Annals of Physical and Rehabilitation Medicine xxx (2018) xxx–xxx

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Review

Exercise and insulin resistance in type 2 diabetes mellitus: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 10 July 2018
Accepted 16 November 2018

Keywords:
Insulin resistance
Homa-IR
Fasting insulin
Glycated hemoglobin
Type 2 diabetes mellitus
Aerobic exercise
Resistance exercise

ABSTRACT

Background: Insulin resistance is a determining factor in the pathophysiology of type 2 diabetes mellitus (T2DM). Exercise is known to improve insulin resistance, but a systematic review of the literature is lacking.
Objective: This systematic review and meta-analysis focused on identifying evidence for the effectiveness of a structured exercise intervention program for insulin resistance in T2DM.
Methods: We searched MEDLINE via PubMed, CINHAL, Scopus and Web of Science, and the Cochrane Central Register of Controlled Trials for reports of studies on fasting insulin, homeostatic model assessment for insulin resistance (Homa-IR), fasting blood sugar, glycated hemoglobin and body mass index in patients with T2DM and healthy controls that were published between 1990 and 2017. Data are reported as the standardized mean difference or mean difference with 95% confidence intervals (CIs).
Results: Among 2242 records retrieved, only 11 full-text articles were available for meta-analysis. Data for 846 participants were analyzed, 440 in the intervention group, and 406 in the control group. The mean difference for fasting insulin level was −1.64 (95% CI; −3.38 to 0.10), Homa-Ir 0.14 (−1.48 to 1.76), fasting blood sugar −5.12 (−7.78 to −2.45), hemoglobin A1c 0.63 (−0.82 to 2.08) and body mass index −0.36 (−1.51 to 0.79).
Conclusion: The evidence highlights the effectiveness of a structured exercise intervention program for insulin resistance in T2DM with a moderate level 2 of evidence.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by chronic hyperglycemia associated with impaired carbohydrates, lipids, and protein metabolism with lack of insulin secretion or decreased sensitivity to insulin metabolic effects [1]. The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly around the world and parallels the increase in obesity prevalence. In 2011, an estimated 366 million people had diabetes, and that number is expected to increase to 552 million by 2030 [2]. T2DM complications are among the leading causes of morbidity and mortality. The long-term complications can be delayed by taking medications as prescribed along with a healthy lifestyle (i.e., diet and physical activity) [1].

Insulin resistance (IR) impairs the ability of muscle cells to take up and store glucose and triglycerides, which results in high levels of glucose and triglycerides circulating in the blood [3]. IR is commonly present in older adults but has become increasingly prevalent at all ages, including middle-aged individuals who are overweight and sedentary [4]. IR is typically defined as decreased sensitivity and responsiveness to insulin-mediated glucose disposal and inhibition of hepatic glucose production [5]. IR plays a significant pathophysiologic role in T2DM. It is commonly associated with visceral adiposity, glucose intolerance, hypertension, dyslipidemia, endothelial dysfunction and elevated levels of markers

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https://doi.org/10.1016/j.rehab.2018.11.001
1877-0657/

of inflammation [5]. IR itself has been shown to significantly increase the incidence and prevalence of cardiovascular disease in individuals with T2DM [6]. Hyperglycaemia causes damage to muscle cells, which results in loss of strength and mass. Loss of muscle strength is also a significant predictor of physical function limitation and disability in DM. It is associated with excess physical disability in older adults, especially in lower-extremity mobility tasks. However, the relation between DM and loss of muscle strength has not been adequately studied [7].

Exercise training and physical activity have been considered a cornerstone in the prevention and treatment of T2DM. Along with glycemic control, exercise has a number of benefits, such as decreasing IR and improving aerobic capacity, muscular strength, body composition, and endothelial functions [5]. Although exercise is effective in improving glycemic control, blood lipid profiles, and other outcomes in T2DM, the effectiveness of different types of exercise is less known.

