

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

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Abstract

Over the last decade, investigators have given increased attention to the effects of resistance training (RT) on several metabolic syndrome variables. The metabolic consequences of reduced muscle mass, as a result of normal aging or decreased physical activity, lead to a high prevalence of metabolic disorders. The purpose of this review is: (i) to perform a meta-analysis of randomized controlled trials (RCTs) regarding the effect of RT on obesity-related impaired glucose tolerance and type 2 diabetes mellitus; and (ii) to investigate the existence of a dose-response relationship between intensity, duration and frequency of RT and the metabolic clustering. Thirteen RCTs were identified through a systematic literature search in MEDLINE ranging from January 1990 to September 2007. We included all RCTs comparing RT with a control group in patients with abnormal glucose regulation. For data analysis, we performed random effects meta-analyses to determine weighted mean differences (WMD) with 95% confidence intervals (CIs) for each endpoint. All data were analysed with the software package Review Manager 4.2.10 of the Cochrane Collaboration. In the 13 RCTs included in our analysis, RT reduced glycosylated haemoglobin (HbA_{1c}) by 0.48% (95% CI -0.76, -0.21; $p=0.0005$), fat mass by 2.33 kg (95% CI -4.71, 0.04; $p=0.05$) and systolic blood pressure by 6.19 mmHg (95% CI 1.00, 11.38; $p=0.02$). There was no statistically significant effect of RT on total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride and diastolic blood pressure. Based on our meta-analysis, RT has a clinically and statistically significant effect on metabolic syndrome risk factors such as obesity, HbA_{1c} levels and systolic blood pressure, and therefore should be recommended in the management of type 2 diabetes and metabolic disorders.

The inclusion of resistance training (RT) as an integral part of an exercise programme has been endorsed by the American Heart Association,^[1] the American College of Sports Medicine^[2] and the American Diabetes Association.^[3] Cross-sectional studies have shown that muscular strength is inversely associated with all-cause mortality^[4] and the prevalence of the metabolic syndrome (MS),^[5] independent of cardiorespiratory fitness levels. However, at present, the evidence that RT reduces cardiovascular disease (CVD) risk factors remains equivocal.^[6]

The purpose of this review is: (i) to perform a meta-analysis of randomized controlled trials (RCTs) regarding the effect of RT on obesity-related impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2D); and (ii) to assess the potential of a dose-response relationship between intensity, duration and frequency of RT exercise and the metabolic clustering. There are discrepancies in findings as to whether RT 3 days per week elicits superior strength gains when

compared with training regimens of lower frequency.^[7,8] The question is whether progressively higher volumes of RT and subsequent increases in muscle mass may reduce multiple CVD risk factors as hypothesized by other investigators.^[9]

1. The Metabolic Syndrome (MS)

The pathogenesis of the MS is multifactorial and progressive. The risk factors of the MS are of metabolic origin and consist of abdominal adipose tissue accumulation, atherogenic dyslipidaemia, elevated plasma glucose, elevated blood pressure and a prothrombotic and pro-inflammatory state. The major risk factors are obesity and insulin resistance (IR) accompanied by increased risk for CVD and T2D. Furthermore, aging, physical inactivity and endocrine, and genetic factors exacerbate the MS.^[10]

There is no standard definition of the MS, but three definitions, two proposed by the WHO and the other one by the National Cholesterol

Education Program Adult Treatment Panel III (NCEP ATP III), are well known. The WHO definitions include IGT, T2D and/or IR together with two more of the following risk factors: (i) arterial BP $\geq 140/90$ mmHg; dyslipidaemia, defined as plasma triglyceride (TG) concentration ≥ 150 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) ≤ 35 mg/dL in men, ≤ 39 mg/dL in women; and (ii) central obesity, defined as waist-to-hip ratio >0.90 in men, >0.85 in women and/or body mass index (BMI) >30 kg/m²; microalbuminuria, defined as urinary albumin excretion rate ≥ 20 μ g/min or albumin-to-creatinine ratio ≥ 30 mg/g.^[11] The NCEP ATP III definition includes the presence of any three of the following risk factors: (i) abdominal obesity, defined as a waist circumference of >102 cm in men, >88 cm in women; (ii) plasma TG ≥ 150 mg/dL; HDL-C <40 mg/dL in men, <50 mg/dL in women; and (iii) BP $\geq 130/85$ mmHg; fasting glucose ≥ 110 mg/dL.^[12] Recently, the International Diabetes Federation replaced WHO criteria with those closer to ATP III. Waist circumference thresholds are ethnic-specific and abdominal adiposity was required for diagnosis.^[13] The prevalence of MS has been shown to vary, depending on which medical society definition is adopted (e.g. in the US adult population between 21.2% and 38.9%). Thus, direct comparisons of prevalence values across MS studies are not valid.^[14]

2. Epidemiology of the MS

Being overweight, especially in the presence of environmental and genetic risk factors, leads to abdominal obesity and ectopic fat deposition with consequent IR. Genetic factors^[15] and environmental factors including a sedentary lifestyle and poor physical fitness,^[16] a diet rich in saturated fat and low in fibre^[17] and a low socioeconomic status^[18] contribute to the development of both overweight and IR.^[19] Furthermore, adipose tissue is a major endocrine organ, secreting substances such as adiponectin, leptin, resistin, tumour necrosis factor- α , interleukin-6 and plasminogen activator inhibitor-1 that may play a critical role in the pathogenesis of the MS.^[20] The manifestations of cardiovascular risk

factors such as abnormal insulin and glucose metabolism, dyslipidaemia, obesity, hypertension, endothelial dysfunction, inflammation and impaired fibrinolysis predispose persons with the MS to another end-stage consequence of the MS, namely CVD.^[21-23] Published evidence indicates that the risk for CVD associated with the MS is greater than the sum of its individual risk factors.^[24]

Epidemiological studies show a strong association for obesity with CVD^[25] and T2D.^[26] Obesity-induced risk factors such as plasma cholesterol, elevated plasma glucose and elevated BP increase the risk for CVD and have thus been called the metabolic complications of obesity.^[27] IR is an underlying risk factor in MS and contributes to prediabetes and, ultimately, to T2D. Approximately 75% of people with prediabetes and 86% of people with T2D have the MS. Both MS and T2D are known to predict CVD. In many patients, the MS culminates in T2D, which further increases the risk of CVD.^[10]

Most patients with the MS have lipid abnormalities, namely raised TG levels, low HDL-C levels and a greater preponderance of small low-density lipoprotein (LDL) particles.^[28] Abdominal obesity is positively correlated with fasting plasma TG and insulin levels and negatively correlated with HDL-C levels.^[29] The atherogenic lipoprotein profile associated with obesity and IR has been found to be largely attributable to intra-abdominal fat.^[30] The combination of abdominal obesity and high plasma TG is a strong marker for the MS.

