Title

The effects of high-intensity interval training on glucose metabolism, cardiorespiratory fitness and weight control in subjects with diabetes: systematic review a meta-analysis.

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ABSTRACT

Aim

The objective of this meta-analysis was to explore the effects of high-intensity interval training (HIIT) compared with control conditions (CON) or moderate intensity continuous training (MICT) on glycemic parameters in diabetes subjects.

Methods

Pubmed, Embase and Google Scholar databases were searched for HIIT interventions that were carried out in diabetic subjects and exploring fasting glucose, glycated haemoglobin (HbA1c), fasting insulin and/or HOMA-IR.

Results

This systematic review retrieved a total of 1741 studies of which 32 articles fulfilled the eligibility criteria. Nineteen trials were included in the meta-analysis since they compared HIIT intervention with CON or MICT group. There was a significantly reduction of fasting glucose of 13.3 mg/dL($p<0.001$), Hb1Ac -0.34% ($p<0.001$), insulin -2.27 UI/L ($p=0.003$), HOMA-IR -0.88 ($p=0.005$) in the HIIT-group compared with CON-group. Nevertheless, this reduction was not significantly different when comparing HIIT with MICT ($p= 0.140$, $p=0.315$, $p=0.520$ and $p=0.389$). Besides, there was a significant increase of absolute VO2max of 0.21 L/min ($p<0.001$) and relative VO2max of 2.94 ml/kg/min ($p<0.001$) in the HIIT-group compared with the CON-group and the MICT-group (0.22 L/min, $p=0.025$) and (0.97 ml/kg/min, $p=0.045$).

Conclusions

These findings revealed that HIIT intervention led to significant improvement in glycemic control and insulin resistance in subjects with diabetes compared with CON-group.

Keywords

High-intensity interval training; Diabetes; glucose metabolism; moderate intensity continuous training.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) causes a greater burden of morbidity and mortality worldwide. It is estimated that 642 million of adults aged 20-79 years will be diabetic by 2040 [1]. To identify strategies that optimize its management, delay its onset and minimize or postpone the complications associated with this disease are a priority for the scientific com-munity. Lifestyle intervention is a fundamental aspect of diabetes care and includes nutrition therapy, physical activity and smoking cessation counseling, among others [2]. Exercise has demonstrated improvements on glycemic control, decreases in cardiovascular risk factors, and enhancement of weight loss and feelings of well-being [3,4]. The American Diabetes Association recommends practicing 60 min/day or more of moderate- or vigorous-intensity aerobic activity, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days/week [2,5]. It is stated that people with T2DM should perform gradually increased aerobic and resistance exercise to reach 150 min/week of moderate-intensity exercise. However, there is no wide consensus about the type, mode, duration, intensity and weekly frequency that should be prescribed to subjects with diabetes.

High-intensity interval training (HIIT) has been recently promoted since it is a feasible effective and time-efficient form of exercise. HIIT involves short intervals of exercise at a high intensity and intervals at rest or at a lower intensity, allowing for less discomfort and inducing a more positive mental wellbeing response than moderate intensity continuous training (MICT) [6,7]. HIIT exercise is defined as exercise with 80-100% peak heart rate alternating with periods of low intensity (40-50% peak heart rate). MICT exercise included continuous exercise with ≤ 70% peak heart rate. Scientific interest on this subject has increased in recent years and several studies have demonstrated that this type of training leads to increase aerobic capacity, cardiometabolic improvement, and weight loss, along with inflammatory markers decrease, among other benefits. Although initially these studies were developed with a healthy population, later they have also been developed with subjects with overweight, obesity, hypertension, even more recently some of them have been carried out in subjects with T2DM [8–10]. The effect of

HIIT on glycemic control in subjects with diabetes has shown heterogeneous results [8–10] and whether this training could have greater benefit than MICT in T2DM is still unclear. Thus, our objective was to perform a systematic review and a meta-analysis of studies exploring the effect of HIIT on subjects with type 1 diabetes mellitus (T1DM) or T2DM on glycemic parameters (fasting glucose and insulin, HOMA-IR, and glycated hemoglobin). To our knowledge, this is the first meta-analysis including all types of clinical trials performed of this training effect on glucose metabolism both in T1DM and T2DM. Taking into account that physical activity is a corner-stone in diabetes management, it is highly relevant to elucidate if there is a type of exercise that could lead to a greater control of the disease.

