DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2014; **30**: 257–268.
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/dmrr.2488

REVIEW ARTICLE

Changes in insulin sensitivity in response to different modalities of exercise: a review of the evidence

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Received: 4 February 2013
Revised: 10 September 2013
Accepted: 8 October 2013

Summary

Type 2 diabetes is an increasingly prevalent condition with complications including blindness and kidney failure. Evidence suggests that type 2 diabetes is associated with a sedentary lifestyle, with physical activity demonstrated to increase glucose uptake and improve glycaemic control. Proposed mechanisms for these effects include the maintenance and improvement of insulin sensitivity via increased glucose transporter type four production. The optimal mode, frequency, intensity and duration of exercise for the improvement of insulin sensitivity are however yet to be identified. We review the evidence from 34 published studies addressing the effects on glycaemic control and insulin sensitivity of aerobic exercise, resistance training and both combined. Effect sizes and confidence intervals are reported for each intervention and meta-analysis presented. The quality of the evidence is tentatively graded, and recommendations for best practice proposed. © 2013 The Authors. *Diabetes/Metabolism Research and Reviews* published by John Wiley & Sons, Ltd.

Keywords insulin sensitivity; aerobic exercise; resistance training; combined modalities

Introduction

Diabetes is responsible for over one million amputees worldwide each year, is a major cause of blindness and is the largest cause of kidney failure in the developed world [1]. The prevalence of type 2 diabetes (T2D) is alarming. In 2010, 285 million people worldwide were classified as suffering with the disease, a figure that is expected to rise to 438 million by 2030 [2]. Latest available figures indicate that 8.3% of the US population [3] and 5.1% of the UK population have the disease [4]. In 2010, the estimated cost of treatment in the UK was £3.5bn per year [5], with US costs estimated at $174bn in 2007 [3].

Type 2 diabetes is characterized by elevated glucose levels in circulating blood, caused by impairment in glucose tolerance following the development of insulin resistance and relative insulin deficiency. Insulin resistance/reduced insulin sensitivity impair the ability of the muscle cells to take up and store glucose and triglycerides. This results in higher levels of glucose and triglycerides circulating in the blood. In a healthy individual, insulin is secreted in response to these rising levels. However, if this does not occur or has little effect, blood glucose levels increase, leading to T2D as recognized by the American Diabetes Association [22]. This level of impaired glucose control is regarded as a major risk factor of cardiovascular disease [6].

The gold standard measure of insulin sensitivity is ascertained via a hyperinsulinemic euglycaemic clamp – this is however highly invasive and time consuming [7]. As a consequence, other validated methods of data collection are often used to predict or indirectly measure insulin sensitivity; these include glycated haemoglobin (HbA_{1c}) levels in both normoglycaemic [8] and hyperglycaemic patients [9], the oral glucose tolerance test [10], homeostatic model assessment (HOMA) [11] and, finally, a calculation using glycaemic and insulin levels upon fasting [7].

A positive energy balance, indicating more energy being ingested than expended, results from low levels of physical activity (PA) and a high calorific diet, resulting in raised levels of glucose and triglycerides in the blood. The muscular contractions associated with PA have the ability to increase glucose uptake via increased glucose transporter type four (GLUT 4) production and increased insulin signalling within skeletal muscle – thus increasing insulin sensitivity [12]. Using PA to maintain or increase insulin sensitivity in individuals at risk of T2D may help to reduce its incidence and lower the economic burden T2D places upon societies.

A sedentary lifestyle has been associated with increased levels of HbA_{1c} [13]. HbA_{1c} indicates average plasma glucose concentration over time, with higher levels indicating poor blood glucose control and decreases in insulin sensitivity that are associated with T2D [14] ($\geq$6.5% is accepted as a criterion for diagnosis of T2D [13]). It has been reported that lifestyle modifications inclusive of a PA programme are at least as effective in treating T2D as any single pharmacological agent [15], and increased levels of PA are associated with significantly delaying the onset of T2D. Further, changes in insulin sensitivity occur independently of changes in body weight [16]. This suggests that PA might function to decrease hepatic and muscle insulin resistance and increase glucose disposal through a number of mechanisms not necessarily associated with body weight. Such mechanisms might include increased post-receptor insulin signalling and increased glucose transporter proteins [16]. Although it has previously been shown that there is a positive relationship between T2D and obesity [17], these results suggest that the association is the result of the sedentary behaviour associated with both conditions, as opposed to one being a direct cause of the other. These findings could influence the way in which T2D is managed and prevented; that is, hypothetically basing recommendation on the promotion of weight loss alone in the absence of PA might be unproductive.