Physical activity is considered to reduce the risk of CVD, T2D and the MS and is an important component of CVD prevention. This concept is supported by prospective epidemiological studies demonstrating that low cardiorespiratory fitness is a strong and independent predictor of all-cause and CVD mortality in adults.^[31-39] Although many investigators have documented that cardiorespiratory fitness reduced T2D and MS risk independent of bodyweight,^[40,41] some found that obesity was more strongly linked with CVD risk factors.^[42-44] Several reports demonstrate that cardiorespiratory fitness is an independent predictor of all-cause or CVD mortality in patients with T2D or the MS and that this association is

independent of BMI.^[45-48] In contrast, a recent report demonstrated that T2D and diabetes-related cardiovascular co-morbidities increased with BMI, regardless of physical activity, and increased with physical inactivity regardless of BMI.^[49] These findings suggest that both physical inactivity and obesity are strongly and independently associated with T2D, cardiovascular risk factors and the MS.

3. Overview: Resistance Training (RT) and Metabolic Risk

Aging is associated with a loss in both muscle mass and the metabolic quality of skeletal muscle. Sarcopenia, the loss of muscle mass associated with aging, is a main cause of muscle weakness in old age and consequently leads to an increased risk for development of IR and T2D.^[50] The aetiology of sarcopenia involves multiple factors such as loss of motoneurons and muscle cell apoptosis and, as a result, the number of muscle fibres considerably decreases with aging.^[51] A major part of these changes is associated with an age-related decrease in the physical activity level and can be counteracted by RT. There is concurring research evidence that RT prevents the age-related decline in skeletal muscle mass which is approximately 0.46 kg of muscle per annum from the 5th decade on and the best available evidence suggests that muscle maintains its plasticity and capacity to hypertrophy even into the 10th decade of life.^[52-54]

Skeletal muscle is the primary metabolic target organ for glucose and triglyceride disposal and is an important determinant of resting metabolic rate. The potential consequences of age-related reduction in skeletal muscle mass are diverse, including reduced muscle strength and power, reduced resting metabolic rate, reduced capacity for lipid oxidation and increased abdominal adiposity. With increasing adiposity in aging, the insulin-mediated glucose uptake in the skeletal muscle of elderly patients is reduced. The maintenance of a large muscle mass can contribute to the prevention of metabolic risk factors – namely obesity, dyslipidaemia and T2D – associated with CVD.^[55]

Both resting and activity-related energy expenditure decline with age,^[56] and decreased energy expenditure can have a major adverse effect on weight maintenance.^[57] Although it is clear that aerobic exercise is associated with much greater energy expenditure during the exercise session than RT, studies have shown that regular RT is effective in promoting weight loss in obese persons.^[58] Many studies have shown that RT is associated with a decrease in fat mass (FM) and a concomitant increase in lean body mass (LBM) and thus little or no change in total body-weight.^[59-67] Because of this, it has been assumed that the main effect of RT on body composition is a shift from fat to muscle mass. RT increases resting metabolic rate as a result of a greater muscle protein turnover. A difference of 10 kg in LBM translates to a difference in energy expenditure of 100 kcal/day, equivalent to 4.7 kg FM per year.^[68] However, a number of studies have shown that RT will increase resting metabolic rate at least if the training is intense enough to induce an increase in LBM.^[69-71] Several studies have demonstrated decreases in visceral adipose tissue after RT programmes.^[64,66,67,72-74] Excessive central obesity and especially visceral adipose tissue have been linked with the development of dyslipidaemia, hypertension, IR, IGT, T2D and CVD.^[53,75,76] A relative increase in body fat is linked with a decline in insulin sensitivity in both obese and elderly individuals. RT has been shown to improve muscle strength in both healthy elderly individuals and individuals with chronic disease and to improve insulin-stimulated glucose uptake in patients with IGT or manifest T2D.^[77] RT and subsequent increases in muscle mass, may improve glucose and insulin responses to a glucose load in healthy^[78,79] and diabetic men and women^[60,80,81] and improve insulin sensitivity in diabetic or insulin-resistant middle-aged and elderly men and women.^[81-85] High-intensity RT decreases glycosylated haemoglobin (HbA_{1c}) levels in diabetic men and women, regardless of age.^[59-62,82,86-90]

Apart from the positive effect on glycaemic control, it is unclear whether RT also has therapeutic effects on other conditions associated with the MS, namely dyslipidaemia and hypertension. At

present, there is little evidence that RT improves lipoprotein-lipid profiles.^[59,61,91] Most studies show no improvement in lipid profiles after RT.^[60,62,72,89,92,93] In some studies this may be due to the fact that lipid values were normal at study entry.^[67,79,94] Although there is general agreement that endurance training lowers resting BP in patients with mild to severe hypertension,^[95] there is only some evidence that both isometric^[96,97] and dynamic^[59,61] RT elicit reductions of both resting systolic and diastolic blood pressure (SBP; DBP) in individuals with hypertension. This is in agreement with two meta-analyses.^[98,99]

RT, when performed regularly and with sufficient intensity, stimulates skeletal muscle to synthesize new muscle proteins (hypertrophy). The effective amount of RT to promote muscle growth in relatively sedentary diseased or aged individuals is an understudied area. It is believed that one to two sets of eight to twelve repetitions per set with an intensity >60% of an individual's one repetition maximum (1 RM) [the maximum load that can be lifted once only throughout a complete range of motion], with eight to ten exercises per session, two to three sessions per week, are likely to have beneficial for health effects with the increase in skeletal muscle mass.^[100] A recent study examining the effects of systematic RT in the elderly (76.2 ± 3.2 years) demonstrated that RT consisting of two training sessions per week was at least as efficient as RT that included three training sessions per week, provided that the number of sets performed was equal.^[8] These findings contradict the results of another study that reported performing RT 3 days per week elicits superior strength gains when compared with RT performed 2 days per week.^[7] However, the latter study was for low volume RT; therefore, a higher RT frequency produced better results. A recent review demonstrated that there was no difference in mean rates of increase in the whole muscle cross-sectional area between two and three sessions per week for longer periods of training.^[101] Systematic reviews comparing RT frequencies in patients with metabolic or CVD risk revealed no apparent association between RT frequencies and changes in risk factors for MS.^[102,103] However, limitations still exist, since

only a few studies were conducted in subjects with risk factors for MS, and most of the included RT studies had a training frequency of 3 days per week.

