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Original Article

Benefit effects of aerobic exercise and resistance training on the management of type 2 diabetes

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Abstract: To examine the effects of combined exercise (aerobic exercise and resistance training) on the management of type 2 diabetes. Articles published in English and Chinese based on a search of MEDLINE, Excerpta Medica Database (EMBASE) and China National Knowledge Infrastructure (CNKI) databases were the source for this meta-analysis. A significant difference in maximal oxygen consumption [VO_{2max}] was demonstrated between the combined exercise and non-exercise groups (Weighted mean difference: WMD = 2.66 ml/[kg/min], 95% CI = 1.80~3.51, P < 0.05). Combined exercise reduced the HbA1c concentration (WMD = -0.40%, 95% CI = -0.54~-0.26, P < 0.05), BMI (WMD = -1.09 kg/m^2, 95% CI = -1.70~-0.49, P < 0.05), decreased the waist circumstance (WMD = -3.48 cm, 95% CI = -5.28~-1.6, P < 0.05), reduced the amount of abdominal subcutaneous fat (WMD = -104.14 cm^2, 95% CI = -136.02~-72.27, P < 0.05), and reduced the amount of abdominal visceral fat (WMD = -32.26 cm^2, 95% CI = -56.87~-7.66, P < 0.05). In addition, combined exercise reduced the SBP (WMD = -5.47 mmHg, 95% CI = -7.74~-3.20, P < 0.05), and DBP (WMD = 2.75 mg/dl, 95% CI = -4.10~-1.41, P < 0.05) and TG (WMD = -12.61 mg/dl, 95% CI = -24.00~-1.21, P < 0.05), and increased the HDL-C (2.91 mg/dl, 95% CI: 1.22-4.61, P < 0.05). Combined exercise is recommended in the management of type 2 diabetes patients.

Keywords: Combined exercise, aerobic exercise, resistance exercise, type 2 diabetes

Introduction

Type 2 diabetes is a metabolic disorder which is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [1-3]. In 2010, it was estimated that there were 285 million diabetics worldwide and 80% live in less developed areas. Physical activity, combined with diet and medication, are recommended treatments for type 2 diabetes by the World Health Organization. Aerobic and resistance exercises have been confirmed to be effective physical activities on improving glycemic control for type 2 diabetes patients [4-7]. Aerobic exercise is physical exercise that involves large muscle groups to improve cardiovascular endurance. Resistance exercise is physical exercise that causes the muscles to contract against an external resistance, the purpose of which is to increase muscle strength and muscle mass [8].

A recent study indicated that combined aerobic and resistance exercise could maximize the impact on the management of type 2 diabetes patients with characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [5, 7]; however, the effects or effective dose (i.e., intensity, duration, and frequency) of combined aerobic and resistance exercise have been inconsistent. Thus, we performed a meta-analysis to determine the effects and effective dose of combined aerobic and resistance exercise on the management of type 2 diabetes patients based on current exercise regimen evidence.

Materials and methods

Search strategy

Articles published in English and Chinese based on a search MEDLINE, EMBASE and China

National Knowledge Infrastructure (CNKI) databases were the source for this meta-analysis. The search strategy for English databases used the following keywords: "combined exercise"; "aerobic exercise"; "resistance exercise"; "aerobic and resistance exercise"; "physical activity"; or "physical exercise"; and "type 2 diabetes". The search strategy for Chinese databases used the following keywords: "aerobic and resistance exercise" and "type 2 diabetes".

In addition, the references of the included studies and review articles which were not captured by our database searches were also reviewed for further relevant studies.

Eligibility criteria

The inclusion criteria were as follows: (1) all randomized controlled trials (RCTs) comparing combined aerobic and resistance exercise with aerobic/resistance/non-exercise control groups in type 2 diabetes patients with characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency; (2) trials $\geq$ 12 weeks were included because an exercise period < 12 weeks would be too short to show an alteration in the glycated hemoglobin (HbA1c) concentration or body mass index (BMI); and (3) the diagnostic criteria for type 2 diabetes was described in the study. The acceptable diagnostic criteria included the criteria described by the World Health Organization (WHO 1999; WHO 2006) or the American Diabetes Association standards (ADA 1997; ADA 2003; ADA 2010). To be consistent with the changes over the years, the related standards were based on the publication year of the study or the author cited in the study.

The exclusion criteria were as follows: (1) studies with a single bout exercise interventions; (2) studies with a combined aerobic and resistance exercise intervention group only; (3) studies with mere recommendations as interventions, without further details; (4) studies in which the combined aerobic and resistance exercise was not either directly supervised or well-documented; and (5) studies in which there was a co-intervention in the experimental group, such as a dietary alteration that was not applied to the control group.

Variables coded from each study

The value of HbA1c, which represents the average plasma glucose concentration over prolonged periods of time, before and after long-term exercise was collected to reflect the effect of combined aerobic and resistance exercise on glycemic control [9]. Moreover, because some studies showed that physical activity can help to decrease fat mass or increase muscle mass in type 2 diabetes patients, body mass indices were also collected. Furthermore, because many type 2 diabetes patients always have abnormal blood lipid profiles or blood pressure, the related values before and after exercise were collected. Adverse events were collected from any related study reports. The detailed items are shown below: (1) primary findings included the HbA1c concentration, body mass indices (BMI, body mass, fat mass, abdominal subcutaneous fat, abdominal visceral fat, waist circumstance, and mid-thigh muscle cross-sectional area), and adverse events (injures and hypoglycaemic reactions; and (2) secondary findings included blood lipids (triglycerides [TG], total cholesterol [TC], high-density lipoprotein-cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], blood pressure (systolic blood pressure SBP] and diastolic blood pressure [DBP]); and fitness (maximal oxygen consumption [VO_{2max}]).

Data collection

The following information was independently extracted by two investigators from all studies: first author; year of publication; trial characteristics (trial design and randomization); participants (total number in intervention/control groups, gender, age, diagnostic criteria, and dropouts); exercise interventions (type, intensity, frequency, and duration), and outcomes.

Statistical analysis

Pooled measures were calculated on the weighted mean difference (WMD) with 95% confidence intervals (CIs) of each outcome of interest (i.e., HbA1c, muscle mass, and fat mass) to assess the effect of combined exercise on the management of type 2 diabetes. Forest plots were used to show the outcomes of this meta-analysis.