Chomistek *et al*. [18] found that men who completed greater levels of vigorous PA (>6 METs) – as detailed in the Health Professionals Follow-up Study ($n = 18\,225$) – exhibited lower levels of HbA_{1c}. Furthermore, those reporting that they completed more than 3 h of vigorous PA per week had a 22% lower risk of myocardial infarction, for which lower HbA_{1c} is a potential mediator. Larsson *et al*. [19] found an inverse association ($p < 0.05$) between self-report leisure time PA and insulin resistance ($n = 1745$ – Swedish participants aged 30–74 years), whereas Dwyer *et al*. [20] reported that by increasing daily step count over a 5-year period, insulin sensitivity, measured via HOMA, could be increased [$n = 592$ – mean age 51.4 (men) 50.3 years (women)]. The authors attribute this improvement to reductions in body mass index (BMI) and waist-to-hip ratio. Further and perhaps most significantly, there was a linear relationship between daily step count and improvements in insulin sensitivity. Those sedentary individuals able to alter their behaviour to meet 10 000 steps per day increased insulin sensitivity threefold compared with a similar person who increased to only 3000 steps [20]. These data suggest a dose–response relationship between PA and insulin sensitivity.

The aforementioned evidence suggests that PA can maintain (i.e. prevent decreases in) insulin sensitivity. There may be a dose–response relationship between the volume [20] and energy expenditure [18] of PA and improvements in insulin sensitivity. This would suggest that an increase in volume and intensity of PA might elicit greater improvements in insulin sensitivity. This would essentially entail an increase in PA meeting the minimum number of METs per week.

The terms 'PA' and 'exercise' are often used interchangeably in the literature. However, it was suggested in the Physical Activity and Health report of the US Surgeon General [21] that the two terms denote two different concepts [21]. PA refers to any bodily movement produced by skeletal muscles that results in an expenditure of energy (expressed in kilocalories) and includes a broad range of occupational, leisure and daily activities. Exercise instead refers to planned or structured PA and can be aerobic exercise (AE), resistance training (RT) or combined aerobic and resistance (COM).

In relation to T2D and PA, recent reports by the American College of Sports Medicine (ACSM) [22] and the Physical Activity Guidelines Advisory Committee [23] highlight the need to design a programme that will provide appropriate exercise to attain maximal benefit at the lowest level of risk. However, despite a large number of related publications – PubMed searches post-1965 (01/10/2012) for 'insulin sensitivity exercise' and 'insulin sensitivity PA' located 5329 and 4895 articles, respectively (the authors note many articles will appear in both searches) – the optimal modes, intensities and frequencies of exercise in this context are unknown.

This review synthesizes the current published evidence regarding the effectiveness of AE, RT and COM on improving insulin sensitivity. From this synthesis, evidence-based

DOI: 10.1002/dmrr

recommendations for exercise in the improvement of insulin sensitivity are presented.

Selection criteria

A comprehensive PubMed search was conducted for articles published between 1965 and 01/10/2012 (search terms were 'aerobic exercise', 'resistance training', 'combined aerobic and resistance training' 'intervention' and 'insulin sensitivity'). Reference lists of identified articles were also searched, and potentially relevant additional papers identified. Articles were selected if specific to the nature of this review, in that they assessed the impact of at least one of the different modes of exercise on insulin sensitivity in healthy or T2D participants. More specifically, articles were only selected if they contained data regarding the mode, intensity, frequency and duration of exercise undertaken (Table 1).

The findings of all studies meeting the inclusion criteria are presented in the sections later. These are classified by AE, RT and COM. By including in the present article only those articles providing details of the specific exercise completed, the most effective interventions are identified, and evidence-based exercise recommendations made. In an attempt to ensure the recommendations made are relevant to the general population and specifically those suffering from T2D, investigations in which participants have underlying and unrelated conditions for which impaired insulin sensitivity is not a risk factor, and chronic diseases such as cancer [24] have been excluded. Studies involving participants with T2D and the metabolic syndrome (MetS) (clustering of multiple, partially or fully expressed metabolic abnormalities such as hypertension, dyslipidemia, obesity and impaired glucose tolerance [25]) have been included [26].

The interventions were evaluated by calculating the Cohen's *d* [27] value (Table 2), presented visually in the Forest charts (Figures 1 and 2). All exercise interventions reviewed that present the mean and standard deviation of data pre-intervention and post-intervention have been included in this analysis. It has not been possible to conduct a full meta-analysis upon this data set because of the varying methods with which insulin sensitivity has been measured (Table 2).

Aerobic exercise

Lehman *et al*. [28] reported that there was absolutely no alteration in HbA_{1c} following a 13-week intervention incorporating 90-min sessions of AE three times a week at an intensity averaging 50–70% VO_{2max} in participants with well-established (7.8 years) T2D. The exercise intervention did however protect against HbA_{1c} increases reported in the control group, suggesting that although significant improvements could not be made, the management of blood glucose did improve. Similar participants (T2D average 7.1 years) were recruited by Rönnemaa *et al*. [29] who reported significant reductions in HbA_{1c} following AE at an intensity of 70% VO_{2max} for 45 min six times per week for 8 weeks – indicating that an increased frequency of exercise training will reduce HbA_{1c} even in those with long-standing T2D. Mourier *et al*. [30] also elicited a significant decrease in HbA_{1c} in T2D participants following an intervention lasting 10 weeks. The intensity of AE was set at 75% VO_{2peak}, and participants completed three 55-min sessions a week. Raz *et al*. [31] replicated these findings, that is, a significant reduction in HbA_{1c} in participants without T2D with an intervention also incorporating 55-min AE sessions three times each week, although at a lower intensity of 65% VO_{2max} – the intervention did last 2 weeks longer however.

