; CON, control group; I², I-squared.
related to a statistically significant decline in BP and lipid control among patients with T2D. The possible reason for the discrepancy may be related to the differences of participants’ characteristics. In the current meta-analysis, participants had T2D and were overweight or obese. Low-grade metabolic inflammation in this group of people can induce changes in the neural mechanisms (eg, hypothalamic–pituitary–adrenal axis), which in turn damage the cognitive function of individuals. Cognitive impairments further attenuate individuals’ motivation and ability to engage in self-management activities and maintain therapeutic lifestyles.66–69 Hence, combined exercise may have limited effect on BP and lipid control in people with T2D and concurrent overweight/obesity. More strategies need to be explored to help patients with T2D and concurrent overweight/obesity to simultaneously manage HbA1c, BP and cholesterol levels.

Exercise frequency is a pivotal determinant which moderates the effect of combined exercise on glycaemic control in patients with T2D and concurrent overweight/obesity.40 41 Our study showed that combined exercise had significant effects on HbA1c and BMI only in subgroup with exercise frequency less than 3 days/week. We would attribute such results to inherent differences between studies with exercise frequency <3 days/week and ≥3 days/week. Specifically, subjects in the studies with exercise frequency more than 3 days/week tended to perform short-duration exercise (3 weeks, 12 weeks), which was likely not enough to make a difference in outcomes. While subjects in the study with exercise frequency less than 3 days/week had been offered with long-term (48 weeks) exercise under supervision. Long-term exercise sessions and professional supervision were identified as important factors associated with prominent improvement of glycaemic and weight control.26 31 Additionally, Balducci even implemented diet management in addition to physical activity counselling. Thus, the results of subgroup analysis should be interpreted with caution.

**Direction for future research and practice**

Considering the benefits of combined exercise, it might be helpful to recommend combined exercise for patients with T2D and concurrent overweight/obesity to improve glycaemic and weight control and decrease insulin resistance. Physical activity counselling, psycho-educational interventions, mobile technologies and peer support groups could be integrated into the exercise to improve the adoption rate of combined exercise.42 Although there are ADA, American College of Sports Medicine and International Diabetes Federation exercise recommendations for diabetic patients,8 9 43 there is little evidence to indicate the ideal exercise duration, exercise intensity and exercise time that would be most appropriate for patients with T2D and concurrent overweight/obesity. Optimal exercise frequency and duration that would be beneficial for patients with T2D and concurrent overweight/obesity requires further investigation. According to the features of effective exercise interventions among the included studies, most research studies performed centre-based exercise with supervision. Hence, we recommend this kind of intervention in future studies to achieve greater metabolic effects.

**Limitations**

Our study has some limitations. First, the intervention components of combined exercise in terms of intervention frequency, intensity, duration and time were inconsistent among the included studies and there was substantial heterogeneity among the trials in the meta-analysis. The results, therefore, should be interpreted with caution. Second, only 10 studies met the inclusion criteria and were eligible for the meta-analysis. Some well-conducted and important RCTs were excluded because of not focusing on combined exercise or targeting patients with T2D and concurrent overweight/obesity.27 44 45 Third, the effectiveness of combined exercise observed in this meta-analysis should be interpreted with caution as the majority of the participants (~62%) included in this analysis were from a single study called the ‘Italian diabetes and exercise study’ with significant positive findings.14 Additionally, the patients in our study were mainly middle-aged and elderly subjects; hence, the effect of combined exercise on young subjects with T2D and concurrent overweight/obesity remains unclear. Finally, the T2D duration varied from 0.1 to 17 years or more and which subgroup of patients could benefit more from the combined exercise remains unclear.

**CONCLUSIONS**

This systematic review provides useful information for the clinical application of the combined exercise in the management of patients with T2D and concurrent overweight/obesity. The results show clear evidence that combined exercise intervention has positive effects on improving glycaemic and weight control, and enhancing insulin sensitivity among patients with T2D and concurrent overweight/obesity. More RCTs with robust methodological design, and more comprehensive body composition measurements are needed to elaborate the intervention effects and mechanisms. This review also highlights the need for further studies to investigate the ideal duration, intensity and time of combined exercise for patients with T2D and concurrent overweight/obesity.

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