All data were initially analyzed with a fixed effect model. Heterogeneity among studies was assessed using the I^2 of Higgins and Thompson. The I^2 parameter was used to quantify any inconsistencies [10]. If substantial heterogeneity was present (I^2 > 40%), the DerSimonian and Laird random effect model (REM)

Table 1. Characteristics of included randomized controlled combined aerobic and resistance exercise intervention trials

Study	Sample Size	Study Design	Study Length	Exercise Prescription (frequency and duration of period)	Primary Findings	Secondary Findings
Stefano et al, 2010	563 T2D Men	Com vs. Control	2 times/week	150 min/wk, moderate intensity	↓HbA1c	↓SBP, ↓DBP, ↑H-DLC, ↓L-DLC
	275 Com, 288 Con		12 months	AE: From 4 to 10 MET-h/week	↓BMI	↓TC, ↑UBS, ↑LBS, ↓Fasting Blood
				RT: 3 MET-h/week		Glucose, ↑VO_{2max}, ↓Waist Circumstance
Timothy et al, 2010	262 T2D Men	Com vs. Control	150 min/week	Com: AE: 50-80% of VO_{2max}, 10 kcal/kg/week	↓HbA1c	↑ VO_{2max}, ↓Body Mass, ↓Fat Mass
	76 Com, 72 AE		9 months	RT: 9 exercise, 4 S/MG/W, 10-12 RM		↓Waist Circumstance
	73 RT, 41 Con			AE: 50-80% of VO_{2max}, 12 kcal/kg/week		
				RT: 9 exercises, 10-12 RM, 4-6 S/MG/W		
Darcye et al, 2003	28 Post-Menopausal	Com vs. Control	3 times/week	Com: AE: 60-75% of HRmax	↓HbA1c	↑VO_{2max}, ↓Total Abdominal Fat
	Women with T2D		16 weeks	RT: 5 exercises, 6 S/MG/W, 12 RM	↓BMI	↑Mid-Thigh Skeletal Muscle
	10 Com, 9 AE			AE: AE in Com with Low-impact		
	9 Con			Low-intensity dynamic movement		
Antti et al, 2003	49 T2D Men	Com vs. Control	2 times/week	AE: 65-75% of the VO_{2max}	↓HbA1c	↑VO_{2max}, ↓SBP
	24 Com, 25 Con		12 months	RT: 8 exercise, 6 S/MG/W, 10-12 of 70-80% RM		
Ronald et al, (Publised through 6 studies) 2007	251 T2D Men	Com vs. Control	3 times/week	DARE trial	↓HbA1c	↓L-DLC, ↑H-DLC, ↓TG, ↓SBP, ↓DBP
	64 Com, 60 AE		22 weeks	AE: From 25 min/time at 70% of HRmax to 45	↓BMI	↑VO_{2max}, ↑UBS, ↑LBS, ↓Body Mass
	64 RT, 63 Con			Min/time at 75% of HRmax		↓Fat Mass, ↓Waist Circumstance
				RT: 7 exercises, 6-9 S/MG/W, 7-9 RM		↓Abdominal Subcutaneous Fat
						↑Mid-thigh Muscle Cross Sectional Area
						Health Status
Li SN, 2013	36 T2D	High intensity Com vs. Control	3 times/week	Com: before 2 wks, 20-30 min/times, 50-60% of HRmax	↓HbA1c	↓Fastingblood-glucose, ↑H-DLC
	12 High Com	Low intensity Com vs. Control	12 weeks	Com: after 2 wks, 50-60 min/times, 50-80% of HRmax	↓BMI	↓L-DLC, ↓Body Mass, ↓Fat Mass
	12 Low Com			High Com: AE: 30-50 min; RT: 70%-80% 1 RM; 8-12 times/movement		↓TG, ↓TC
	12 con			Low Com: AE: 30-50 min; RT: 45%-55% 1 RM; 18-22 times/movement		
				Com: AE: with yoga, aerobics movement; 4-30 min		
				Com: RT: 2 exercises: standing squats; shoulder press		

T2D = Type 2 Diabetes, Com = Combined Aerobic and Resistance Exercise, AE = Aerobic Exercise, RT = Resistance Exercise, HR = Heart Rate, HbA1c = Glycated Hemoglobin, BMI = Body Mass Index, VO_{2max} = Maximal Oxygen Uptake, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, H-DLC = High-Density Lipoprotein Cholesterol, L-DLC = Low-Density Lipoprotein Cholesterol, TC = Total Cholesterol, TG = Triglyceride, UBS = Upper Body Strength, LBS = Lower Body Strength, RPE = Rating of perceived exertion for the lower extremities, 9 exercise: *Upper body exercise*: bench press, seated row, shoulder press and pull down. *Leg Exercise*: leg press, extension and flexion. *Abdominal crunches* and *Back extensions*. 5 exercise: leg press, leg curl, hip extension, chest press and latissimus pull down. 7 exercise: [Group A] abdominal crunch, seated row, biceps curl, bench press, leg press, shoulder press, leg extension. [Group B] abdominal crunch, lateral pull-down, triceps push-down, chest press, leg press, upright row, leg curls.

Table 2. Comparison Outline for Combined exercise vs. Non-exercise

Outcome of measurement title	No. of studies	No. of participants	Statistical method	Effect size (Combined exercise groups vs. Non-exercise groups)
1. Glycated heamoglobin (%)	6	899	Mean Difference (95% CI)	-0.40 [-0.54, -0.26]
2. Body mass index (kg/m²)	4	682	Mean Difference (95% CI)	-1.09 [-1.70, -0.49]
3. Body mass (kg)	4	194	Mean Difference (95% CI)	-3.25 [-7.52, -1.03]
4. Fat mass (kg)	4	283	Mean Difference (95% CI)	-1.90 [-2.05, -1.76]
5. Waist circumstance (cm)	2	690	Mean Difference (95% CI)	-3.48 [-5.28, -1.68]
6. Abdominal subcutaneous fat (cm)	2	142	Mean Difference (95% CI)	-104.14 [-136.02,-72.27]
7. Abdominal visceral fat (cm)	2	142	Mean Difference (95% CI)	-32.26 [-56.87, 28.08]
8. Adverse events-shoulder pain	2	181	Odds Ratio (95% CI)	1.67 [0.63, 4.45]
9. Adverse events-shin splints	2	181	Odds Ratio (95% CI)	1.68 [0.44, 6.43]
10. Adverse events-low back pain	2	181	Odds Ratio (95% CI)	2.53 [0.58, 10.99]
11. Maximal oxygen consumption (ml/kg*min)	3	739	Mean Difference (95% CI)	2.66 [1.80, 3.51]
12. Triglycerides (mg/mL)	4	738	Mean Difference (95% CI)	-12.61 [-24.00, -1.21]
13. Low density lipoprotein cholesterol (mg/mL)	4	737	Mean Difference (95% CI)	16.27 [-9.58,42.11]
14. High density lipoprotein cholesterol (mg/mL)	4	738	Mean Difference (95% CI)	2.91 [1.22, 4.61]
15. Systolic blood pressure (mmHg)	3	739	Mean Difference (95% CI)	-5.47 [-7.74, -3.20]
16. Diastolic blood pressure(mmHg)	3	690	Mean Difference (95% CI)	-2.75 [-4.10, -1.59]
17. Upper body strength (kg)	2	817	Mean Difference (95% CI)	11.98 [9.27, 14.70]
18. Lower body strength (kg)	2	690	Mean Difference (95% CI)	38.26 [27.15, 49.37]