Kohno *et al*. [32] reported that within hospitalized hypertensive patients, significant reductions in plasma insulin were observed following exercise involving only a 3-min warm-up, a 6-min cycle at 75% VO_{2max} and a 3-min cool down, performed four times daily for 3 weeks. This improvement has added significance as decreases in insulin sensitivity lead to a greater retention of magnesium and as a consequence increases in blood pressure [32],

Table 1. Article selection criteria and search methodology

Article search methodology		
Selection criteria	• Original published research • 1965–01/10/2012	
		Articles located
PubMed search terms	• Aerobic exercise intervention insulin sensitivity • Resistance training intervention insulin sensitivity • Combined aerobic and resistance training intervention insulin sensitivity	1104
Filtering	• Randomized controlled trials • Single group interventions • Specific detail of mode, intensity, frequency and duration of exercise	30
Final Checks	• Examination of identified papers reference lists for other articles meeting selection criteria	34

DOI: 10.1002/dmrr

Table 2. Interventions effect size (Cohen's *d*) and 95% confidence interval (lower and upper)

Author	*n*	Mode	Measure	Effect size	Lower CI	Upper CI
T2D participants						
Lehmann *et al*. [28]	29	AE	HbA_{1c}	0.000	−1.012	1.012
Rönnemaa *et al*. [29]	25	AE	HbA_{1c}	0.571	−0.367	1.510
Mourier *et al*. [30]	21	AE	HbA_{1c}	1.840	0.610	3.070
Raz *et al*. [31]	40	AE	HbA_{1c}	0.291	−0.511	1.093
Van Dijk *et al*. [34]	30	AE	FBG	2.286	1.077	3.495
Vind *et al*. [39] (T2D)	26	AE	IMGD	1.214	1.013	1.416
Jorge *et al*. [43]	48	AE	FPG	0.511	0.269	0.753
Jorge *et al*. [43]	48	RT	FPG	0.401	0.192	0.610
Jorge *et al*. [43]	48	COM	FPG	0.318	0.089	0.548
Honkola *et al*. [44]	38	RT	HbA_{1c}	0.091	-o.925	1.107
Dunstan *et al*. [45]	27	RT	FPG	0.235	−0.667	1.138
Castaneda *et al*. [47]	62	RT	HbA_{1c}	4.400	2.603	6.197
Cauza *et al*. [48]	22	RT	HbA_{1c}	1.263	0.166	2.360
Kwon *et al*. [50]	28	RT	HbA_{1c}	0.333	−0.711	1.377
Brooks *et al*. [51]	62	RT	HbA_{1c}	0.667	−0.333	1.666
Tessier *et al*. [53]	39	COM	OGTT	0.377	−0.324	1.078
Balducci *et al*. [54]	120	COM	FPG	0.742	0.504	0.980
Tokmakidis et al. [55]	9	COM	HbA_{1c}	0.593	−0.457	1.642
Sigal *et al*. [57]	251	AE	HbA_{1c}	0.287	−0.752	1.326
Sigal *et al*. [57]	251	RT	HbA_{1c}	0.201	−0.826	1.227
Sigal *et al*. [57]	251	COM	HbA_{1c}	0.594	−0.478	1.666
Larose *et al*. [59]	251	AE	HbA_{1c}	0.596	−0.452	1.643
Larose *et al*. [59]	251	RT	HbA_{1c}	0.445	−0.584	1.474
Larose *et al*. [59]	251	COM	HbA_{1c}	0.902	−0.191	1.996
Balducci *et al*. [60]	606	COM	HbA_{1c}	0.336	−0.726	1.398
Mean effect size (T2D participants)				0.780	−0.112	1.671
Non-T2D participants						
Magkos *et al*. [33]	30	AE	HOMA	0.551	−1.871	2.913
Babraj *et al*. [35]	16	AE	CI	3.273	2.822	3.723
Hood *et al*. [36]	7	AE	FPI	0.469	−0.573	1.51
Vind *et al*. (2011) (non-T2D)	26	AE	IMGD	2.808	2.602	3.013
Totsikas *et al*. [42]	219	AE	OGTT	0.311	−0.441	1.063
Hansen *et al*. [49]	18	RT	2HGLT	0.366	−0.645	1.376
Schrauwen-Hinderling *et al*. [56]	14	COM	FBG	3.000	1.349	4.651
Mean effect size (non-T2D participants)				1.540	0.463	2.607

CI, Cederholm index, FBG, fasting blood glucose; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HbA_{1c}, glycated haemoglobin; HOMA, homeostatic model assessment; IMGD, insulin-mediated glucose disposal, OGTT, oral glucose tolerance test; 2HGLT = 2-h glucose load test.

although could only be feasibly replicated in highly controlled environments such as hospitals because of the high frequency of exercise training.

Magkos *et al*. [33] demonstrated that an excess of 1 hour of moderate intensity exercise at 60% VO_{2max} was required to improve whole body basal insulin sensitivity. The same authors identified a curvilinear relationship between energy expenditure and insulin sensitivity in single bouts of exercise in recreationally active, non-obese men, whereby those expending the most energy saw the greatest benefits, providing further indications that insulin sensitivity is related to energy expenditure.