4. Impaired Glucose Regulation and Type 2 Diabetes Mellitus: A Meta-Analysis

Impaired fasting glucose and IGT refer to the conditions in which blood glucose levels are higher than normal but do not meet the diagnostic criteria for T2D. Both disorders are associated with a significantly increased risk of developing T2D, with the highest risk among individuals exhibiting both conditions.^[104] IGT is associated with IR and is also a risk factor for all-cause mortality.^[105] According to the criteria of the WHO, IGT is defined as 2-hour glucose levels of 140–199 mg/dL (7.8–11.0 mmol) on the 75 g oral glucose tolerance test.^[106]

T2D is a metabolic disorder that is primarily characterized by IR, relative insulin deficiency and hyperglycaemia. Furthermore, T2D is often associated with obesity, hypertension, elevated cholesterol and the MS. The WHO definition of T2D is fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) or plasma glucose ≥11.1 mmol/L (200 mg/dL) 2 hours after a 75 g oral dose of glucose measured with a glucose tolerance test.^[106]

The beneficial effect of physical activity in patients with abnormal glucose regulation is very well documented, and there is international consensus that physical training comprises one of the three cornerstones of the treatment, together with diet and medicine.^[107,108] Two RCTs including persons with IGT have found that lifestyle modification protects against the development of T2D.^[34,35] Large observational cohort studies have found that higher levels of aerobic fitness and physical activity are associated with significantly lower cardiovascular and overall mortality, to a much greater extent than could be explained by glucose lowering alone.^[46,109,110]

Most of the information available concerns aerobic endurance training (AET) in the treatment of IR and T2D. Recent systematic reviews focused on the relationship between exercise and/or physical activity and glycaemic control

in patients with T2D.^[3,111,112] Results indicate that physical training significantly improves glycaemic control and reduces visceral adipose tissue and plasma TG in people with T2D, even without weight loss. One further meta-analysis, including 27 RCTs, examined the effects of different modes of exercise training on glucose control and risk factors for complications in patients with T2D.^[113] Differences among the effects of AET, RT and combined training on HbA_{1c} were minor. For training lasting ≥ 12 weeks, the overall effect was a small beneficial reduction (HbA_{1c} 0.8% \pm 0.3%). Aerobic and combined exercise had small or moderate effects on BP. All three modes of exercise produced trivial or unclear effects on blood lipids. The effects of RT on glycaemic control and risk factors associated with CVD in T2D were small (HbA_{1c}), unclear (BP) or trivial (blood lipids), and combined training was generally superior to RT alone.

Of the 27 studies in the meta-analysis of Snowling and Hopkins,^[113] six used RT and five combined AET and RT. Since then, there have been some new studies of RT although, so far, limited and unclear data are available concerning the effects of RT on the metabolic clustering among individuals with abnormal glucose metabolism.

For the purposes of this review, we have evaluated the RCT data on the effects of RT on obesity-related metabolic risk factors in adult men and women with IGT or T2D.

4.1 Methods of the Meta-Analysis

4.1.1 Literature Search

We performed a systematic literature review. An English language literature search from 1990 to September 2007 was conducted via MEDLINE. The following key words were used alone or in various combinations in computer searches: 'resistance training', 'metabolic syndrome', 'impaired glucose tolerance', 'type 2 diabetes', 'obesity', 'blood pressure' and 'lipids'. The reference lists from original and review articles were also reviewed to identify other relevant studies.

4.1.2 Inclusion Criteria

We considered all RCTs comparing RT with an exercise or non-exercise control group in

patients with impaired glucose metabolism or T2D. We included trials of 6 weeks or longer, because we wanted to evaluate the effect of on-going RT rather than acute single bouts of RT. A training period of <6 weeks would be too short to expect alterations in glycaemic control and body composition. The exclusion criteria for this review were as follows:

- studies with single-bout RT interventions;
- studies with mere recommendations as intervention, without further detail;
- studies where the RT was not either directly supervised or well documented;
- studies with a dietary co-intervention in the experimental group that was not also applied to the control group. However, we did not exclude studies with the same diet applied to both the intervention group and the control group and hence the RT in the intervention group was the only difference between the two groups.

The participants were males and females with impaired glucose regulation or T2D. All patients fulfilled the diagnosis criteria for IGT or T2D according to the WHO or the American Diabetes Association standards.^[11,108] We considered RCTs where RT prescriptions included specific recommendations for the type, intensity, frequency and duration of RT with a specific objective. This systematic review included studies involving the following four types of intervention:

- RT versus non-exercise control;
- RT plus AET versus non-exercise control;
- RT versus AET;
- RT plus diet versus diet alone.

4.1.3 Assessed Outcomes

The primary outcomes of our systematic review were glycaemic control measured in percent HbA_{1c} and FM (kg). Secondary outcomes included blood lipids (mg/dL), i.e. total cholesterol (CHOL), HDL-C, LDL cholesterol (LDL-C), TG, and BP (mmHg) measures, both SBP and DBP.

4.1.4 Data Extraction

We used a standardized data extraction form to extract data on study population, intervention and outcome in each study. This form included the following items: (i) general information

including title, authors, source, setting and year of publication; (ii) trial characteristics including design and randomization; (iii) characteristics of participants such as inclusion criteria, exclusion criteria, total number in intervention/control groups, sex, age, diagnostic criteria, baseline characteristics and dropouts; (iv) intervention type, intensity, and frequency as well as duration of trial and outcomes specified in the methods; and (v) results. For continuous variables we extracted the number of participants, baseline and post-intervention means with standard deviation for the intervention and control groups. There were no dichotomous variable outcomes. Study characteristics were reported in evidence tables.

4.1.5 Statistical Analysis

For each outcome of interest, we performed a meta-analysis to determine the pooled effect of the intervention in terms of weighted mean differences (WMD) between the post-intervention values of the intervention and control groups.

All data were analysed with a software program (Review Manager 4.2.10) from the Cochrane Collaboration (www.cochrane.org/software/revman.htm). Heterogeneity between trial results was tested with a standard Chi-squared (χ^2) test. The I^2 parameter was used to quantify any inconsistency ($I^2 = [(Q-df) \times 100\%$, where Q is the χ^2 statistic and df are the degrees of freedom). A value for $I^2 > 50\%$ has been considered to be substantial heterogeneity.^[114]

To consider heterogeneity, we used the random-effects model to estimate WMD and 95% confidence intervals. We used the funnel plot method to assess the potential of a publication bias (i.e. the tendency for studies that yield statistically significant results that are more likely to be submitted and accepted for publication).