Table 3. Comparison Outline for Combined exercise vs. Aerobic exercise

Outcome of measurement title	No. of studies	No. of participants	Statistical method	Effect size (Combined exercise groups vs. Aerobic exercise groups)
1. Glycated heamoglobin (%)	2	129	Mean Difference (95% CI)	-0.13 [-0.36, 0.11]
2. Body mass (kg)	2	272	Mean Difference (95% CI)	-1.60 [-7.39, 4.19]
3. Upper body strength (kg)	1 (2 measurements)	248	Mean Difference (95% CI)	8.10 [-0.44, 16.63]

was adopted as the pooling method; otherwise, the inverse-variance fixed effect model (FEM) was adopted. Once the heterogeneity was found, the potential sources of heterogeneity with various subgroup and sensitivity analyses were determined.

Sub-group analysis: Sub-group analysis included age, gender (male or female), body mass (BMI < 25 kg/m^2 or > 25 kg/m^2), medication (receiving medication or not receiving medication), and exercise dose (intensity, frequency, and duration).

Sensitivity analysis: 'Leave one out' sensitivity analysis [5] was used to evaluate the key studies with substantial impact on between-study heterogeneity.

Furthermore, an evaluation form was used to assess the study quality according to the Cochrane Collaboration tool. All of the data was analyzed with Review Manager 5 software, which can be downloaded from the Cochrane Collaboration.

Results

Characteristics of studies

The initial search yielded 11470 studies from the 3 databases (Embase [n = 22], Pubmed [175] and CNKI [11273]). Based on the content of the abstract, 16 studies were selected for further examination. Among these studies, 6 met the inclusion criteria [8, 11-18] and 1 study reported the results through 6 studies [8, 14-16, 18, 19]. Ten studies were excluded; 2 studies had a duration of intervention < 16 weeks [20, 21], 5 studies had no control group [20-24], the participants in the control group of 1 study did not have type 2 diabetes [25]; 3 studies was not RCTs [26-28]; and 1 study did

Table 4. Comparison Outline for Combined exercise vs. Resistance exercise

Outcome of measurement title		No. of studies	No. of participants	Statistical method	Effect size (Combined exercise groups vs. Resistance exercise groups)
1.	Glycated heamoglobin (%)	2	236	Mean Difference (95% CI)	-0.25 [-0.45, -0.44]
2.	Body mass (kg)	2	277	Mean Difference (95% CI)	-1.28 [-7.08, 4.52]
3.	Upper body strength (kg)	1 (2 measurements)	256	Mean Difference (95% CI)	3.10 [-5.13, 11.32]

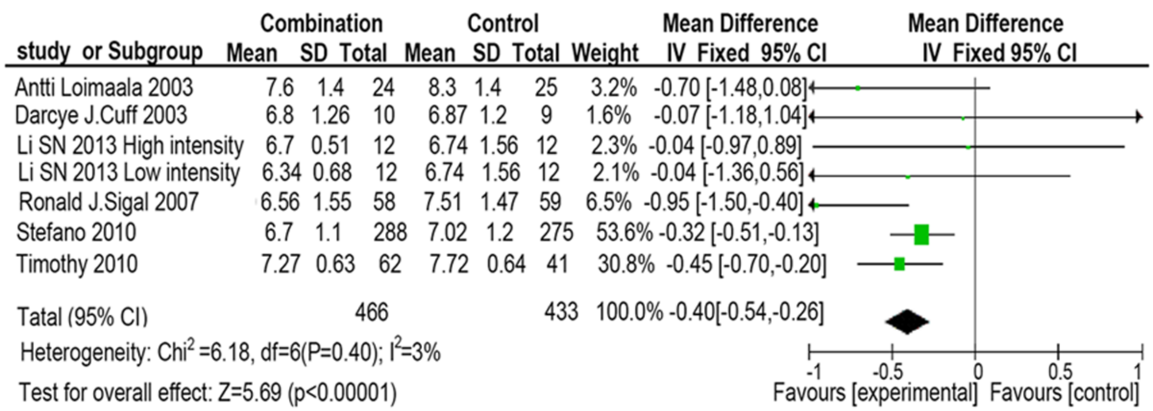

Figure 1. Combined exercise vs. Non -exercise, Glycated Heamoglobin (%).

not reveal the details of the exercise intervention [24] (**Table 1**).

Study types: All 6 of the included studies were RCTs. The studies were conducted in 5 different countries (Canada, Italy, the Netherlands, Finland and China) [11-13, 17, 18]. The types of exercise intervention were combined aerobic and resistance exercise in all of the studies, with a non-exercise group as the control group. Three studies also had aerobic exercise or resistance exercise alone as the control group [12, 13, 18].

Participants: The included studies involved 1189 participants, who were all diagnosed with type 2 diabetes. The number of participants in a single study ranged from 28 to 563. Four hundred seventy-three participants received the combined aerobic and resistance exercise intervention. The mean age of all the participants was approximately 50 years.

Interventions: The types of aerobic exercise interventions included aerobic, yoga, aerobic dancing, treadmill, recumbent steppers, elliptical cycle ergometer, stationary bicycles, rowing machines, step up, jogging, or walking. Resistance exercise included weight training targeting all body muscle groups. For the upper body, bench press, seated row, shoulder press, pull down, chest press, abdominal crunches, or back extensions were included. For the lower body, leg press, leg extension, leg extension, leg curls, or hip extension were included.

The duration of the exercise intervention was 12 weeks, 16 weeks, 22 weeks, 9 months, and 1 year [12, 13, 18]. For single exercise intervention, the duration of aerobic exercise varied from 30-75 min, and 4-9 exercises per session, and 2-3 sessions per time for resistance exercise.

Most exercise interventions involved 2-3 times per week, lasting 60-150 min.

The intensity of aerobic and resistance exercise was from moderate-to-high. For aerobic exercise, the intensity was 50%-80% of the VO_{2max} or 60%-75% of the maximum heart rate (HR_{max}). The resistance exercise involved 2-9 exercises per set targeting all muscle groups and 4-9 sets per week; each exercise was conducted with 7-22 maximal repetitions.

Quantitative synthesis

The comparison outlines for the meta-analysis between the combined exercise and control groups are shown in tables (**Tables 2-4**).