Aerobic exercise is traditionally the most-studied exercise; it recruits large groups of muscles and includes walking, cycling, swimming, and jogging [8]. However, 80% of people with T2DM are overweight or obese, and many have mobility problems, peripheral neuropathy, visual impairment, or cardiovascular disease. For this population, achieving the required volume and intensity of aerobic exercise may not be easy, and resistance training may be more efficient. Resistance training uses muscular strength to move a weight or to work against a resistive load, causing isolated, brief activity of single muscle groups; it has received increasing attention in the last decade [9].

Exercise training has long been known as an important non-pharmacological tool for the treatment of diabetes [10]. The American College of Sports Medicine highlighted structured exercises backed by a substantial body of evidence for treating and managing diabetes [11]. Together, exercise and lifestyle modifications can actually reduce the progression of IR [12]. Recent evidence suggested that a combination of aerobic and resistance training (combined exercise) is more beneficial than either training modality alone. Aerobic exercise enhances insulin sensitivity, and resistance training may improve blood glucose uptake by increasing muscle mass, with glucose transporter type 4 expression mechanisms appearing to be synergistic [13].

This systematic review and meta-analysis reviewed the effect of exercise programs (aerobic and resistance training) in T2DM patients to further analyze potential specific exercise characteristics and their effects on IR and glycemic control.

2. Subjects and methods

This study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for quality of reporting meta-analysis. Studies were identified by an electronic search and hand search. We searched the databases MEDLINE via PubMed, CINHAL, Scopus and Web of Science, and the Cochrane Central Register of Controlled Trials. We also used Google Scholar to find out additional full-text articles from the earliest record to June 2017. The search strategy combined terms related to aerobic exercise training, strength training, and IR. Specifically, the keywords used were "strength training, weight training, resistance training, progressive training, progressive resistance, weightlifting; or aerobic exercise, endurance exercise, aerobic training, endurance training, cardio training, exercise, physical endurance, physical exertion; and insulin sensitivity, IR, tolerance test, oral glucose tolerance test (OGTT), insulin tolerance test (ITT)". The review included studies that compared the effectiveness of a structured exercise intervention with a control group that received no physical exercise to find out the effect on different outcome measures of interest.

2.1. Study selection

Studies were included in the systematic review with meta-analysis if they were of T2DM in people 18 years or older and the exercise training intervention involving aerobic exercise (continuous, intermittent, or high-intensity interval training), progressive RI, or both. Studies had to investigate the primary outcome insulin resistance, including fasting insulin (FI), homeostatic model assessment for insulin resistance (Homa-IR), fasting blood sugar (FBS), glycated hemoglobin (Hba_{1c}) or body mass index (BMI). Homa-IR was calculated as fasting insulin (ulU/L) × fasting glucose (nmol/L)/22.5 [5].

2.2. Data extraction and calculations

Data were extracted on the participant characteristics age, sex, BMI, exercise intervention (mode of exercise, exercise frequency, intensity, duration, and intervention duration) and measures of insulin sensitivity independently by 2 researchers (ASK, SG), with disagreements resolved by discussion with 2 investigators (AGM, BAS) (Table 1).

Table 1
Demographic data for studies in the systematic review.

Author name	Year	Journal	Type of study	Sample size	Type of intervention		Duration of intervention
					Intervention group	Control group	
Katsui et al.	2001	Diabetes care	Non-RCT	55	Aerobic training and diet	No group	6 weeks
Short et al.	2003	Diabetes	RCT	90	Aerobic control and exercise program	Flexibility exercises	16 weeks
O'Donovan et al.	2005	Eur J Appl Physiol	RCT	67	High and moderate intensity exercise	No exercise	24 weeks
Lazarevic et al.	2006	Diabetes Metab	RCT	30	Structured and supervised aerobic exercise program	No exercise	6 months
Michishita et al.	2008	Diabetes Res Clin Pract	Non-RCT	30	Submaximal exercise testing – NGT, IGT, DM	No group	12 weeks
Misra et al.	2008	Diabetes Care	Non-RCT	30	Supervised Progressive resistance exercise training protocol	No group	12 weeks
Jorge et al.	2011	Metabolism	RCT	48	Aerobic, resistance, and combined exercise training	No exercise	12 weeks
El-Kader et al.	2011	Journal Adv Res	Non-RCT	40	Aerobic and resistance exercise training	No group	3 months
Geirsdottir et al.	2012	Journal Gerontol	RCT	237	Resistance exercise program	Healthy older group	12 weeks
Mavros et al.	2013	Diabetes Care	RCT	103	High-intensity progressive resistance training	Sham	12 months
Motahari-Tabari et al.	2015	Global J Health Science	RCT	53	Aerobic exercise	No group	8 weeks

RCT, randomized controlled trial; DM, diabetes mellitus; NGT, normal glucose tolerance; IGT, impaired glucose tolerance.