4.2 Results of the Meta-Analysis

4.2.1 Included Studies and Study Characteristics

Out of 25 potentially appropriate papers selected for closer examination,^[59-62,72,79-90,92,115-121] 13 studies finally met the inclusion criteria.^[59-62,72,79,83,84,87,88,92,115,117] The main reasons for exclusion were as follows: studies did not compare similar groups (e.g. abnormal

glucose tolerance versus normal glucose tolerance),^[80,85,119-121] the study had no control group;^[81,86,89,90] the study was a follow-up;^[116] studies were home-based;^[118] and multiple publications of studies.^[82] The characteristics of the included studies are presented in table I.

All of the final 13 studies selected for the review were RCTs. They were conducted in Australia,^[62,117] Austria,^[61] Canada,^[72] Finland,^[83,87,88] Italy,^[59] Japan,^[84] New Zealand^[92] and the US.^[60,79,115] The studies included involved 513 participants. The number of participants in a single study ranged from 17 to 120, with a pooled total of 425 participants in studies reporting HbA_{1c}; of these, 219 participants received the RT intervention. The mean age of the groups was between 46.8 and 67.6 years.

Detailed descriptions of the exact RT regimens are provided in table I. This systematic review included studies involving the following four types of RT interventions: RT versus non-exercise control;^[60,79,83,84,87,92,115,117] RT plus AET versus AET or non-exercise control;^[59,72,88] RT versus AET;^[61,79,83] and RT plus diet versus diet alone.^[62]

The duration of the interventions ranged from 6 weeks in one study,^[84] 8 to 10 weeks in three studies,^[83,92,117] 4 months in three studies,^[60,61,72] 5 months in two studies,^[79,87] 6 months in one study,^[62] 12 months in two studies,^[59,88] to 2 years in one study.^[115] Most interventions involved three training sessions per week with RT occurring on non-consecutive days. Two studies involved two sessions per week^[87,88] and one short study, five sessions per week.^[84]

Interventions were either progressive RT^[60-62,79,83,84,87,92,115,117] or combinations of RT and AET.^[59,72,88] The percentage of the 1 RM or 10–15 repetition maximum (10–15 RM) were scales used to define the intensity of RT. One set consisted of 10–15 repetitions without interruption, until severe fatigue occurred and completion of further repetitions was impossible. The training load was systematically adapted to keep the maximum possible repetition per set between 10 and 15. A 10–15 RM is equivalent to 70–80% 1 RM for most exercises^[122] but may not be accurate for selected exercises.^[123] The intensity of the

Table I. Characteristics of included randomized controlled resistance training (RT) intervention trials

Study	Sample size	Study design	Study length	RT prescription	Primary findings	Secondary findings
Baldi and Snowling ^[92]	18 T2D men 9 RT, 9 control	RT vs control	3 d/wk for 10 wk	10 exercises; intensity: 10–15 RM; dose: 6 S/MG/W	↓ HbA _{1c} with RT (<i>p</i> = 0.057) ↑ LBM with RT (<i>p</i> < 0.05)	↓ fasting insulin ↓ fasting glucose (<i>p</i> < 0.05) ↔ 2 h glucose or insulin with RT
Balducci et al. ^[59]	120 T2D 62 RT, 58 control	Combined RT + AET vs control	3 d/wk for 1 y	RT: 6 exercises 40–60% 1 RM; dose: 9 S/MG/W; AET: 40–80% HRR; dose: 90 min/wk	↓ HbA _{1c} with RT + AET (<i>p</i> < 0.0001) ↓ BMI (<i>p</i> < 0.0001) ↑ LBM (<i>p</i> < 0.0001)	↑ HDL (<i>p</i> < 0.0001) ↓ LDL, TG ↓ SBP (<i>p</i> < 0.04) ↓ DBP (<i>p</i> < 0.0001)
Brandon et al. ^[115]	31 T2D 16 RT, 15 control	RT vs control	2.6 d/wk for 2 y	50–70% 1 RM 6–9 S/MG/W	↓ FM	
Castaneda et al. ^[60]	62 T2D 31 RT, 31 control	RT vs control	3 d/wk for 16 wk	5 exercises 60–80% 1 RM 9 S/MG/W	↓ HbA _{1c} , FM with RT (<i>p</i> < 0.01) ↑ LBM (<i>p</i> < 0.05)	↓ SBP ↔ HDL, LDL, TG, fasting glucose
Cauza et al. ^[61]	39 T2D 22 RT, 17 AET	RT vs AET	3 d/wk for 16 wk	RT: 8 exercises; intensity: 10–15 RM; dose: 3–6 S/MG/W; AET: 60% $\dot{V}O_{2max}$ 45–90 min/wk	↓ HbA _{1c} with RT (<i>p</i> < 0.01) ↓ FM with RT ↑ LBM with RT	↓ fasting glucose ↓ fasting insulin ↑ HDL, ↓ LDL, ↓ TG ↓ SBP, ↓ DBP with RT
Cuff et al. ^[72]	28 T2D women 10 RT + AET, 9 AET, 9 control	Combined RT + AET vs AET vs control	3 d/wk for 16 wk	RT: 5 exercises; intensity: 12 RM; dose: 6 S/MG/W; AET: 60–75% HRR; dose: 60 min/wk	↔ HbA _{1c} ↑ glucose disposal rate with RT + AET	↓ abdominal visceral and subcutaneous tissue (<i>p</i> < 0.05) in both groups ↔ blood lipids
Dunstan et al. ^[62]	36 T2D 19 RT + WL, 17 WL control	Combined RT + WL vs WL only	3 d/wk for 6 mo	RT: 9 exercises intensity: 75–85% 1 RM; dose: 9 S/MG/W	↓ HbA _{1c} with RT + WL (<i>p</i> < 0.01) ↓ FM in both groups (<i>p</i> < 0.01)	↔ HDL, LDL, TG, fasting glucose ↔ SBP, DBP in both groups
Dunstan et al. ^[117]	27 T2D 15 RT, 12 control	RT (CWT) vs control	3 d/wk for 8 wk	RT: 10 exercises; intensity: 50–55% 1 RM; dose: 6–9 S/MG/W	↔ HbA _{1c} ↓ 2 h glucose ↓ 2 h insulin	↔ fasting glucose, fasting insulin ↔ SBP, DBP
Eriksson et al. ^[83]	22 IGT 8 RT, 7 AET, 7 control	RT (CWT) vs AET vs control	3 d/wk for 10 wk RT, for 6 mo AET	RT: 50–60% 1 RM; dose: 9 S/MG/W; AET: 60% HRR 120–150 min/wk	↔ FM for RT	↔ fasting glucose, fasting insulin ↑ HDL with RT ↔ SBP, DBP