2. MATERIAL AND METHODS

This meta-analysis has been reported according to the preferred reporting items for systematic reviews and metanalyses (PRISMA) guidelines [11]. The Evaluation of Quality Assessment instruments checklist is available in Tables S1 and S2.

2.1 Search strategy and study selection

A systematic search of the relevant literature was performed until May 1, 2020 with the use of PubMed, Cochrane Library and Scopus database in order to identify interventional studies investigating the effect of HIIT on glucose metabolism in subjects with diabetes. If available, we also included systematic reviews, meta-analysis and clinical guidelines. References of in-cluded studies and reviews were manually checked for additional studies. The structured search strategies used the combination of HIIT exercise and different outcomes related to glycemic profile in subjects with diabetes: [HIIT OR High Intensity Interval Training] AND [Glucose OR Diabetic OR Insulin OR HOMA OR Glycated haemoglobin OR DM2 OR Diabetes mellitus]. Articles retrieved were then included or excluded based on the following criteria. Inclusion criteria included: a) articles published in a peer-reviewed journal; b) randomized controlled trial or clinical trial; c) studies conducted in adults older than 18 years old; d) studies conducted in humans with T2DM; e) studies which performed HIIT exercise compared to MICT exercise or

no exercise; f) studies which reported data about fasting glucose and/or glycated haemoglobin and/or insulin and/or HOMA-IR. Exclusion criteria involved: a) case studies; b) letters, commentaries, conference papers, or narrative reviews; c) studies not conducted in humans; d) studies conducted in children. The search was limited to literature presented in English. The study selection and data extraction were performed by seven different researches (ILM, JGG, LM, SPC, LBR, AMB and RMG) being fully reviewed by two of them (ILM and RMG).

2.2 Outcome measures

Main outcomes of interest were changes in glucose, insulin, glycated haemoglobin and HOMA-IR. Body weight, body mass index (BMI) and maximal oxygen uptake (VO2 max) variation after intervention were secondary outcomes.

2.3 Data collection and data synthesis

Outcomes for glucose metabolism, body weight and maximal oxygen uptake were extracted and registered in a database for analysis, including baseline and post-intervention mean ± standard deviation values, and mean difference (MD) and 95% confidence intervals were reported. If not reported, the MD between pre-intervention and post-intervention was calculated by subtracting baseline from post-intervention values. MD was calculated as a difference change from baseline and was applied when different methods were used to establish the same outcome measure. Standard deviation (SD) of the mean difference were obtained as follows: SD = square root [(SD pre-exercise)^2 + (SD post-exercise)^2 – (2R x SD pre-exercise x SD post-exercise)], assuming an effect model due to the moderately high (>50%) heterogeneity, which has quantitatively assessed using the Higgins index I2. Authors of included studies were contacted for missing values if required.

2.4 Statistical analysis

Between-group meta-analyses were completed for continuous data by using the change in the mean and standard deviation of outcome measures as outlined previously. A random effects inverse variance analysis was used with the effects measure of median deviation for fasting

glucose, glycated hemoglobin, insulin, HOMA-IR, VO_2 max and BMI measures. Heterogeneity was quantified using the Cochrane Q test and Higgins I2. Egger funnel plots were pro-vided to assess the risk of publication bias and were commented on in the results only in case of significant publication bias (**Figures S1-S7**). Independent sample t-tests were conducted to assess differences between HIIT and MICT interventions in training hours per week during the interventions or between HIIT- non exercise. Within-group meta-analyses were completed for continuous data using the baseline and post-intervention values for each intervention. Random effects inverse variance analysis was also used with the same effects measures as above. Level of significance was set at $p < 0.05$ and 95% confidence intervals. Due to the heterogeneity of HIIT intervention, we did a sub-analysis included comparing the HIIT- MICT intervention, se-lecting only articles which realized HIIT interventions with intervals between 1 and 4 min (80-95% of maximum oxygen consumption or> 90% of maximum heart rate), with a total duration of one HIIT session ≥ 20 min. Statistical analysis was performed using statistical computing was conducted using package (meta) in R software (version 3.5.0) [12].