Van Dijk *et al*. [34] investigated whether there was any benefit in exercising daily when compared with every other day if energy expenditure was controlled. No significant between-group differences were observed in reductions in fasting blood glucose (both were significantly improved by the intervention). Participants were asked to cycle for either 60 min every other day at 50% maximal exertion or 30 min every day; thus, the energy expenditure was controlled between the two groups. This suggests that although energy expenditure is critical, everyday exercise may not elicit additional benefits over exercise every 2 days, whilst allowing time for recovery and presenting a far more palatable public health message.

High intensity exercise has been presented as an effective and time efficient way of improving insulin sensitivity [35]. Babraj *et al*. [35] implemented a protocol that consisted of four to six 30-s cycle sprints three times a week. This was shown to increase insulin sensitivity by 23% in young participants (mean age = 21 ± 2) of normal weight (mean BMI = 23.7 ± 3.1 kg/m^2) in just 2 weeks. It must be noted however that this type of exercise may not be appropriate for some populations who may be at risk from such high levels of exertion.

This is a factor considered by Hood *et al*. [36] who designed a protocol for older, sedentary and overweight

DOI: 10.1002/dmrr

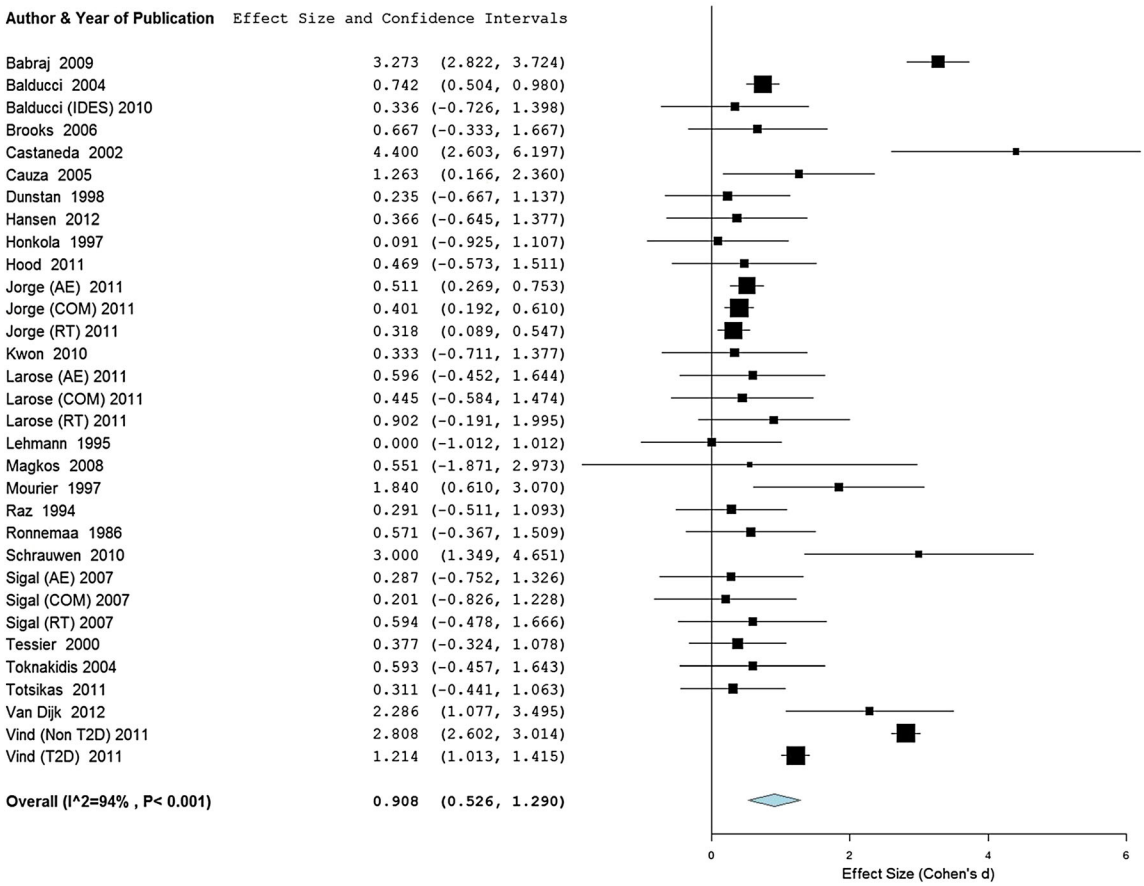


Figure 1. Forest plot describing effect sizes of interventions described (where possible). Confidence intervals calculated at 95%. Created using – metafor: Viechtbauer, Wolfgang. 'Conducting meta-analyses in R with the metafor package'. Journal of 36 (2010)