Continued next page

Table 1. Contd

Study	Sample size	Study design	Study length	RT prescription	Primary findings	Secondary findings
Honkola et al. ^[87]	38 T2D 18 RT, 20 control	RT (CWT) vs control	2 d/wk for 5 mo	RT: 8–10 exercises; intensity: 12–15 RM; dose: 4 S/MG/W	↓ HbA _{1c} with RT (p < 0.05)	↓ CHOL, LDL, TG with RT (p < 0.05) ↔ SBP, ↓ DBP
Ishii et al. ^[84]	17 T2D 9 RT, 8 control	RT vs control	5 d/wk for 4–6 wk	RT: 9 exercises; intensity: 50–50% 1 RM; dose: 10 S/MG/W	↔ HbA _{1c} with RT ↔ FM, LBM with RT	↑ glucose disposal rate with RT
Loimaala et al. ^[88]	49 T2D men 24 RT + AET, 25 control	Combined RT + AET vs control	2 d/wk for 1 y	RT: 70–80% 1 RM 6 S/MG/W; AET: 65–75% $\dot{V}O_{2max}$ 60 min/wk	↓ HbA _{1c} with RT (p < 0.05)	↓ SBP with RT + AET
Smutok et al. ^[79]	18 IGR 8 RT, 8 AET, 10 control	RT vs AET vs control	3 d/wk for 5 mo	RT: 12–15 RM 6 S/MG/W; AET: 75–85% HRR 90 min/wk	↔ FM, LBM with RT	↓ 2 h glucose ↓ 2 h insulin

AET = aerobic endurance training; **BMI** = body mass index; **CHOL** = total cholesterol; **CWT** = circuit weight training; **DBP** = diastolic blood pressure; **FM** = fat mass; **HbA_{1c}** = glycosylated haemoglobin; **HDL** = high-density lipoprotein; **HRR** = heart rate reserve; **IGR** = impaired glucose regulation; **IGT** = impaired glucose tolerance; **LBM** = lean body mass; **LDL** = low-density lipoprotein; **RM** = repetition maximum; **SBP** = systolic blood pressure; **S/MG/W** = sets for each muscle group per week; **T2D** = type 2 diabetes; **TG** = triglycerides; **VO_{2max}** = maximum oxygen uptake; **WL** = weight loss; ↑ indicates higher/more, ↓ indicates lower/less; ↔ indicates unchanged.

interventions ranged from 40% 1 RM^[84] to 85% 1 RM.^[62] The maximum numbers of sets for each muscle group per week (S/MG/W) at the end of the intervention programme ranged from four S/MG/W^[87] to ten S/MG/W.^[84] The most common dose of RT at the end of the intervention was six S/MG/W or nine S/MG/W.

4.2.2 Study Quality

The methodological quality of RCTs included in this review was not assessed by assigning a formal scoring system. Rather, key components of methodological quality such as blinding, randomization, compliance and dropouts, are described for each of the studies. Blinding of the people administering the intervention and of the participants performing the exercise is not possible in exercise intervention trials, so blinding of these was not assessed as a quality criterion. Although blinding of the outcome assessment is feasible, no trial reported blinding of the outcome assessors. All selected trials were described as randomized. All studies included in the review reported no significant differences in the main characteristics of the participants at baseline. Compliance with exercise was between 85%^[115] and 90%^[62,83,92] and in some trials more than 90%.^[60,61,72] Compliance with exercise was not mentioned in some studies.^[59,79,84,87,88,117] Dropouts in the intervention group ranged from zero in seven studies,^[72,79,83,84,87,88,92] to two,^[60] four^[61] and six^[117] in one study each, 17–19% in two studies^[59,62] and 45% in one study.^[115]

In this review, HbA_{1c} was used as the principal measure for glycaemic control. Ten of 13 studies measured HbA_{1c}, involving a total of 425 participants^[59–62,72,84,87,88,92,117] of these: 219 participants received the RT intervention; seven of 13 studies measured fasting plasma glucose concentration;^[59–62,83,92,117] four studies reported results of oral glucose tolerance tests;^[61,62,79,117] eight of 13 studies reported results for FM in percentage of body mass^[59,79,84,115] or absolute in kilograms;^[60–62,92] one study reported visceral and subcutaneous adipose tissue;^[72] TG and CHOL were reported in seven studies;^[59–62,83,87,92] six of these also reported HDL-C^[59–62,83,87] and four LDL-C,^[60–62,87] and eight studies provided

data on BP, seven recording both SBP and DBP^[59-62,83,87,117] and one recording only SBP.^[88]

4.2.3 Pooled Effects of RT

Our meta-analysis showed that the pooled effect of RT on HbA_{1c} was a reduction of 0.48% (95% CI -0.76, -0.21). This is both clinically and statistically significant (p<0.0005). FM was reduced by a statistically significant 2.33 kg with RT (95% CI -4.71, 0.04; p=0.05). There was a significant decrease in visceral adipose tissue reported in one study (-119.8 cm², 95% CI -154.8, -84.8; p<0.05). There were no significant differences between the RT group and the control group in CHOL (WMD -7.75 mg/dL, 95% CI -17.02, 1.51; p=0.10), HDL-C (WMD -0.68 mg/dL, 95% CI -3.68, 2.31; p=0.66), LDL-C (WMD -7.72 mg/dL, 95% CI -17.92, 2.48; p=0.14), TG (WMD -18.53 mg/dL, 95% CI -38.43, 1.36; p=0.07) and in DBP (WMD 0.86 mmHg, 95% CI -1.73, 3.45; p=0.51). The change in SBP with RT was statistically significant (WMD -6.19 mmHg, 95% CI -11.38, -1.00; p=0.02). Table II summarizes the pooled results for the intervention effects. Figure 1 shows the results from each study group for HbA_{1c} change (WMD point estimate and 95% CI) in response to RT graphically displayed as a forest plot.