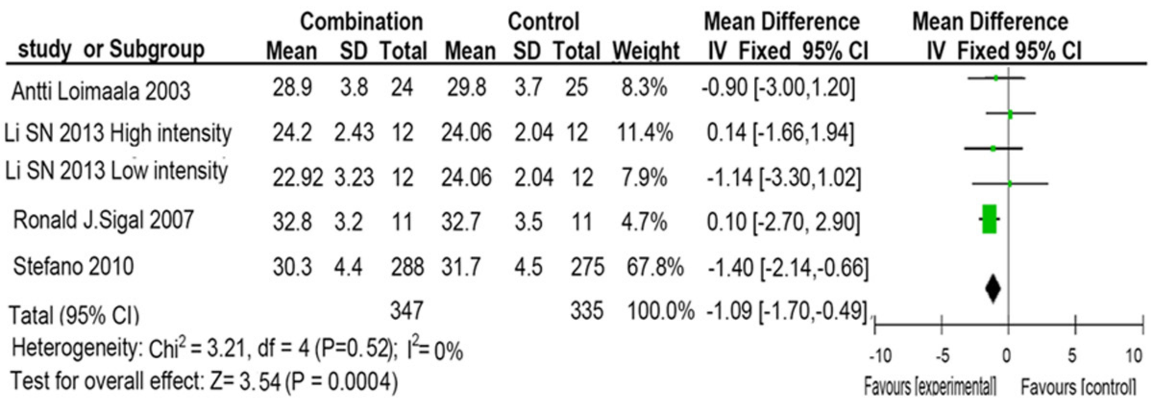

Figure 2. Combined exercise vs. Non-exercise, Body Mass Index (kg/m^2).

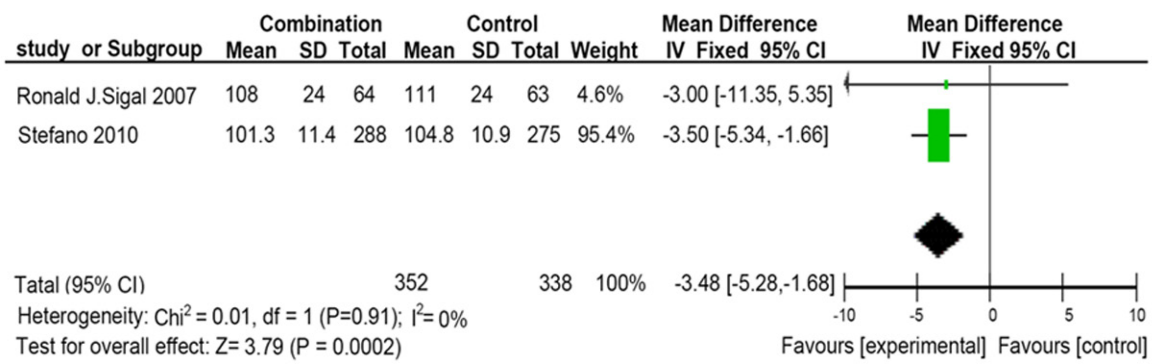

Figure 3. Combined exercise vs. Non-exercise, Waist Circumstance (cm).

Blood glucose: All of the 6 studies (one of the studies with two kinds of strength training) reported the HbA1c concentration, which was the primary measurement of blood glucose. Specifically, HbA1c was significantly reduced in the combined exercise group compared with the non-exercise group (WMD = -0.40%, 95% CI = -0.54~-0.26, I^2 = 3%, P < 0.05) (**Figure 1**).

Stefano et al also showed that the fasting blood glucose level were reported after 12 months and 12 weeks of exercise intervention. One study showed significant reduction in the fasting blood glucose level between before and after the training in the combined exercise group (-68%, 95% CI = -9.4~8.1, P < 0.001), another study also showed significant difference in the fasting blood glucose level between before and after the training in the combined exercise group (for high intensity: -17%, 95% CI = -38.1~4.7, P < 0.01; for low intensity: -11%, 95% CI = -30.3~9.2, P < 0.01). However, there was no significant difference in the fasting blood glucose level between the combined exercise group and non-exercise groups (WMD = -6.10%, 95% CI = -12.99~0.79, I^2 = 0%, P > 0.05). One study in which also analyzed the difference in insulin resistance (Homeostasis Model Assessment Insulin Resistance [HOMA-IR]) [29] before and after exercise intervention between the combined exercise and non-exercise groups. The results were similar to the fasting blood glucose level; the only significant reduction occurred in the combined exercise group (WMD = -1.18%, 95% CI = -2.30~0, P = 0.001).

Two studies were eligible for testing the effect of combined exercise and aerobic exercise or resistance exercise alone on blood glucose [12, 18]. No significant reduction in the HbA1c occurred in the combined exercise group compared to the aerobic exercise group (WMD = -13%, 95% CI = -0.36~0.11, I^2 = 4%), but a significant difference existed in the combined exercise versus the resistance exercise group (WMD = -25%, 95% CI = -0.45~-0.04, I^2 = 48%, P < 0.05).

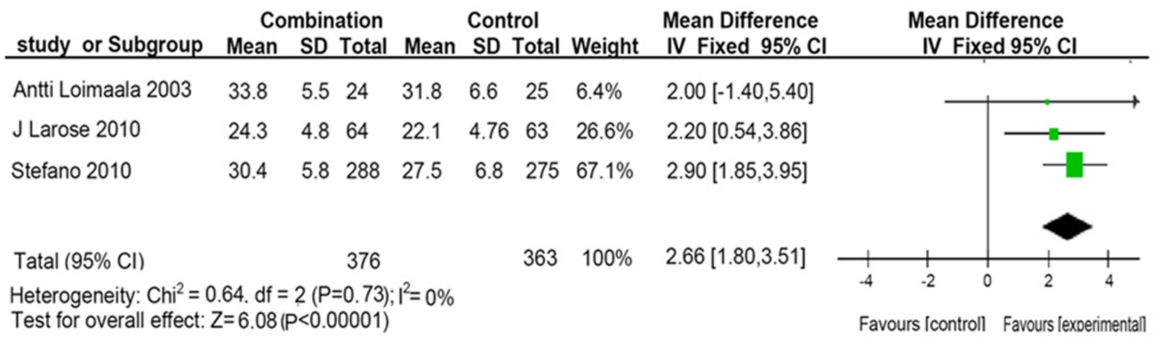

Figure 4. Combined exercise vs. Non-exercise, Maximal Oxygen Consumption (ml/kg*min).