2.3. Assessment of risk of bias

Two researchers (ASK, AGM) assessed the methodological quality of the included studies with blinding by using a modified Downs and Black checklist recommended by the Cochrane Handbook for Systematic Reviews of Interventions [14]. The tool consists of 27 items rated from 1, no and unable to determine, to 1, yes and includes criteria such as a clear description of the aims, interventions, outcome measurements and participants; representativeness of participant groups; appropriateness of statistical analyses; and correct reporting. The checklist was slightly modified so that the final item (no. 27) related to statistical power was consistent with the scoring used for the other items (i.e., from the original score of 0 to 5 to 0, no and unable to determine, to 1, yes) (Table 2).

2.4. Statistical analysis

All outcomes were continuous, so we computed the mean difference for treatment effect. In the meta-analysis, we synthesized the mean difference because study authors had used different outcomes. For studies that were not included in the meta-analysis, we computed and presented the mean difference.

Meta-analysis was performed when at least 2 studies were similar in terms of the population, intervention, comparison, outcomes (PICO) process and study design providing relevant data. We adopted a random-effects model for the meta-analysis because we anticipated considerable heterogeneity among the studies. To assess heterogeneity, we used the Chi^2 statistic ($P < 0.1$ considered statistically significant) and evaluated heterogeneity with the I^2 statistic (>60% considered substantial heterogeneity). Meta-analysis involved use of RevMan 5.2. We present forest plots for all meta-analyses. When meta-analysis was not appropriate, the effect size is presented with 95% confidence intervals (CIs).

3. Results

From the electronic database search, 2242 articles were identified; 98 full-text articles were eligible for full-text review, and 11 articles were included in the final review (Fig. 1). Articles were excluded because of inappropriate title and study methodology; no control group; improper study design, outcome measure, statistical analysis, and tools used in the study; inappropriate data; and report written in other than the English language.

Data for 846 participants were analyzed: 440 in the intervention group, and 406 in the control group. People with T2DM and healthy age-matched controls were included. The descriptive characteristics of participants are in Table 1. Most participants were recruited from hospital and outpatient settings.

3.1. Outcome measures

3.1.1. Fasting insulin (FI) level

Four studies were analyzed for FI level [1,3,10,15]; 135 participants were in the intervention group and 106 in the control group. Heterogeneity [I^2] was 85% ($P_{Heterogeneity} = 0.0002$). The mean difference was −1.64 (95% CI −3.38 to 0.10) for the intervention versus control group (Fig. 2).

3.1.2. Homa-IR

Four studies were analyzed for Homa-IR [10,15,16,17]; 83 participants were in the intervention group, and 92 in the control group. Heterogeneity [I^2] was 89% ($P_{Heterogeneity} = 0.00001$). The mean difference was 0.14 (95% CI −1.48 to 1.76) for the intervention versus control group (Fig. 3).

3.1.3. Fasting blood sugar (FBS)

Five studies were analyzed for FBS [1,10,15,16,18]; 144 participants were in the intervention group and 118 in the control

Table 2
Downs and Black checklist for methodological quality of studies.