4.2.4 Heterogeneity and Dose-Response Relationship

Of the outcomes tested, there was substantial heterogeneity in the results of trials for the outcomes of HbA_{1c} (I²=87.1%), FM (I²=88.6%), TG (I²=84.8%), CHOL (I²=90.8%), LDL-C (I²=92.2%), HDL-C (I²=82.0%), SBP (I²=94.9%) and DBP (I²=94.4%). The different RT interventions and protocols employed (concerning frequency, duration, intensity and dose), different exercise equipment used and diversity in the initial strength status of the participants in the studies may explain the heterogeneity. Heterogeneity in the results of trials for the outcomes and insufficient data from reviewed RCTs made it difficult to establish dose-response relationships between intensity and volume of RT and the metabolic clustering in patients with abnormal glucose regulation. Regression-based analyses revealed

Table II. Pooled estimates of effect size (95% confidence intervals [CIs]) expressed as weighted mean difference (WMD) for the effect of resistance training on glycaemic control (glycosylated haemoglobin [HbA_{1c}]), fat mass (FM), blood lipids (total cholesterol [CHOL], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglycerides [TG]) and systolic and diastolic blood pressure (SBP; DBP) in overweight/obese adults with type 2 diabetes mellitus

Risk factor	Effect size	95% CI	p-Value	I ²
HbA _{1c} (%)	-0.48	-0.76, -0.21	0.0005	87.1
FM (mg/dL)	-2.33	-4.71, 0.04	0.05	88.6
CHOL (mg/dL)	-7.75	-17.02, 1.51	0.10	90.8
HDL-C (mg/dL)	-0.68	-3.68, 2.31	0.66	82.0
LDL-C (mg/dL)	-7.72	-17.92, 2.48	0.14	92.2
TG (mg/dL)	-18.53	-38.43, 1.36	0.07	84.8
SBP (mg/dL)	-6.19	-11.38, -1.00	0.02	94.9
DBP (mg/dL)	0.86	-1.73, 3.45	0.51	94.4

I²=inconsistency.

no statistically significant dose-response relationships between volume of RT and the metabolic clustering in patients with abnormal glucose regulation; however, there was a tendency towards a greater reduction of SBP and DBP with increasing volume of RT. The only factor that explained part of the heterogeneity was duration of intervention period with a moderate positive impact on HbA_{1c} and DBP with increasing study duration.

4.2.5 Publication Bias

The funnel plot with respect to effect size changes for HbA_{1c}, FM, CHOL, HDL-C, LDL-C, TG, and SBP and DBP responses to RT indicates no asymmetry, suggesting no potential publication bias (figure 2). However, interpretative caution is urged in that the above analyses are based on the context of a limited number of study groups.

4.3 Discussion of the Meta-Analysis

4.3.1 Using RT as a Treatment for Glycaemic Control

An RT intervention resulted in a clinically significant improvement in glycaemic control compared with controls. The decrease of 0.48% HbA_{1c} (ten trials) was achieved over relatively short periods of time, since the shortest studies in the review were of 6- to 8-weeks' duration. Most

studies had a duration of 10 to 20 weeks, and there were three studies with an intervention of 6 months or more. The mean reduction of 0.48% HbA_{1c} achieved compares well with reported reductions achieved through medications. Meta-analysis has shown that metformin can lower HbA_{1c} levels by 0.9% compared with placebo. The clinical significance of a 0.5% decrease in HbA_{1c} can be gauged by studying large prospective intervention studies examining morbidity and mortality outcomes in people with T2D.^[124] Data suggest that a 1% rise in HbA_{1c} represents a 21% increase in risk for any diabetes-related death, a 14% increased risk for myocardial infarction and a 37% increased risk for microvascular complications. The impact of a decrease of 0.5% HbA_{1c} equates to a 50% improvement towards a target value of 7% HbA_{1c} and a 25% improvement towards a normal value of 6% HbA_{1c}, for a person diagnosed with 8% HbA_{1c}. It is unclear whether the improvement in glycaemic control can be maintained in the longer term. In the 6-month post-intervention follow-up reported by one author,^[116] the participants

continuing with supervised RT maintained the improvement in glycaemic control, while in one other 6-month home-based follow-up, the improvements were lost.^[118] The reason could result from the difficulty in motivating people to maintain RT prescriptions as part of a regular lifestyle. The major finding from one study was that completing RT and AET over extended durations will result in similar improvements to glycaemic control.^[61] However, this finding requires further validation, as the RT group appeared to spend a larger volume of time training than the AET group. Another limitation of this study was that participants randomized for the RT group had higher baseline levels for HbA_{1c} than participants randomized for the AET group. Based on this meta-analysis, the greatest improvements to glycaemic control occurred when HbA_{1c} was poor (>8.0%) at baseline. Clinically relevant improvements of 0.5% were generally seen with moderate-high intensity RT or where the duration of training was 10 weeks or longer. The exception to this was a 4- to 6-week application of low intensity RT 5 days per week

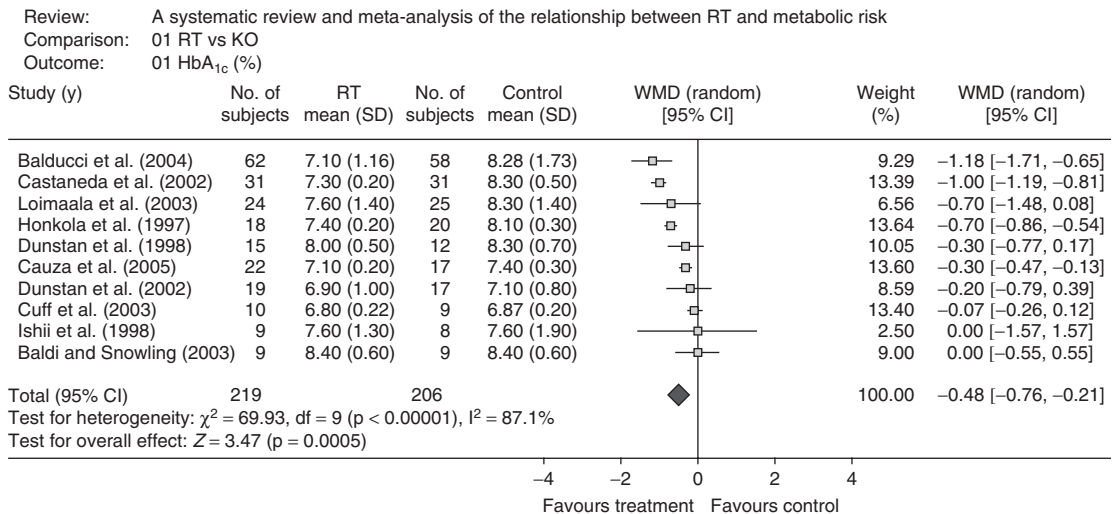


Fig. 1. Forest plot showing the results of a meta-analysis as pooled weighted mean difference (WMD) with 95% confidence intervals (CIs) in glycosylated haemoglobin (HbA_{1c}), for the ten included randomized controlled resistance training (RT) studies. For each RT study, the shaded square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of this effect. The area of the shaded square reflects the relative weight of the study in the meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the ten study groups. Included studies: Honkola et al.,^[87] Dunstan et al.,^[117] Ishii et al.,^[64] Castaneda et al.,^[60] Dunstan et al.,^[62] Baldi and Snowling,^[92] Cuff et al.,^[72] Loimaala et al.,^[88] Balducci et al.,^[59] Cauza et al.^[61] χ^2 =Chi squared; df =degrees of freedom; I^2 =inconsistency; **KO**=control; **RT**=resistance training; **Z**=overall effect.