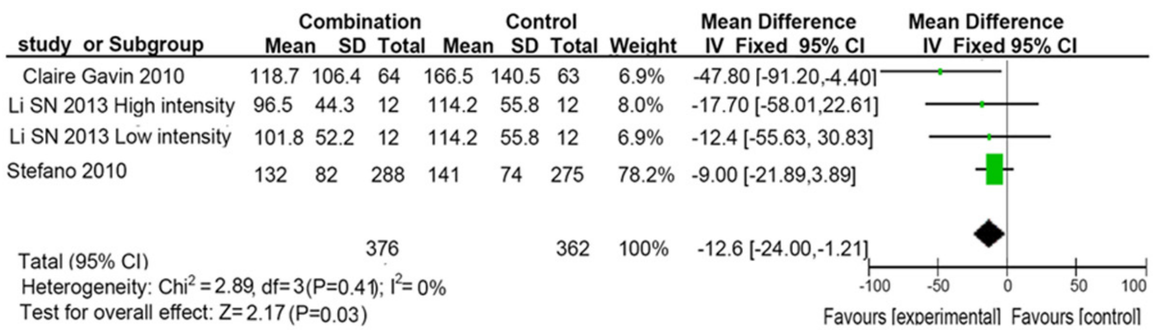

Figure 5. Combined exercise vs. Non-exercise, Triglycerides (mg/dL).

Body mass index: Three studies were included to assess the effect of exercise on the BMI [12, 17, 18]. There was a significant reduction in the BMI in the combined exercise group compared to the non-exercise group (WMD = -1.09 kg/m^2, 95% CI = -1.70~-0.49, I^2 = 0%, $P < 0.05$) (**Figure 2**).

Waist circumstance: Two studies were included to assess the effect of exercise on waist circumstance. There was a significant decrease in the waist circumstance in the combined exercise group compared to the non-exercise group (WMD = -3.48 cm, 95% CI = -5.28~-1.6, I^2 = 0%, $P < 0.05$) (**Figure 3**). Another study showed the changes in waist circumstance before and after exercise [12]. There was a 2.8 cm reduction in the combined exercise group, which was the greatest reduction among all groups in the study. The reduction was also significantly different from the non-exercise group.

Abdominal subcutaneous fat and abdominal visceral fat: Two studies [13, 18] were included to assess the effect of exercise on abdominal subcutaneous fat and abdominal visceral fat. There was a significant reduction of abdominal subcutaneous fat (WMD = -104.14 cm^2, 95% CI = -136.02~-72.27, I^2 = 78%, $P < 0.05$) and abdominal visceral fat (WMD = -32.26 cm^2, 95% CI = -56.87~-7.66, I^2 = 0%, $P < 0.05$) in the combined exercise group compared with the non-exercise group.

Body mass: Two studies were included to assess the effect of exercise on body mass [12, 13]. No significant difference existed between the three groups on the reduction of body mass (WMD = -3.25 kg, 95% CI = -7.52~1.03, I^2 = 0%, P = 0.14).

Two studies were used to determine the difference in body mass between the combined exercise and aerobic exercise or resistance exercise group, but no significant difference was found between the two groups (WMD = -1.60 kg, 95% CI = -7.39~4.19, I^2 = 0%, P = 0.59 [combined exercise vs. aerobic exercise] and WMD = -1.28 kg, 95% CI = -7.08~4.52, I^2 = 0%, P = 0.67 [combined exercise vs. resistance exercise]).

Adverse events: Two studies reported the prevalence of adverse events during training

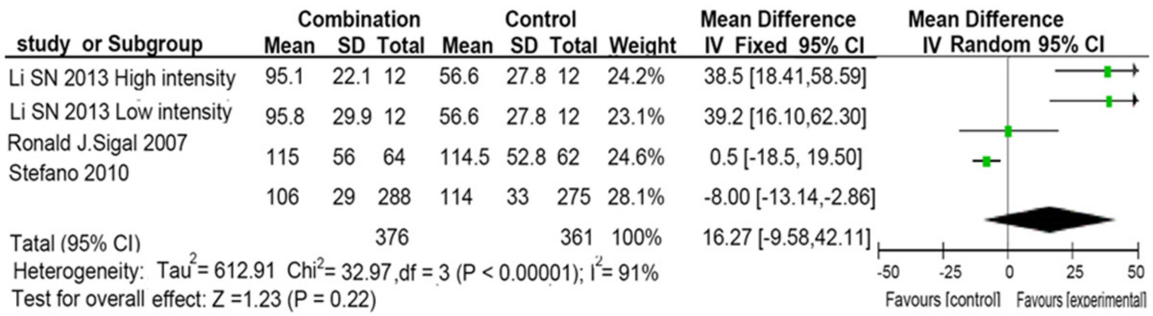

Figure 6. Combined exercise vs. Non-exercise, Low Density Lipoprotein Cholesterol (mg/dL).

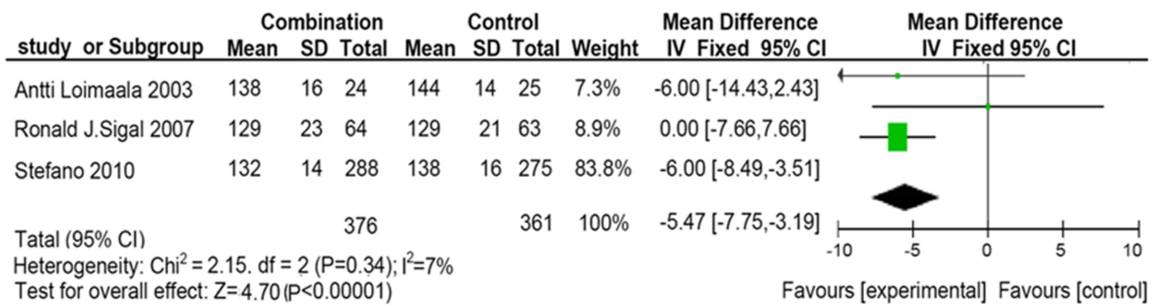

Figure 7. Combined exercise vs. Non-exercise, Systolic Blood Pressure (mmHg).

[11, 18]; most adverse events were sports injuries and hypoglycemia. The prevalence of the three most common sports injuries (shoulder pain, low back pain, and spin splints) were analyzed in this meta-analysis, and all the results showed no significant difference on the prevalence of sports injuries between the combined exercise and non-exercise groups (P > 0.1). Moreover, no severe hypoglycemia, which indicates the need for medication, was reported during the training.

Maximal oxygen consumption (VO_{2max}): Three studies [11, 12, 17] were included to assess the effect of exercise on the VO_{2max} after excluding one study [13], which showed the VO_{2max} data after training. A significant difference in VO_{2max} was found between the combined exercise and non-exercise groups (WMD = 2.66 ml/[kg/min], 95% CI = 1.80~3.51, I^2 = 0%, P < 0.05) (**Figure 4**).