2.5 Quality measures

The quality of each included trial was assessed based on the previously validated methodology developed by Kmet et al [13]. The methodology was derived from a checklist for assessing the quality of quantitative studies, which included the following criteria: 1) Question, objective sufficiently described?; 2) Study design evident and appropriate?; 3) Method of subject, comparison group selection or source of information and input variables described and appropriate?; 4) Subject and comparison group (if applicable) characteristics sufficiently de-scribed?; 5) If interventional and random allocation was possible, was it reported?; 6) If interventional and blinding of investigators was possible, was it reported?; 7) If interventional and blinding of subjects was possible, was it reported?; 8) Outcome and (if applicable) exposure measure(s) well defined and robust to measurement, misclassification bias? Means of assessment reported?; 9) Sample size appropriate?; 10) Analytic methods described, justified and ap-propriate?; 11) Some estimate of variance is reported for the main results?; 12) Controlling for

confounding?; 13) Results reported in sufficient detail?; 14) Conclusion supported by the results?. Each question was answered with “yes”, “partial”, “no” or “not applicable”. Scoring process was done according to the following formula: ((number of “yes” x2) + (number of “partial” x1) / (total possible sum (28) – (number of “not applicable” x2)). The score ranged from 0 to 1; thus, the closer the value is to 1, the higher is the quality of the trial. Quality assessment of each trial was performed by seven different researches (ILM, JGG, LM, SPC, LBR, AMB and RMG). Two researchers performed the quality checklist of each trial. If a discordance was found (difference mean score more than 0.1 points), a third review by a different researcher was performed.

3. RESULTS

This section may be divided by subheadings. It should provide a concise and precise de-scription of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

3.1 Study selection

The systematic search retrieved a total of 1741 studies of which 1112 were identified in Pubmed, 348 in Cochrane and 281 in Scopus. After removing 281 duplicated articles, we screened 1460 manuscripts of which 821 were excluded because of they were not carried out in humans or they were not clinical trials. We reviewed the abstract of 639 articles, excluding 533 articles for not meeting selection criteria. We made full-text reviews of 106 articles, excluding 74 for various reasons: not carried out in diabetic patient (n = 33), not reporting fasting glycaemic metabolism parameters (n=25), not performing HIIT (n = 6), carried out in subjects under 18 years of age (n=4), five used the same patients and one of them was a letter. Thirty-two articles fulfilled the eligibility criteria of which 19 were included in the quantitative synthesis (meta-analysis) and 13 were excluded from this analysis and were only included in qualitative synthesis for different reasons. Most excluded articles did not have a control group (n=8), two of them had a control group which did not include subjects with T2DM and three of them did not report complete data (**Figure 1**).

3.2 Participants and main study characteristics

A detailed description of the studies included in the meta-analysis can be found in **Table 1**. The 19 studies included a total of 708 participants (aged 22-80 years). There was some heterogeneity in clinical characteristics of the study populations. In summary, 19 studies recruited subjects with T2DM of whom 9 included subjects without diabetic complications [14–22], two of them had subjects with stable body weight [15,18], one of studies did not provide any antidiabetic treatment [14]. Among 19 studies, 17 recruited participants of both sexes, only one of them included only postmenopausal women [23] and one only recruited men with T2DM [24]. Twelve studies had a 2-armed intervention [14,18,21–30]: six of them analyzed the effect of HIIT exercise compared with a control group [14,18,21,22,27,28], who did not do exercise; while the other six compared the effect of HIIT exercise with MICT [23–26,29,30]. Eight studies had 3-armed interventions, including HIIT, control and MICT groups. Diabetes pharmacologic treatment differed among 19 studies included in the meta-analysis: twelve articles recruited participants who were only taking oral antidiabetics, five included participants receiving insulin, two did not report any drug detail and one reported that participants did not take any diabetic medication.

Table S3 shows the main characteristics of the 13 articles included in the qualitative analysis. The studies included a total of 336 participants with mean age of 50.7 years (range 22-80 years). Nine studies recruited subjects with T2DM [31–39], two studies included prediabetic and subjects with diabetes [40,41], one study included T2DM subjects and healthy participants [42] and, finally, one study included subjects with T2DM, dyslipidemia, hypertension and a group of healthy subjects who carried out HIIT [43]. Four studies reported a single arm intervention, including only subjects who performed HIIT; six studies had 2-armed intervention, including participants who did HIIT exercise and MICT or not exercise; and three studies reported 3 or more-armed study groups.