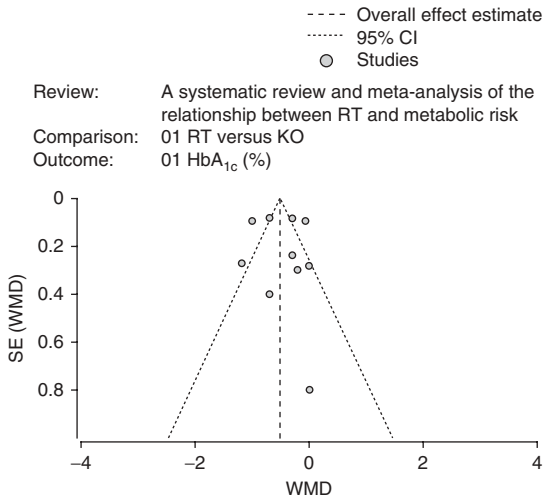


Fig. 2. Funnel plot showing study precision, against the weighted mean difference (WMD) effect estimate with 95% confidence intervals (CIs) for glycosylated haemoglobin (HbA_{1c}). **KO**=control; **RT**=resistance training; **SE**=standard error.

resulting in a 2.0% improvement of HbA_{1c}.^[84] However, participants of the referenced study were of remarkable light weight and had a low BMI, reducing the generalizability of this study. The effect of combining RT with AET on glycaemic control remains unclear, with only one study that made a direct comparison between combined training and isolated AET intervention reporting no effect.^[72] In one study,^[62] the combination of RT and moderate dietary restriction was associated with a 3-fold greater decrease in HbA_{1c} levels after 6 months compared with moderate weight loss without RT, and this was not mediated by concomitant reductions in bodyweight, waist circumference and FM. It is possible that an increase in LBM after RT may be an important mediator of the improved glycaemic control. An increase in the number of GLUT4 transporters is discussed specifically,^[77] because the transporter protein GLUT4 expression at the plasma membrane is related to fibre volume in human skeletal muscle fibres.^[125] One study found the improvement in LBM after a 10-week RT programme had a greater impact on HbA_{1c} levels than the reduction in FM, suggesting that increases in muscle mass improved glycaemic control.^[92] Furthermore, RT-induced

changes in HbA_{1c} have been inversely correlated with changes in the quadriceps cross-sectional area.^[86] It has been proposed that hyperglycaemia has a direct adverse effect on muscle contractile function and force generation.^[126]

4.3.2 Impact on MS Risk Modification

In addition to the decrease in HbA_{1c}, there was a significant overall decrease of 2.3 kg in FM (eight trials) and in visceral adipose tissue.^[72] Thus, RT is contributing to the decrease of one of the major risk factors for the MS. Despite the decrease in fat, there was no decrease in body mass and this probably reflects an increase in muscle mass, which is heavier than adipose tissue. Data show that RT may be an effective alternative to improve body composition and maintain the reduced FM in obese patients after exercise training or energy intake restriction.^[65] The implementation of RT within a dietary intake restriction programme has been studied intensively.^[74,127-130] The addition of RT prevents the loss of LBM, secondary to dietary restriction.^[131,132] RT twice a week increases LBM by 1–2 kg per 6 months and could prevent age-associated loss of LBM.^[54] As a result, RT could prevent age-related decline of resting metabolic rate, which is closely correlated to losses in LBM.^[133] RT contributes to elevations of resting metabolic rate as a result of a greater muscle protein turnover.^[134] Studies of the usefulness of RT in the context of weight loss have had mixed results. Although it is clear that AET is associated with much greater energy expenditure during the exercise session than RT, several studies have shown that regular RT is effective in promoting weight loss in obese persons.^[58,65,135-137] RT appears to provide a unique stimulus to spare catabolism of body protein and thus alter the relationship between the LBM and FM.^[136] An RT intervention did not result in any significant weight loss but could prevent age-associated fat gains over a period of years.^[65] In a recent study, RT (8 weeks, 3 times weekly at 60% 1 RM) significantly changed body mass (+0.58%), percentage of body fat (–13.05%), LBM (+5.05%) and FM (–12.11%) when compared with the control group.^[137] It appears that there is a relationship between RT and BMI, as

indicated in this study, which demonstrated an increase in BMI. Therefore, the use of BMI in ascribing CHD risk should be undertaken with caution in individuals with increased LBM, as would be expected, following RT.

Recently, exercise-induced oxidative stress and homocysteine and cholesterol were analysed in normal-weight and overweight elderly adults after a 6-month RT programme.^[138] Oxidative stress is suggested to be a potential contributor to early and advanced stages of CVD.^[139] Lipid hydroperoxides and homocysteine levels were lower in both the overweight and normal-weight RT groups compared with control groups. The change in muscle strength was associated with homocysteine at 6 months, whereas the change in lipid hydroperoxides was associated with the change in body fat. The present study showed that RT reduces exercise-induced oxidative stress and homocysteine regardless of adiposity, indicating that this protection can be afforded in an older, overweight/obese population as effectively as in healthy elderly adults, which might indicate protection against oxidative insults (i.e. ischaemia). A potential mechanism for RT-induced reduction of oxidative stress could include contraction-induced antioxidant enzyme upregulation.^[140]

An RT intervention resulted in a significant lowering of SBP by 6.2 mmHg (eight trials) compared with the controls, but there was no significant difference between groups in total CHOL (seven trials), HDL-C (six trials), LDL-C (four trials), TG (seven trials) and DBP (seven trials). These results are in conflict with the results of one study that found positive effects of RT on blood lipid levels in elderly women,^[91] while in one other trial,^[93] no significant alterations in blood lipid profiles were documented after 8 weeks of RT (five exercises, three sets at 80% of 10 RM) in healthy, sedentary postmenopausal women. At present, there are few and conflicting data on the effects of RT on blood lipid levels in healthy elderly people and patients with dyslipidaemia.^[141-146] The principal finding of one study was that RT can reduce coronary risk factors without changes in bodyweight or body composition.^[9] Unfortunately, no information is available about the effect of RT on individuals with dyslipidaemia.