TG: Two studies reported the effect of combined exercise on TG [11, 14]. This meta-analysis showed a significant change in TG levels between the combined exercise and non-exercise groups (WMD = -12.61 mg/dl, 95% CI = -24.00~-1.21, I^2 = 0%, P < 0.05) (**Figure 5**).

LDL-C and HDL-C: Two studies were included in this meta-analysis to assess the effect of combined exercise on LDL-C and HDL-C [11, 14]. As a result, there was a significant increase in HDL-C (WMD = 2.91 mg/dl, 95% CI: 1.22 to 4.61, I^2 = 0%, P < 0.05) in the combined exercise group when compared with the non-exercise group (**Figure 6**), but there was no significant difference in LDL-C (WMD = 16.27 mg/dl, 95% CI = -9.58~42.11, I^2 = 91%, P = 0.22) between the combined exercise group and non-exercise group.

Blood pressure: Three studies [11, 17, 18] were included to assess the effect of combined exercise on SBP and two studies [11, 17] measured the DBP. As a result, there was a 5.47 mmHg significant reduction of SBP (WMD = -5.47 mmHg, 95% CI = -7.74~-3.20, I^2 = 0%, P < 0.05) (**Figure 7**) and a 2.75 mmHg reduction of DBP (WMD = 2.75 mg/dl, 95% CI = -4.10~-1.41, I^2 = 0%, P < 0.05) in the combined exercise group compared with the non-exercise group.

Muscle strength: Two studies [11, 18] with three measurements were included to assess the effect of combined exercise on upper body muscle strength (UBS). There was a significant increase in UBS in the combined exercise group

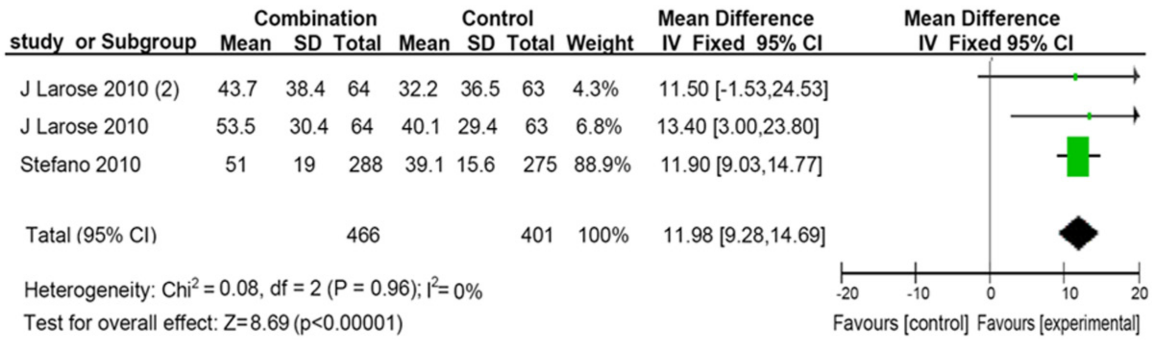

Figure 8. Combined exercise vs. Non-exercise, Upper Body Strength (kg).

compared with the non-exercise group (WMD = 11.98 kg, 95% CI = 9.27~14.70, I^2 = 0%, P < 0.05) (**Figure 8**). Moreover, one study [11] with two measurements was included to compare the difference in UBS between the combined exercise group and the aerobic exercise or resistance exercise group alone. No significant increase existed in the combined exercise group compared with the aerobic exercise (WMD = 8.10 kg, 95% CI = -0.44~16.63, I^2 = 0%, P = 0.06) and resistance exercise groups (WMD = 3.10 kg, 95% CI = -5.13~11.32, I^2 = 0%, P = 0.46).

Two studies [11, 17] were included to assess the effect of combined exercise on lower body strength (LBS). There was a 38.26 kg significant increase in LBS in the combined exercise group compared with the non-exercise group (WMD = 38.26 kg, 95% CI = 27.15~49.37, I^2 = 0%, P < 0.05).

Study quality

All of the included studies were RCTs. Allocation concealment was also reported in two studies [11, 18]. There were no significant differences with respect to the main characteristics among participants in all of the studies at baseline. The dropout rates of the included studies were 0 [13], to 2% [17], 6% [12], 7% [11], and 12% [18] (**Figure 8**).

Sub-group analysis

We noted that there was a significant heterogeneity in the meta analysis of LDL-C (I^2 = 91%, X^2 = 32.97, P < 0.00001) between the combined exercise and non-exercise groups. Therefore, in order to investigate the source of the heterogeneity of the results, we conducted subgroup analyses of the included trails based on exercise duration and BMI. The results showed that there was a significant difference in the LDL-C concentration between the combined exercise and non-exercise groups (WMD = 38.80%, 95% CI = 23.64~53.96, I^2 = 0%, P < 0.05 and WMD = -7.42%, 95% CI = -12.38~-2.46, I^2 = 0%, P < 0.05) for the BMI (< 25 kg/m^2) group and BMI (> 25 kg/m^2) group, respectively. There was, however, no significant difference for the > 6 months or < 6 months exercise duration group. This finding reflected that the BMI of patients may be the causes of the heterogeneity of the results of LDL-C.

Discussion

From the results shown in the meta-analysis and relevant studies, we found that combined, aerobic, and resistance exercise can make a contribution to blood glucose control for type 2 diabetes patients. In this meta-analysis there was a 40% reduction in the HbA1c concentration in the combined exercise group compared with the non-exercise group. Some studies have confirmed that the glucose level of patients and the benefits derived from exercise have a positive correlation [9, 11, 30]; however, the HbA1c concentration was 0.40% less than other meta-analyses analyzing the effects of aerobic or resistance exercise alone on the management of HbA1c [9, 30]. This result may be because the HbA1c baseline in all of the included studies was approximately 7%, which is less than the baseline value in other reviews [9, 30]. Moreover, two of the included studies also showed a significant reduction on fasting blood glucose and insulin resistance in the combined exercise group.

However, no significant difference in the HbA1c concentration was found between the combined exercise and aerobic exercise or resistance exercise group, but the Joanie study arrived at the opposite conclusion [8]. One non-randomized control trial also showed that combined exercise reduced the HbA1c concentration more than aerobic exercise alone [26].

Furthermore, according to the suggestion by United Kingdom Prospective Diabetes Study Group [29], a 1% increase in the HbA1c concentration represents a 14% increased risk for myocardial infarction and a 37% increased risk for microvascular complications. As no severe adverse events were reported in the relevant studies herein, the 0.40% reduction in this meta-analysis may accompany a 6% decreased risk for myocardial infarction and a 15% decreased risk for microvascular complications for type 2 diabetes patients with a HbA1c concentration of 7%.