Downs and Black questions	Katsui et al. (2001)	Short et al. (2003)	O'Donovan et al. (2005)	Lazarevic et al. (2006)	Michishita (2008)	Misra et al. (2008)	Jorge et al. (2011)	El-Kader (2011)	Geirsdottir (2012)	Mavros et al. (2013)	Motahari-Tabari et al. (2015)
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
8	N	N	Y	Y	Y	N	Y	N	N	N	N
9	N	N	Y	N	N	N	N	N	N	N	N
10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
13	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
14	N	Y	Y	N	UTD	Y	N	N	UTD	Y	N
15	N	Y	Y	N	UTD	Y	N	N	UTD	Y	Y
16	UTD	Y	Y	N	UTD	Y	N	N	N	Y	N
17	Y	Y	Y	Y	UTD	Y	Y	N	N	UTD	N
18	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
19	UTD	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
20	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
21	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
22	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
23	N	Y	Y	Y	Y	UTD	Y	UTD	Y	Y	Y
24	Y	Y	Y	Y	UTD	N	Y	N	Y	Y	Y
25	UTD	Y	Y	Y	N	N	Y	N	Y	Y	Y
26	UTD	UTD	Y	Y	UTD	UTD	Y	UTD	Y	Y	Y
27	N	N	N	N	N	N	N	N	N	N	N
Total Score	16	22	26	22	18	20	22	16	20	23	21

UTD: unable to determine.

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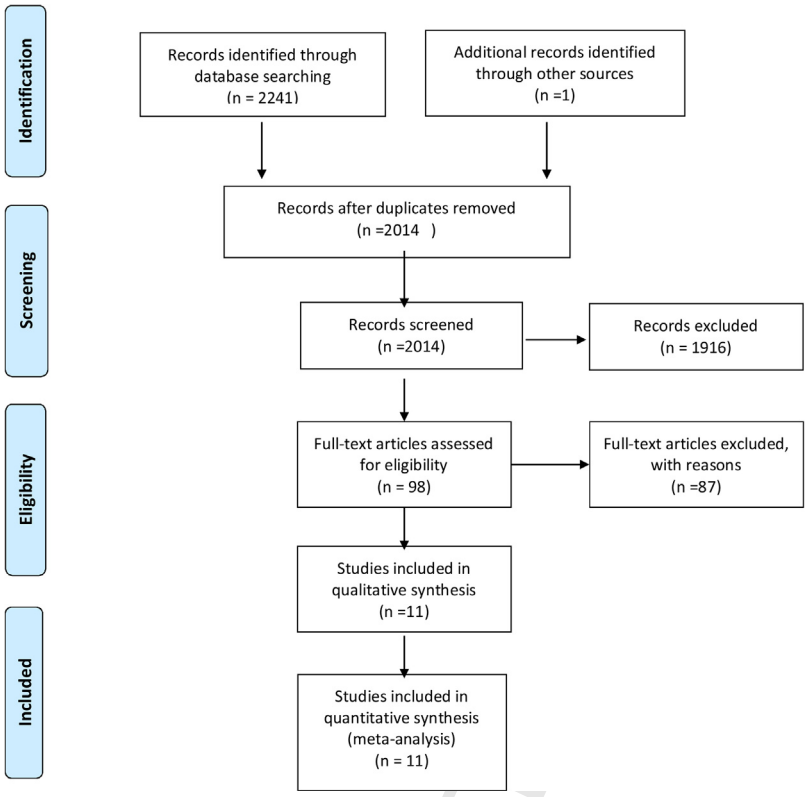

Fig. 1. Flow chart for selection process of studies for the meta-analysis.

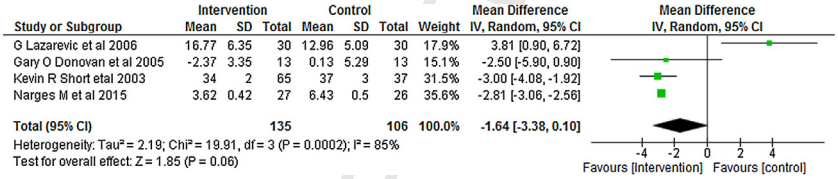

Fig. 2. Forest plot for analysis of fasting insulin level.

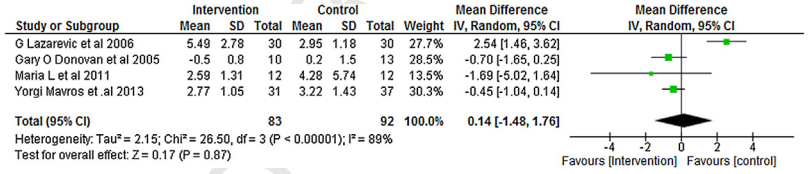

Fig. 3. Forest plot for analysis of homeostatic model assessment for insulin resistance.

group. Heterogeneity [I^2] was 99% ($P_{Heterogeneity}$ = 0.00001). The mean difference was −5.12 (95% CI −7.78 to −2.45) for the intervention versus control group (Fig. 4).