3.3 Training description

Training description of those studies included in meta-analysis can be found in **Table 1**. Briefly, most of the studies involved cycling (n=6) or ergocycling (n=6), two included a combination of walking and jogging on a treadmill, one performed a combination of cycling and walking, another three carried out fast walking and one of them did not report what kind exercise realized their participants. HIIT exercise included heterogeneous design involving: from 4 intervals of 1 minute to 60 intervals of 8 seconds, with a heart rate max between 70 to 100%, interspersed by intervals from 12 seconds to 4 minutes with a heart rate max of 40-50%. Besides, most HIIT exercise included warm-up and cool down periods from 3 to 10 minutes. Training duration per session widely ranged from 10 to 135 minutes with a frequency from 2 to 5 days per week. Intervention's duration of the studies varied from 8 to 16 weeks.

Training exercise of articles included in the qualitative analysis included cycling or ergocycling (n=11), running or jogging (n=2), functional weightlifting (n=1) and elliptical (n=1) (**Table S3**). HIIT exercise included heterogeneous design including: from 3 intervals of 3.5 minutes to 20 intervals of 30 seconds, with a heart rate of between 70 to 95% maximum, interspersed generally by intervals of one minute of active recovery. However, in most studies the HIIT protocols did not report warm-up and cool down times. Training duration per session ranged from 10 to 60 minutes, with a frequency of one to three days per week. The duration of interventions studies varied from 6 to 16 weeks.

3.4 Changes in glycemic metabolism

3.4.1 Fasting glucose

Among 19 studies included in this meta-analysis, fifteen reported fasting glucose data pre- and post-exercise intervention and seven described significant differences after the HIIT intervention. Cassidy et al [27] and Suryanegara et al [21] reported that fasting glucose levels did not significantly vary among participants doing HIIT, while the significantly increased in participants not practicing any exercise. Besides, two studies [19,22] showed that the HIIT group showed significant reductions in fasting glucose compared with control groups. Winding et al [44] demonstrated that the HIIT group showed significantly decrease in fasting glucose while in

endurance training and control groups had no significant declines. Finally, Mitranun et al [16] showed significant decreases in fasting glucose in HIIT and continuous training groups (**Table 2**).

Data of fasting glucose levels reported by fifteen studies was included in the meta-analysis. Of these, 13 of them (81.3%) compared the HIIT group with at least one control group (no exercise or MICT group). There was a reduction in fasting glucose of 13.3 mg/dL (-19.83 to -6.79 mg/dL, p<0.001) in the HIIT group compared with the no exercise group (**Figure 2A**). However, this re-duction was not significantly different when comparing HIIT with MICT groups -3.76 mg/dL (-8.75 to 1.23 mg/dL, p= 0.140, **Figure 2B**). The sub-analysis included four articles with homogenous HIIT intervention showing there was a reduction in fasting glucose of 5.83 mg/dL (-11.50 to -0.17 mg/dL, p<0.043) in the HIIT group compared with the MICT group. However, this re-duction was not significantly different using the prediction interval (-18.27 to 6.60 mg/dL).

3.4.2 Hb1Ac

Of 19 studies included in the meta-analysis, seventeen of them reported Hb1Ac levels pre- and post-exercise intervention. Ten of them described significant differences after training HIIT intervention. Six studies [14,16,17,22,29,44] reported significant decreases of Hb1Ac only in the HIIT group, without significant differences in control or MICT groups. However, one study [23] showed significant decreases both in HIIT and MICT groups. Finally, Suryanegara et al [21] described significant reductions of Hb1Ac in both groups (HIIT and no exercise group) (**Table 2**).

Data of Hb1Ac reported by seventeen studies was included in the meta-analysis. Of these, 15 of them (83.3%) compared HIIT to at least one control group (no exercise or MICT group). Hb1Ac concentration decreased by -0.34% (-0.52 to -0.16%, p<0.001) in the HIIT group which was significant different when it was compared with the no exercise group (**Figure 3A**). However, this reduction was not significantly different when comparing HIIT exercise with MICT exercise (-0.07%, -0.20 to 0.06, p=0.315, **Figure 3B**). The sub-analysis included eight articles with

homogenous HIIT intervention showing there was a not significant reduction in Hb1Ac of -0.0938 (-0.2437 to 0.0561, p=0.220) in the HIIT group compared with the MICT group. Furthermore, this reduction was also not significantly different using the prediction interval (-0.28 to 0.09 %).