Combined exercise tends to increase cardiorespiratory fitness for type 2 diabetes. According to this meta-analysis, the VO_{2max}, blood pressure (SBP and DBP), and blood lipids (HDL-C, other than LDL-C) showed a significant difference between the combined exercise group and non-exercise group after training. Type 2 diabetes patients always have abnormalities in cardiorespiratory fitness, which are the main risk factors for metabolic disorders [9, 14, 30]. Studies have shown that the prevalence of type 2 diabetes has a tendency to increase with age, and aging is also associated with a decline in cardiorespiratory fitness [30-34]. Thus, combined exercise was advisable for aging type 2 diabetes patients. Moreover, most studies have reported that aerobic or resistance exercise alone have limited effects on cardiorespiratory fitness, especially on control of blood pressure or blood lipids [9, 30, 35]. In this review, combined exercise was shown to have an effect on the control of both blood pressure and blood lipids. Furthermore, studies have also confirmed that combined exercise can increase endothelial function, such as the main coronary artery, and cardiovascular autonomic regulation, which may have clinical importance on preventing sudden death in type 2 diabetes patients [17, 36]. In the Sadanori RCT study [30], the prevalence of cardiovascular events was also shown to be lower in the combined exercise group than the non-exercise group.

Combined exercise tends to increase muscle strength and indices of balance body for type 2 diabetes patients. This meta-analysis verified that combined exercise increases UBS and LBS. It has been shown that muscle strength is decreased in type 2 diabetes patients, especially on aging people. This phenomenon was due to a loss in both muscle mass and the metabolic quality of skeletal muscle, such as sarcopenia [30]. The loss of muscle mass also led to an increased risk for type 2 diabetes [37]. Moreover, skeletal muscle is the primary metabolic target organ for glucose and TG disposal and is an important determinant of the resting metabolic rate [30]. Thus, combined exercise can prevent the reduction in muscle strength and increasing the metabolic rate, especially for aging patients. In contrast, the meta-analysis also showed a significant effect of combined exercise on decreasing the BMI and waist circumstance. Three included studies also showed that fat mass was significant decreased between the combined exercise group and non-exercise group [13, 18]. Because weight control is one of the important recommendations for type 2 diabetes patients to prevent complications, the effects of combined exercise on balance body can be beneficial.

In this review, the effective volume of the exercise was 60-150 min per week at 50-80% VO_{2max} or 60-75% HR_{max} for aerobic exercise and 4-9 exercises at 7-22 repetitions targeting major muscles per set and 2-9 sets per week for resistance exercise. The weekly volume in this review was consistent with the recommendation by the ADA [38]; however, there was a discrepancy regarding the frequency of exercise. In this review, the frequency of exercise was from 2-3 times per week, while the ADA recommended was $\leq$ 2 consecutive days without exercise. The discrepancy might be because it was not convenient for participants to go to special places taking part in the training > 3 times a week. Because the entire exercise volume was similar to the ADA recommendation, the exercise volume in this review was recommended to type 2 diabetes patients and a higher frequency was suggested.

The exercise duration in the review ranged from 12 weeks to 1 year. In the sub-group analysis of LDL-C, we found that LDL-C was significant decreased both in the BMI (< 25 kg/m^2) group and BMI (> 25 kg/m^2) group. This may indicate that the BMI of patients can make a contribution to the management of type 2 diabetes, such as the blood lipad level, but large-scale of studies need to be investigated in the future based on above classification features because of only three studies considered measuring LDL-C.

One study assessing the effect of combined exercise on quality of life showed that mental health status decreased in the combined exercise group [19]. The author explained that combined exercise might make people more fatigued than aerobic or resistance exercise alone. Due to insufficient data in this review, more related studies are suggested. Gradual combined exercise is suggested, which may help patients decrease the sense of fatigue during training [9].

For better interpretation of the results, several potential limitations of this meta-analysis should be acknowledged. The included study number in the meta-analysis was only six studies. Moreover, the statistics comparison about exercise effects between combined exercise and aerobic or resistance exercise alone was limited. Furthermore, less of the data were conducted from Asian countries.

In conclusion, combined exercise can be recommended in the management of type 2 diabetes patients, especially for elderly patients. Moreover, 2-3 times per week, moderate-to-high intensity of the combined aerobic and resistance exercise are suitable to be conducted for type 2 diabetes patients.

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Disclosure of conflict of interest

None.

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References

[1] Wimalawansa SJ. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. J Steroid Biochem Mol Biol 2018; 175: 177-189.

[2] Zhang M, Zhou Z, Wang J and Li S. MiR-130b promotes obesity associated adipose tissue inflammation and insulin resistance in diabetes mice through alleviating M2 macrophage polarization via repression of PPAR-gamma. Immunol Lett 2016; 180: 1-8.

[3] Zhang Z, Turer E, Li X, Zhan X, Choi M, Tang M, Press A, Smith SR, Divoux A, Moresco EM and Beutler B. Insulin resistance and diabetes caused by genetic or diet-induced KBTBD2 deficiency in mice. Proc Natl Acad Sci U S A 2016; 113: E6418-E6426.

[4] Jorge ML, de Oliveira VN, Resende NM, Paraiso LF, Calixto A, Diniz AL, Resende ES, Ropelle ER, Carvalheira JB, Espindola FS, Jorge PT and Geloneze B. The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. Metabolism 2011; 60: 1244-1252.

[5] Kang SJ, Ko KJ and Baek UH. Effects of 12 weeks combined aerobic and resistance exercise on heart rate variability in type 2 diabetes mellitus patients. J Phys Ther Sci 2016; 28: 2088-2093.

[6] Schreuder TH, Van Den Munckhof I, Poelkens F, Hopman MT and Thijssen DH. Combined aerobic and resistance exercise training decreases peripheral but not central artery wall thickness in subjects with type 2 diabetes. Eur J Appl Physiol 2015; 115: 317-326.

[7] Tomas-Carus P, Ortega-Alonso A, Pietilainen KH, Santos V, Goncalves H, Ramos J and Raimundo A. A randomized controlled trial on the effects of combined aerobic-resistance exercise on muscle strength and fatigue, glycemic control and health-related quality of life of type 2 diabetes patients. J Sports Med Phys Fitness 2016; 56: 572-8.

[8] Larose J, Sigal RJ, Boule NG, Wells GA, Prud'homme D, Fortier MS, Reid RD, Tulloch H, Coyle D, Phillips P, Jennings A, Khandwala F and Kenny GP. Effect of exercise training on physical fitness in type II diabetes mellitus. Med Sci Sports Exerc 2010; 42: 1439-1447.

[9] Thomas DE, Elliott EJ and Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006; CD002968.