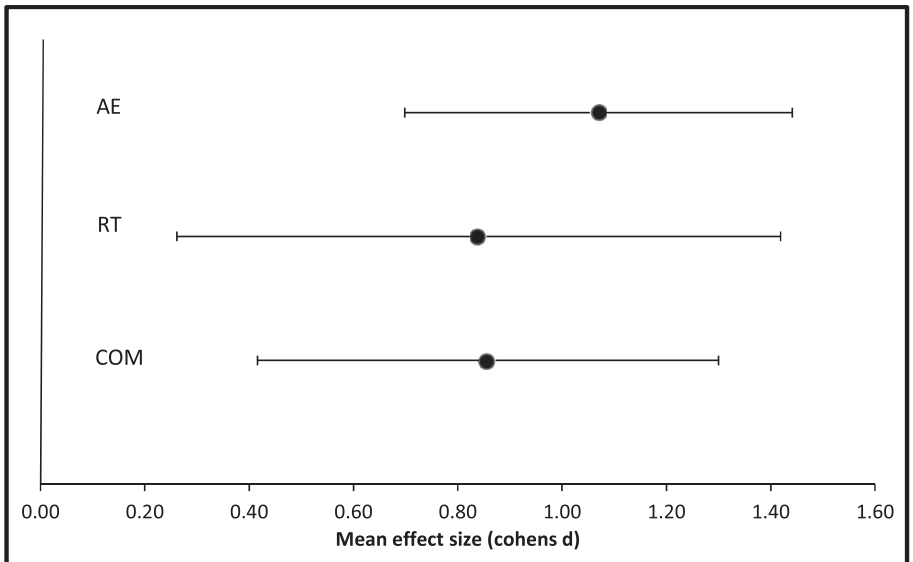
participants (mean age = 45 ± 5, mean BMI = 27 ± 5 kg/m^2) that consisted of six sessions of 10 times 1-min cycles at 60% peak power separated by 1-min rest intervals. GLUT 4 protein content increased by 260%, whereas insulin sensitivity improved by 35% after 2 weeks of training (three sessions per week). A combination of low intensity cycling and two all-out sprints increasing from 10 to 20 s improved insulin sensitivity by 28% after 6 weeks of training [37]. Metcalfe *et al*. reported that the average rate of perceived exertion score for each session was 13 and that adherence was 97%, an important consideration when designing public health interventions.

These studies suggest that customizing interval training for differing individuals/populations may present a practical and time-efficient strategy for improving glycaemic control. When all-out exercise is not feasible, that is, in the elderly or new to exercise, the intensity can be lowered to 60% maximal, and duration increased to 1 min and still be effective [36].

Yfanti *et al*. [38] investigated whether antioxidant supplementation in healthy physically active men ($n = 21$) could enhance the effects of aerobic endurance training upon insulin sensitivity. It was found that following 12 weeks of training five times a week, insulin-stimulated glucose uptake increased by 17.2% in the supplementation group. The placebo group improved by 18.9%. Although these data suggest no beneficial effects of antioxidant supplementation upon insulin sensitivity, clear effects of exercise were evident. In all participants, these improvements were augmented by significant increases in GLUT 4, hexokinase II and protein kinase B (Akt), which play key roles in glucose metabolism. Vind *et al*. [39] propose similar mechanisms for the improvements in insulin-mediated glucose disposal observed following an aerobic training programme consisting of 10 weeks training on a stationary cycle four to five times a week at approximately 65% VO_2max. Subjects were obese, the experimental group with T2D ($n = 26$) and normoglycaemic controls. Significant improvements were observed in both groups (~20%), but the glucose disposal rates of the diabetic patients remained 38% lower than their non-diabetic counterparts. This suggests that although insulin sensitivity was increased, 10 weeks is not long enough to improve glucose disposal to non-T2D levels.

Not all aerobic training programmes are associated with improvements in insulin sensitivity. Mujumdar *et al*. [40]

DOI: 10.1002/dmrr



Exercise Modality	Effect size	Lower CI	Upper CI
Aerobic Exercise (AE)	1.07	0.7	1.44
Resistance Training (RT)	0.84	0.26	1.42
Combined Aerobic & Resistance Training (COM)	0.86	0.42	1.30

Figure 2. Mean effect size and 95% confidence interval per exercise modality

implemented a 6-month programme that involved progressive marathon running training (6 miles per week increasing over time to 55) that did not significantly alter HOMA insulin resistance scores in middle-aged untrained participants. Given the findings earlier and elsewhere, this is surprising and might suggest either a chance outcome or even hint at publication bias in the area (i.e. there may be other unpublished data also suggesting a null effect. This is of course speculative). Either way, the findings in question warrant replication.

Bacchi *et al*. [41] compared supervised AE [three times a week over 4 months at 60–65% heart rate (HR) reserve] to RT (three times a week over 4 months at 70–80% 1RM – nine exercises covering all major muscle groups), both significantly reduced HbA_{1c}. Effects did not differ between groups but were predicted by baseline HbA_{1c} levels, subsequent increases in cardiorespiratory fitness (CRF) and reductions in truncal fat. These findings are at odds with those of Totsikas *et al*. [42] who reported that improvements in insulin sensitivity were more likely in those with the highest CRF at baseline – and therefore likely poorer glycaemic control – following a lifestyle intervention. The authors provide little detail of the mechanisms that support this finding other than that the intervention was only partly supervised and that the participants with the greatest CRF were more compliant to exercise recommendations.