3.4.3 Insulin

Among 19 studies included in the current meta-analysis, only eight of them reported fasting insulin data pre- and post-exercise intervention and half of them (4 studies) described significantly differences after training HIIT intervention. Two groups showed a benefit of HIIT in fasting insulin levels: Karstoft et al [15] reported only significant decreases in the HIIT group while control and MICT groups experienced significant increases and no variation, respectively; while Ghardashi Afousi et al [19] reported significant decreases in HIIT and MICT groups. However, the other two studies reported negative or neutral effect of HIIT intervention on fasting insulin: one of them showed that HIIT lead to significant increases in fasting insulin levels [18]. The other one demonstrated that HIIT did not cause any effect and only the MICT group showed a significant decrease in fasting insulin [26] (**Table 2**).

Data of fasting insulin informed by eight studies was included in the meta-analysis. Among, 5 (62.5%) compared HIIT to at least one control group (no exercise or MICT group). There was a significant reduction in insulin -2.27 UI/L (-3.78 to –0.75 UI/L, p=0.003) in the HIIT group compared with the no exercise group. Nevertheless, the predicted value did not show significant decreases (-5-59 to 1.06, **Figure 4A**). Besides, the reduction was not significantly different when comparing HIIT with MICT (-0.53 UI/L, -2.14 to 1.08, p=0.520, **Figure 4B**).

3.4.4 HOMA-IR

Of 19 studies that were included in the meta-analysis, eleven of them reported HOMA-IR values pre- and post-exercise intervention and six of them described significant differences after training HIIT intervention. Five studies [14,19,22,26,44] showed significantly decreases of HOMA-IR in participants practicing HIIT, although two of them showed significantly decreases in the MICT

group as well [19,26]. In contrast, Hollekim-Strand et al [17] showed there was not a significant variation of HOMA levels in HIIT and MICT groups after training intervention (**Table 2**).

Data of HOMA-IR reported by eleven studies was included in the meta-analysis. Of these, 10 of them (90.9%) compared HIIT to at least one control group (no exercise or MICT group). HOMA-IR varied by -0.88 (-1.49 to –0.26 UI/L, p=0.005) in the HIIT group compared with the no exercise group. However, the predicted value did not show significantly decreases (-2.50 to 0.75), due to the small differences and the limited number of studies included in this me-ta-analysis (**Figure 5A**). The reduction was not significantly different when comparing HIIT exercise with MICT exercise -0.17, (-0.57 to 0.22, p=0.389, **Figure 5B**). Visual interpretation of funnel and bubble plots suggested limited publication bias in HOMA-IR when comparing HIIT both with no exercise and MICT (p=0.038 and p=0.0076, respectively; **Figure S4**).

3.4.5 Qualitative synthesis

Of 13 studies included in qualitative synthesis, 69% (9/13), 50% (4/8) and 40% (2/5) reported significant differences in fasting glucose, Hb1Ac and HOMA-IR respectively, between pre- and post-values after training HIIT intervention. (**Table S3**).

3.5 Changes in anthropometric characteristics

Although change in anthropometric characteristics was not the main objective of the current study, we analysed the effect of HIIT intervention on BMI and cardiorespiratory fitness, ex-pressed as absolute or relative VO2max, due to the great relevance that the change in these parameters has for the interpretation of the results of glycemic parameters.

3.5.1 BMI

Of 19 studies included in the meta-analysis, thirteen of them reported BMI pre- and post-exercise intervention and seven of them described significant differences after training HIIT intervention. Most studies (87.5%) [14–17,22,29,44], showed that significantly decreased in BMI occurred only in the HIIT group, without significantly differences in control or MICT groups (**Table 2**).

Data on BMI reported by thirteen studies was included in the meta-analysis. Of these, 11 of them (84.6%) compared HIIT to at least one control group (no exercise or MICT group). There was not a significantly reduction in BMI (which varied by -0.31 kg/m2, -0.85 to 0.24 kg/m2, p=0.267) in the HIIT group compared with the no exercise group (**Figure 6A**). Besides, the re-duction was not significantly different when comparing HIIT with MICT neither (-0.096 kg/m2, -0.544 to 0.353 kg/m2, p=0.676, **Figure 6B**).