3.1.4. Glycated hemoglobin (Hba_{1c})

Three studies were analyzed for Hba_{1c} [1,7,10,16]; 78 participants were in the intervention group and 90 in the control group. Heterogeneity [I^2] was 94% ($P_{Heterogeneity}$ = 0.00001). The mean difference was 0.63 (95% CI −0.82 to 2.08) for the intervention versus control group (Fig. 5).

3.2. Body mass index (BMI)

Five studies were analyzed for BMI [10,15–18]; 156 participants were in the intervention group and 140 in the control group. Heterogeneity (I^2) was 59% ($P_{heterogeneity}$ = 0.05). The mean difference was −0.36 (95% CI −1.51 to 0.79) for the intervention versus control group (Fig. 6).

4. Discussion

IR plays a significant pathophysiologic role in T2DM and is also a risk factor for the development of cardiovascular disease [3]. To the best of our knowledge, this is the first systematic review with a meta-analysis reporting the effect of structured exercise training on IR in T2DM. The different outcome measures for quantitative analysis were FI level, Homa-IR, FBS, HbA_{1C} and BMI. We performed a meta-analysis to compare the intervention and control groups. The results suggest that as compared with controls, interventions such as regular exercise improve insulin sensitivity in T2DM.

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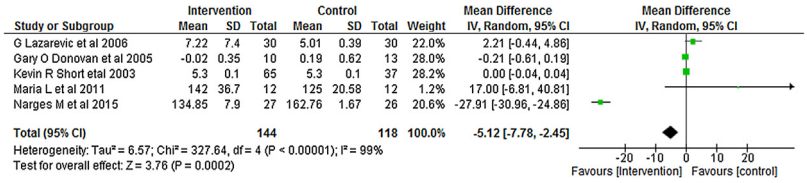

Fig. 4. Forest plot for analysis of fasting blood sugar.

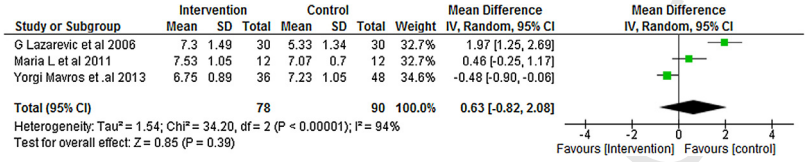

Fig. 5. Forest plot for analysis of glycated hemoglobin.

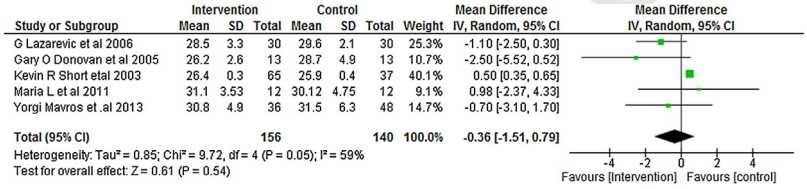

Fig. 6. Forest plot for analysis of body mass index.

Regular exercise is well known to improve blood glucose control and enhance insulin sensitivity. IR is marked by a decreased responsiveness to metabolic actions of insulin such as insulin-stimulated glucose disposal and inhibition of hepatic glucose output. Dynamic measures of insulin sensitivity mimic stimulated insulin action and reflect the peripheral insulin-mediated glucose uptake.

FI level was used as a primary outcome measure in the studies reviewed. The studies by O'Donovan et al. [16], Short et al. [17], and Motahari-Tabari et al. [1] found a significant difference in post-intervention FI level in the intervention versus control group, whereas the study by Lazarevic et al. [11] could not find a significant difference. Meta-analysis of FI level showed high heterogeneity between the studies: $I^2 = 85\%$. We found a combined negative effect of FI level, which suggests that the mean value was lower in the intervention group (−1.64, 95% CI −3.38 to 0.10). Previous studies reported that exercise training decreases insulin resistance. Dela et al. [19] showed that 3 months of aerobic training improved beta-cell function in T2DM, and another study showed that a 12-week aerobic exercise intervention improved beta-cell function in older obese adults and patients with T2DM [20].