Jorge *et al*. [43] found AE to be less effective than RT or COM in a comparative study. However, T2D patients who completed 60 min of cycling at an intensity relative to lactate threshold three times a week for 12 weeks were able to significantly lower fasting plasma glucose.

Based upon the evidence of most published research meeting the selection criteria of this review, it can be concluded that AE is effective in improving insulin sensitivity at a variety of intensities and to differing degrees. Significant improvements can be elicited by interval training (high intensity exercise separated by rest intervals) [35,36] as well as continuous effort [33]. As one study suggests, however, there may be other training interventions that are as effective or even more effective at improving insulin sensitivity, which could include RT and COM.

Resistance training

Honkola *et al*. [44] implemented RT within a circuit training session twice a week for 22 weeks – each session lasting 45 min and incorporating two sets of 12–15 repetitions. It was reported that there were no alterations in HbA_{1c} levels. Similar to Lehman *et al*. [28], participants had well-established T2D (average 8 years). Once again, there was an increase in HbA_{1c} found in the control group however – suggesting that glycaemic control was improved if not overall HbA_{1c} levels.

Dunstan *et al*. [45] investigated the effect of circuit weight training at 55% 1RM in 27 adults (mean age

DOI: 10.1002/dmrr

51 years) three times a week for 8 weeks. The training programme elicited significant strength improvements in all exercises (demonstrating training effect) along with improvements in glucose and insulin levels following a 12-h fast when compared with controls [45]. Dunstan *et al*. [46] followed this work with an investigation incorporating a higher intensity RT – 75–80% 1RM – in older participants with T2D ($n = 36$ aged between 60 and 80 years) for an increased duration of 26 weeks. Both RT and the control group incorporated a weight loss programme. HbA_{1c} was reduced to a significantly greater extent following RT at both 13 and 26 weeks. There was no difference between body weight and fat mass reduction between groups. RT increased lean mass however, although it was reduced following the weight loss programme alone. This data further strengthen the argument that weight loss interventions to reduce the risk of T2D are flawed unless attempts are made to maintain muscle mass via RT. Eighty per cent 1RM was also the training intensity employed by Castaneda *et al*. [47] in elderly T2D subjects ($n = 62$ mean age 66 years) three times a week over a shorter intervention period of 16 weeks. HbA_{1c} was again significantly reduced with muscular glycogen stores increased, suggesting greater insulin action; no such changes were evident in the control group.

Cauza *et al*. [48] compared the effects of a 4-month hypertrophic strength training programme with endurance training at 60% VO_{2max} upon measures of insulin sensitivity. Participants had T2D and trained on three non-consecutive days of the week. The RT group reduced HbA_{1c} by 8.3% and significantly reduced blood glucose levels and insulin resistance. No such improvements were found in the AE training group.

Maximal RT (five sets, three to four repetitions at 60–85% 1RM) was compared with endurance RT (three sets, 12–15 repetitions at 45–65% 1RM) by Hansen *et al*. [49]. The intervention lasted 4 months, and all subjects had impaired glucose tolerance at baseline. It was observed that both interventions decreased insulin resistance but by differing mechanisms. Maximal RT increased muscular glucose uptake capacity, whereas endurance RT increased the insulin sensitivity of the muscles. Kwon *et al*. [50] investigated the effectiveness of low intensity RT (40–50% 1RM) and were unsuccessful at improving insulin sensitivity tested via the insulin tolerance test in overweight participants with T2D. The training was conducted over a 12-week period, with exercise three times per week, suggesting that the intensity was the determinant factor and that intensities of over 50% are required to generate a significant response unless supplemented with increases in sets and repetitions [49].

Brooks *et al*. [51] investigated the effects of 16 weeks RT – 60–80% 1RM (weeks 1–8) and 70–80% 1RM (weeks 10–14) compared with conventional care in 62 T2D community-dwelling individuals over the age of 55 years. Insulin sensitivity (measured via HOMA and HbA_{1c}) and muscle quality, that is, the strength per unit of muscle mass, were both significantly improved compared with controls.

Possible mechanisms by which insulin action increases with exercise have been attributed to increased expression of GLUT4 and other signalling proteins [26]. Holten *et al*. [26] investigated the mechanisms behind improvements in insulin sensitivity in subjects with T2D by employing an RT intervention (weeks 1 + 2 50% 1RM, weeks 3–6 70–80% 1RM – three sessions per week) in one leg only. Muscle biopsies taken post-intervention showed increases in GLUT4 and various insulin signalling protein activity levels in the trained leg only. This suggests that the improvements in insulin action were a result of local physiological adaptation. That adaptations occurred locally have implications for the use of RT as a method of increasing insulin sensitivity; it implies that large muscle groups should be trained to stimulate the greatest improvements and, furthermore, that improvements will be greater if more muscles are activated.