[10] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[11] Balducci S, Zanuso S, Nicolucci A, De Feo P, Cavallo S, Cardelli P, Fallucca S, Alessi E, Fallucca F, Pugliese G; Italian Diabetes Exercise Study (IDES) Investigators. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian diabetes and exercise study (IDES). Arch Intern Med 2010; 170: 1794-1803.

[12] Church TS, Blair SN, Cocreham S, Johannsen N, Johnson W, Kramer K, Mikus CR, Myers V, Nauta M, Rodarte RQ, Sparks L, Thompson A and Earnest CP. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA 2010; 304: 2253-2262.

[13] Cuff DJ, Meneilly GS, Martin A, Ignaszewski A, Tildesley HD and Frohlich JJ. Effective exercise modality to reduce insulin resistance in women with type 2 diabetes. Diabetes Care 2003; 26: 2977-2982.

[14] Gavin C, Sigal RJ, Cousins M, Menard ML, Atkinson M, Khandwala F, Kenny GP, Proctor S, Ooi TC; Diabetes Aerobic and Resistance Exercise (DARE) trial investigators. Resistance exercise but not aerobic exercise lowers remnant-like lipoprotein particle cholesterol in type 2 diabetes: a randomized controlled trial. Atherosclerosis 2010; 213: 552-557.

[15] Jennings AE, Alberga A, Sigal RJ, Jay O, Boule NG and Kenny GP. The effect of exercise training on resting metabolic rate in type 2 diabetes mellitus. Med Sci Sports Exerc 2009; 41: 1558-1565.

[16] Larose J, Sigal RJ, Khandwala F, Prud'homme D, Boulé NG, Kenny GP; Diabetes Aerobic and Resistance Exercise (DARE) trial investigators. Associations between physical fitness and HbA(1)(c) in type 2 diabetes mellitus. Diabetologia 2011; 54: 93-102.

[17] Loimaala A, Huikuri HV, Koobi T, Rinne M, Nenonen A and Vuori I. Exercise training improves baroreflex sensitivity in type 2 diabetes. Diabetes 2003; 52: 1837-1842.

[18] Sigal RJ, Kenny GP, Boule NG, Wells GA, Prud'homme D, Fortier M, Reid RD, Tulloch H, Coyle D, Phillips P, Jennings A and Jaffey J. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med 2007; 147: 357-369.

[19] Reid RD, Tulloch HE, Sigal RJ, Kenny GP, Fortier M, McDonnell L, Wells GA, Boule NG, Phillips P and Coyle D. Effects of aerobic exercise, resistance exercise or both, on patient-reported health status and well-being in type 2 diabetes mellitus: a randomised trial. Diabetologia 2010; 53: 632-640.

[20] Maiorana A, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, Taylor R and Green D. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol 2001; 38: 860-866.

[21] Maiorana A, O'Driscoll G, Goodman C, Taylor R and Green D. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabetes Res Clin Pract 2002; 56: 115-123.

[22] Fatone C, Guescini M, Balducci S, Battistoni S, Settequattrini A, Pippi R, Stocchi L, Mantuano M, Stocchi V and De Feo P. Two weekly sessions of combined aerobic and resistance exercise are sufficient to provide beneficial effects in subjects with Type 2 diabetes mellitus and metabolic syndrome. J Endocrinol Invest 2010; 33: 489-495.

[23] Kluding PM, Singh R, Goetz J, Rucker J, Bracciano S and Curry N. Feasibility and effectiveness of a pilot health promotion program for adults with type 2 diabetes: lessons learned. Diabetes Educ 2010; 36: 595-602.

[24] Tokmakidis SP, Zois CE, Volaklis KA, Kotsa K and Touvra AM. The effects of a combined strength and aerobic exercise program on glucose control and insulin action in women with type 2 diabetes. Eur J Appl Physiol 2004; 92: 437-442.

[25] Svacinova H, Novakova M, Placheta Z, Kohzuki M, Nagasaka M, Minami N, Dobsak P and Siegelova J. Benefit of combined cardiac rehabilitation on exercise capacity and cardiovascular parameters in patients with type 2 diabetes. Tohoku J Exp Med 2008; 215: 103-111.

[26] Marcus RL, Smith S, Morrell G, Addison O, Dibble LE, Wahoff-Stice D and Lastayo PC. Comparison of combined aerobic and high-force eccentric resistance exercise with aerobic exercise only for people with type 2 diabetes mellitus. Phys Ther 2008; 88: 1345-1354.

[27] Segerstrom AB, Glans F, Eriksson KF, Holmback AM, Groop L, Thorsson O and Wollmer P. Impact of exercise intensity and duration on insulin sensitivity in women with T2D. Eur J Intern Med 2010; 21: 404-408.

[28] Zois C, Tokmakidis SP, Volaklis KA, Kotsa K, Touvra AM, Douda E and Yovos IG. Lipoprotein profile, glycemic control and physical fitness after strength and aerobic training in post-menopausal women with type 2 diabetes. Eur J Appl Physiol 2009; 106: 901-907.

[29] Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC and Holman RR. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-412.

[30] Strasser B, Siebert U and Schobersberger W. Resistance training in the treatment of the metabolic syndrome: a systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. Sports Med 2010; 40: 397-415.
[31] Manini TM, Everhart JE, Patel KV, Schoeller DA, Colbert LH, Visser M, Tylavsky F, Bauer DC, Goodpaster BH and Harris TB. Daily activity energy expenditure and mortality among older adults. JAMA 2006; 296: 171-179.
[32] Roberts SB and Rosenberg I. Nutrition and aging: changes in the regulation of energy metabolism with aging. Physiol Rev 2006; 86: 651-667.
[33] Starling RD. Energy expenditure and aging: effects of physical activity. Int J Sport Nutr Exerc Metab 2001; 11 Suppl: S208-217.
[34] Stiegler P and Cunliffe A. The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. Sports Med 2006; 36: 239-262.
[35] Wei M, Gibbons LW, Kampert JB, Nichaman MZ and Blair SN. Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 2000; 132: 605-611.
[36] Okada S, Hiuge A, Makino H, Nagumo A, Takaki H, Konishi H, Goto Y, Yoshimasa Y and Miyamoto Y. Effect of exercise intervention on endothelial function and incidence of cardiovascular disease in patients with type 2 diabetes. J Atheroscler Thromb 2010; 17: 828-833.
[37] Sayer AA, Syddall HE, Dennison EM, Martin HJ, Phillips DI, Cooper C, Byrne CD and Hertfordshire C. Grip strength and the metabolic syndrome: findings from the Hertfordshire Cohort Study. QJM 2007; 100: 707-713.
[38] Sigal RJ, Kenny GP, Wasserman DH, Castaneda-Sceppa C and White RD. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006; 29: 1433-1438.