O'Donovan et al. [16], Maria et al. [18], and Mavros et al. [19] found a significant difference in Homa-IR in the intervention versus control group. However, the study by Lazarevic et al. [11] could not find a significant difference.

Analysis of FBS showed a favorable effect of the intervention but no significant difference between the intervention and the control. Out of 5 studies, only 1, by Motahari-Tabari et al. [1] showed a significant difference in FBS level in the intervention group. The remaining studies, by Lazarevic et al. [11], O'Donovan et al. [16], Short et al. [17], and Maria et al. [18], found a significant reduction in post-intervention FBS level in both control and intervention groups but with no statistical significance. Meta-analysis of FBS revealed high heterogeneity ($I^2 = 99\%$) and also negative combined effects, which suggests that the mean value was lower in the intervention group (−5.12, 95% CI, −7.78 to −2.45).

Only one of the 3 studies of HbA_{1C}, by Mavros et al. [19], found a significant difference post-intervention, with high heterogeneity among the studies: $I^2 = 94\%$. The mean value was lower in the intervention group (0.639, 95% CI −0.82, 2.08). A previous review and meta-analysis found that structured exercise training had a positive effect on HbA_{1c} level in adults with T2DM as compared with controls. Individuals who exercised ≥150 min per week showed a significant reduction in HbA_{1c} (−0.89%) as compared with those who exercised < 150 min [21]. Another systematic review and meta-analysis investigating the effect of short-term exercise training (≤2 weeks) on glycemic control, as measured by continuous glucose monitoring in T2DM, showed that exercise significantly reduced hyperglycemia (>10.0 mmol/L) but did not significantly change FBS level [22].

We included 5 studies of BMI in the meta-analysis. Lazarevic et al. [11], O'Donovan et al. [16], and Mavros et al. [19] found a significant difference after the intervention as compared with controls, whereas 2 other studies, by Short et al. [17] and Maria et al. [18], could not find a significant difference between the intervention and control groups. Meta-analysis of BMI findings found moderate heterogeneity among studies: $I^2 = 59\%$. The mean BMI value in the intervention group was reduced (−0.36, 95% CI −1.51 to 0.79). A recent review of individuals with T2DM highlighted that supervised exercise training resulted in substantial response variations in glucose homeostasis, insulin sensitivity, and mitochondrial muscle density, with approximately 15% to 20% of individuals failing to show improved metabolic health with exercise [23].

There are a few limitations in the systematic review and meta-analysis when interpreting the results. Only 11 studies met the inclusion criteria and were eligible for the sub-analyses, and these were limited by small sample sizes and short duration of the intervention and some without a control group. Given the potential efficacy of exercise and the generally positive findings of existing studies, there is a clear need for further research examining the effectiveness of structured exercise interventions for IR. In the current analysis, the methods used to determine FI differed among studies. Many did not assess abdominal fat percentage, which could be a strong independent factor related to IR and glucose levels. Furthermore, differences in exercise prescription (type,

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intensity, duration, frequency, and intervention length) contributed to the heterogeneity. According to the Down and Black scale, all of the studies had moderate quality, which may also have contributed to the heterogeneity of the results. Therefore, we recommend further research to investigate optimal exercise prescription for treating insulin sensitivity in T2DM.

5. Conclusion

Exercise represents an effective interventional strategy to improve glycaemic control in T2DM. This systematic review with meta-analyses provides useful information for the clinical application of exercise in the management of T2DM. The results show clear evidence for the effectiveness of structured exercise programs, which therefore may be recommended to reduce IR in T2DM. However, the sample size for all studies was low. Hence, we need studies with adequate sample size and randomized controlled trials to provide statistically significant results.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgments

World Diabetes Foundation (WDF 15-941), "Diabetic Foot Care: Stepping Ahead".

Centre for Diabetic Foot Care and Research, Manipal Academy of Higher Education.

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