Further mechanisms and inhibitors to RT upon insulin sensitivity were found when Layne *et al*. [52] compared RT subjects with and without the MetS. Eight weeks RT elicited improvements in both strength and stamina in all subjects. Insulin sensitivity however was only improved significantly in those without MetS. Layne *et al*. attribute these differences to changes in GLUT 4 levels, which increased 67% in non-MetS sufferers compared with 36% in the MetS group. Further, muscle 5 adenosine monophosphate-activated protein kinase rose 43% in non-MetS and only 8% in MetS. Conversely muscle mammalian target of rapamycin was higher in the MetS sufferers than in the non-MetS sufferers, suggesting that the higher activation of mammalian target of rapamycin inhibited the training-related increases in 5 adenosine monophosphate-activated protein kinase in those suffering from MetS, which would have increased GLUT 4 and hexokinase II levels and in turn increased glucose uptake by the muscles [52].

The evidence presented earlier suggests that RT is effective in improving insulin sensitivity when the intensity is above 50% 1RM and that adaptations are made locally in the trained muscles.

Combined modalities

By combining AE and RT, it may be possible to obtain greater increases in insulin sensitivity than with either AE or RT alone. This was the case when AE, RT and

DOI: 10.1002/dmrr

COM and their impact upon muscle insulin signalling in T2D patients were investigated [43]. Jorge *et al*. [43] investigated the effect of a 7-min exercise RT circuit incorporating large muscle groups completed three times a week over 12 weeks, finding it to improve insulin resistance index scores by 65%. The addition of AE to the RT circuit elicited significantly greater improvements however – a 90% improvement in insulin resistance index scores.

Tessier *et al*. [53] combined AE at 60–79% HR max and RT (two sets of 20 repetitions) into sessions lasting 60 min, three times a week for 16 weeks. Significant improvements were reported in the oral glucose tolerance test. Balducci *et al*. [54] investigated 30 min of AE at 40–80% heart rate reserve and 30 min of RT 40–60% 1RM (reassessed every 3 weeks) when completed three times a week by sedentary individuals. After 1 year, significant reductions in fasting blood glucose were observed, decreasing by 36 mg/dl. This suggests that previously sedentary individuals combining AE and RT, even at low intensities, can have positive outcomes, although the intervention period was particularly long.

A COM intervention lasting only 4 months was employed by Tokmakidis *et al*. [55] with female T2D post-menopausal subjects. The frequency and intensity of exercise employed were higher than those of the previously cited study – two AE sessions per week beginning at 60–70% heart rate max and increasing to 70–80% after 2 months and two RT sessions a week at 60% 1RM (three sets of 12 repetitions). HbA_{1c} levels decreased by 12.5%, whereas glucose tolerance improved by 38%.

Schrauwen *et al*. [56] investigated an even shorter 12-week intervention with obese but non T2D subjects (mean BMI = 29.9 ± 0.01 kg/m^2). The intervention combined 30-min AE at 55% VO_2max and RT at 75% 1RM (two sets × eight repetitions, following eight repetitions at 55% warm-up) and was completed three times a week. Fasting blood glucose concentrations were lowered from 6.3 ± 0.2 to 5.7 ± 0.2 mmol/L, and HbA_{1c} levels significantly improved. These findings suggest that positive effects can be observed following relatively short intervention periods ($\geq$12 weeks) when incorporating both aerobic and RT in the same exercise session.

The three modes of exercise training assessed in this review were compared by Sigal *et al*. [57] in a randomized controlled trial involving participants ranging in age from 39 to 70 years. In this investigation, the COM group completed the full AE and RT programmes (AE: 15–20 min 60% HR max progressing to 45 min 75% HR max three times a week RT. Two/three sets at max weight lifted seven to nine times, three times a week), and consequently, the training volume was far greater than in the other groups. This was reflected in the results, which showed that although all three training modes were effective in lowering HbA_{1c}, the COM approach was the most effective, supporting the previously established dose–response relationship between PA volume and insulin sensitivity improvements [58].

In a more recent study, Larose *et al*. [59] correlated HbA_{1c} with increases in CRF. The COM training programme elicited an increase in $VO2_{peak}$ and ventilatory threshold and, consequently, significantly decreased HbA_{1c} levels. AE and RT also elicited positive effects on glucose control independently, although these effects were smaller than the COM training programme. However, as with the previous study, it is not possible to compare the respective effects of each programme independently because the COM group employed the full AE and RT programmes, which would have increased the overall volume performed. On the basis of the dose–response relationship between exercise volume and insulin sensitivity, it can come as little surprise that the effects were greater in conditions in which the overall volume of exercise was greater [20].

The Italian Diabetes and Exercise Study [60] demonstrated the effectiveness of a combined protocol compared with PA alone in 606 sedentary subjects with T2D and MetS. Subjects were randomized into one of the two groups, a control group who received counselling only or an exercise group who completed aerobic and RT in a structured environment twice weekly for 12 months. HbA_{1c} levels were observed to be lower in the exercise group along with several other markers of cardiovascular health. Although the counselling-only group increased their PA to the recommended dosage of five times 30-min PA a week, there was no significant impact upon HbA_{1c} or cardiovascular health profile. This suggests that greater levels of PA are required to improve the health status of individuals with MetS than is currently recommended [61] and that a supervised, structured combined exercise programme will be effective if administered properly.