Only one of the above-mentioned studies included patients with abnormal lipoprotein-lipid levels.^[144] The RT programme resulted in no significant changes in plasma concentrations of TG, total CHOL and HDL-C.

This meta-analysis confirms that RT does not increase resting BP, as was once thought, and might even have potential benefits on resting SBP. The BP-lowering effect of RT seems to be independent of weight loss and is believed to be mediated via reduced sympathetically induced vasoconstriction in the trained state and decreased catecholamine levels.^[147,148] A decrease of approximately 6.2 mmHg for resting SBP is not insubstantial, since a reduction of as little as 3 mmHg in SBP has been estimated to reduce CHD by 5–9%, stroke by 8–14% and all-cause mortality by 4%.^[149] RCTs examining the effects of RT on resting BP in adults have resulted in mixed findings. A meta-analysis of nine RCTs on mostly dynamic RT revealed a net weight reduction in BP of 3.2/3.5 mmHg associated with RT.^[147] These results are in agreement with two further meta-analyses that also examined the effects of long-term RT on resting SBP and DBP in normotensive and hypertensive adults;^[98,99] however, limitations still exist. No information is available about the effect of RT on hypertensive subjects alone. Only three of the included studies were conducted with hypertensive individuals. Additional studies about the effect of RT in the hypertensive population are needed, as it has been shown that the reduction in BP is more pronounced in patients who are hypertensive at baseline.^[147,150,151]

4.3.3 Dose Response: How Much RT is Needed?

Considering the benefits of RT for major risk factors of the MS, an important question is: how much RT (intensity, duration, frequency and volume) is needed to confer such benefits? Insufficient data from reviewed RCTs and, furthermore, substantial heterogeneity in the results of trials for the outcomes, made it difficult to establish dose-response relationships between intensity and volume of RT and metabolic clustering in patients with abnormal glucose regulation. Improvements in glycaemic control were achieved

over a range of exercise intensities and volumes. For example, improvements in HbA_{1c} were observed following low intensity at 50% 1 RM,^[59,117] moderate intensity at 60–70% 1 RM^[60,61] and high intensity at 75–85% 1 RM.^[62,88] Furthermore, improvements in glycaemic control were observed following low volume (four sets per muscle group per week),^[87] moderate volume (six sets per muscle group per week)^[61,88] and high volume (nine sets per muscle group per week)^[59] of RT. However, we found a small positive correlation between the total duration of RT and changes in HbA_{1c}. Most studies of longer duration (>10 weeks),^[59,60,87,88] but not all studies,^[62] revealed more beneficial effects on glycaemic control than short-term studies (≤10 weeks).^[84,92,117]

We found no dose-response relationship between intensity of RT and glycaemic control in patients with IGT and T2D, but there was a tendency towards a low negative impact of intensity on HDL-C. One study of low intensity (50% 1 RM) observed a greater improvement in HDL-C,^[59] while other studies of high intensities (70–80% 1 RM) revealed no improvements or even diminished HDL-C levels.^[60–62] Regression-based analyses suggest no apparent association between RT frequency and glycaemic control but indicate a trend to a negative correlation for some outcomes of lipid profile in patients with abnormal glucose regulation. One study found LDL-C and TG were more strongly affected when exercising twice a week compared with studies exercising three times per week.^[87]

The effect of RT on resting SBP and DBP appears to be dose dependent, since decreases in resting BP were more pronounced when the RT programme was of high volume. Studies of high volume (nine sets per muscle group per week)^[59,60] revealed more beneficial effects on resting SBP and DBP than studies of low volume (four to six sets per muscle group per week).^[61,87] Relatively modest increases in RT frequency had hypotensive effects, since resting SBP and DBP were further reduced when exercising three times per week compared with twice a week.^[59,60,87,88] However, the referenced studies of low frequency RT were also of low volume and therefore higher frequency RT was superior. Furthermore, we

found a small positive correlation between the total duration of RT and reductions in DBP.

In summary, RT is at least as effective as AET in improving glycaemic control. The skeletal muscle is responsible for up to 40% of total weight and may induce beneficial changes in glycaemic control via muscle mass development. Possible mechanisms could include enhanced muscle contraction-induced glucose uptake in the muscle, increased GLUT4 content and insulin signalling in skeletal muscle in patients with IGT and T2D. Longer intervention duration of RT appears most beneficial, while higher intensity is more likely to have a harmful effect on glycaemic control. This meta-analysis confirms that RT might also have potential benefits on resting BP. The antihypertensive effect of RT is believed to be mediated via decreased sympathetic and increased vagal activity in the trained state. It seems that there is some tendency towards a dose-response relationship between volume of RT and risk factors associated with CVD in patients with abnormal glucose regulation. Progressively higher volumes of RT may reduce resting SBP and DBP more significantly. However, interpretative caution is urged on the fact, that the analyses in this review are based on the context of a limited number of study groups.

5. Conclusions

Although our meta-analysis has several limitations such as the limited number of study groups and the heterogeneity in the results of trials for the outcomes, this systematic review found that RT significantly decreases HbA_{1c} levels in people with abnormal glucose metabolism. Furthermore, there is now good evidence that RT reduces total body FM and visceral adipose tissue independently from dietary restriction. There is now clear evidence that RT elicits significant reductions in resting SBP and tends to improve lipoprotein-lipid profiles. Improved glycaemic control, decreased FM, improved blood lipid profiles and decreased BP are important for reducing microvascular and macrovascular complications in people with metabolic risk. As with increasing adiposity in aging and loss of muscle

mass, the insulin-mediated glucose uptake and TG disposal in the skeletal muscle of elderly persons is reduced and the maintenance of a large muscle mass can contribute to the prevention of T2D, which is associated with CVD. Thus, RT is contributing to the decrease of major risk factors for the MS and should be recommended for the management of T2D and metabolic disorders. Furthermore, although the number of studies on the effects of RT on BP is small, this meta-analysis confirms that RT does not increase BP, as was once thought, and may even have potential benefits on resting SBP. As it is unclear whether the improvement in glycaemic control with RT can be maintained in the longer term, further studies with post-intervention follow-ups of at least 6 months are required to assess whether RT prescriptions can be maintained as part of a regular lifestyle and whether the improved metabolic clustering can be maintained over longer periods.

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