The earlier evidence suggests the potentially substantial effect that combining aerobic and RT might have upon insulin sensitivity in both healthy and T2D individuals. These data do not indicate however whether it is the volume of exercise or the modality that affects insulin sensitivity and glycaemic control. Further to this, there is an inconsistency between the ways exercise sessions are structured; that is, some studies incorporate AE and RT into the same session [54,56,60], whereas others place the different modalities in different exercise sessions [55,57,59]. A similar problem is evident in relation to the order in which the different exercises are completed when combined. Further large-scale studies, controlling the volume of AE, RT and COM exercise programmes, are required, along with investigations into the differing effect of AE and RT in different orders and structured together or separately before definitive statements can be made.

DOI: 10.1002/dmrr

Table 3. Evidence categories. Modified from American College of Sports Medicine and evidence grading for clinical practice recommendations for the American Diabetes Association [22]

ACSM evidence categories		
Evidence category	Source of evidence	Definition
A	Randomized, controlled trials (overwhelming data)	Provides a consistent pattern of findings with substantial studies
B	Randomized, controlled trials (limited data)	Few randomized trials exist, which are small in size.
C	Nonrandomized trials, observational studies	Outcomes are from uncontrolled, nonrandomized and/or observational studies.
D	Panel consensus judgement	Panels expert opinion when the evidence is insufficient to place it in categories A–C

ACSM, American College of Sports Medicine.

Evidence grading

To derive the tables of exercise recommendations later, PA was classified (i.e. AE, RT and COM) and graded based upon the level of evidence provided and extent to which insulin sensitivity is improved. This grading is based upon the system implemented by the American Diabetes Association and ACSM in their joint position stand [22] (Table 3). The grading is intended to highlight the extent to which different modes of exercise have been shown in the literature to improve insulin sensitivity in multiple populations and through a wide range of interventions (Table 4).

Table 4. Evidence grading for different exercise modalities based upon evidence examined

Current level of evidence – insulin sensitivity			
Mode of exercise	Number of papers located in PubMed search(1104)	Number of papers assessed(34)	Level of evidence
Aerobic exercise	845	16	A
Resistance training	237	10	B
Combined training	22	8	B

Exercise recommendations

Based upon the exercise detailed in the earlier research and the effect of this exercise on insulin sensitivity, exercise recommendations have been formulated (Table 5). Interventions that have demonstrated particular effectiveness, that is, high intensity AE [35] and COM [60], have been incorporated, whereas interventions where particular intensities have been compared the most effective have been recommended. The evidence presented for PA suggests a dose–response relationship between volume of activity and improvements in insulin sensitivity; therefore, the established minimum amounts (30 min of PA five times weekly) recommended by the ACSM [61] are proposed as a minimum. These evidence-based PA/exercise recommendations should aid in the prescription and delivery of exercise as a measure to prevent and manage T2D.

Table 5. Evidence-based exercise recommendations for maintaining/improving insulin sensitivity in different demographics

Insulin sensitivity: exercise recommendations	
Healthy (Insulin sensitivity maintenance)	Increase PA to more than 30 min per day five times a week [22,58]. Include high intensity aerobic exercise (>75%VO2) [35] three times a week combined with strength training in all major muscle groups [26] at 70% 1RM [48] twice a week separated by more than 24 h [34].
With type 2 diabetes (Insulin sensitivity improvement)	Increase PA to more than 30 min per day five times a week [22,58]. Include long duration (>1 h) moderate intensity (60% VO2max) [33] aerobic training three times a week combined with low intensity and high repetition resistance training (50–60% 1RM) [50] in all major muscle groups [26] twice a week separated by more than 24 h [34].
Those with type 2 diabetes and limited mobility (Disabled, elderly populations, etc.)	Increase PA as much as is feasible [58]. Include low intensity aerobic exercise (40–80% HR reserve)/PA [54] combined with resistance training at low intensity 50–55% 1RM [50] in all major muscle groups [26] three times a week separated by more than 24 h [34].

PA, physical activity; HR, heart rate.

DOI: 10.1002/dmrr

Conclusion

This review supports the proposal that PA is beneficial in improving metabolic control in general and in improving insulin sensitivity specifically.

Regular leisure time PA can maintain insulin sensitivity and improve glycaemic control in those with T2D. There may be a dose–response relationship between the intensity and duration of PA and improvements in insulin sensitivity, in which case the progression to higher levels of systematic PA (i.e. exercise) may elicit greater benefits.

Aerobic exercise appears effective in improving insulin sensitivity even though there is no present evidence to suggest that those benefits transcend those of lifestyle PA unless high intensities are implemented. Interval training has been shown to be particularly effective at both moderate and high intensities, prescribed according to the participant's ability to meet demands of the exercise.

Evidence suggests that RT is effective, most likely because of an increase in muscle GLUT4 and in various insulin signalling protein activity levels in the trained muscles. RT seems to be effective at intensities above 50% of 1RM, a fact that is reflected in the recommendations for exercise training in subjects with T2D presented in this review.

It appears that combining AE and RT is the most efficient training strategy in improving insulin sensitivity, although further research controlling the volume of training is warranted.

This review confirms the effect of different modalities of exercise in improving insulin sensitivity. Having clearly considered the baseline condition of their patients, clinicians should consider the possibility of prescribing COM training to obtain the optimal benefits in their patients.

Conflict of interest

None declared.

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