3.5.2 Cardiorespiratory fitness

Cardiorespiratory fitness was expressed as absolute (L/min) or relative (mL/kg/min) VO2max which was reported by sixteen studies (80%). Of these, nine showed significant increases of absolute or relative VO2max in the HIIT group, without significant variation in MICT group among four studies [15,17,26,29]. In contrast, two studies showed significant increases of VO2max both in the HIIT group and the control group. Similarly, three studies reported that HIIT and MICT groups experienced significant increasing of VO2max, without a significant variation in the control group [16,19,44] (**Table 2**).

Data of VO2max informed by fifteen studies was included in the meta-analysis. Of these, nine (60%) reported data of absolute VO2max, while thirteen (86.7%) showed data of relative VO2max. There was a significant increase of absolute VO2max of 0.21 L/min (0.12 to 0.29 L/min, p<0.001) in the HIIT group compared with the no exercise group (**Figure 7A**). The increase was also significant when comparing HIIT with MICT (0.22 L/min, 0.04 to 0.40 L/min, p=0.025). However, the predicted value of the comparison of HIIT vs MICT exercises, was not significant due to the limited number of studies included in this meta-analysis (**Figure 7B**). Along the same lines, relative VO2max, which is expressed according to body weight, significantly increased by 3.02 ml/kg/min (2.36 to 3.67 ml/kg/min, p<0.001) in the HIIT group compared with the no exercise group (**Figure 8A**). In addition, the increase was also significant when comparing HIIT with MICT (0.97 ml/kg/min, 0.29 to 1.65 ml/kg/min, p=0.045, **Figure 8B**). However, both predictive values were not significant indicating that it is necessary to increase the number of studies for a more accurate analysis. Visual interpretation of funnel and bubble plots suggested

limited publication bias in absolute levels VO2max when HIIT and MICT were compared (p=0.014, **Figure S6**).

3.5.3 Qualitative synthesis

Of 13 studies included in qualitative synthesis, 9 and 4 of them, respectively, reported data of BMI and cardiorespiratory fitness before and after exercise. Of them 44.4% (4/9) and 100% (4/4) reported significant differences in BMI and cardiorespiratory fitness respectively, between pre- and post-values after training HIIT intervention (**Table S3**).

3.6 Quality of the studies

The overall quality score of the included studies in meta-analysis is summarized in **Table 2**, with a quality score ranging from 0.59 to 0.96, and a mean score of 0.75. Detailed description of quality assessment for each study is included in **Table S1**. The greatest concerning issues were randomization of descriptions, blinding of investigators and subjects, sample size calculation and controlling for confounding factors. Among 19 studies that were included in the meta-analysis, only 7 of them included a sample size calculation and two of them partially described it. Besides, none study made a statistical analysis taking into account the confounding factors and only three of them taking into account partially.

The overall quality score of the included studies in the review analysis is summarized in Table S3. These studies showed lower quality score than studies included in the meta-analysis with a score that ranged from 0.30 to 0.86 and a mean score of 0.60. **Table S2** shows the detailed description of quality assessment for each study included in the systematic review. The issues a greatest concerning was randomization of descriptions, blinding of investigators and subjects, sample size calculation and controlling for confounding factors. Among seven systematic-review studies which included a randomized clinical trial design, only two of them carried out a blinded intervention. Among 13 included trials, 3 of them included a sample size calculation and one of them partially described it. In addition, only one study did a statistical analysis taking into account the confounding factors.

4. DISCUSSION

The main finding of this meta-analysis is that HIIT led to higher improvement in glucose metabolism parameters (both glucose, HbA1c, insulin and HOMA-IR) in subjects with T2DM compared with no practicing exercise practice. Exercise induced a similar benefit on glycemic homeostasis compared with MICT. The decrease in BMI was similar after intervention with both exercise protocols but, importantly, the meta-analysis revealed that HIIT caused higher significant VO2max increases than MICT. Most studies reported that HIIT was well tolerated and safe and participants showed a high compliance for this protocol intervention. Among 19 studies included in the meta-analysis, only one recruited subject with T1DM so our findings could not be extrapolated for this disease.

Previous meta-analysis exploring the effects of HIIT and MICT in subjects with T2DM included few studies and showed heterogenous results in glucose metabolism [45–48], being the current article the first meta-analysis which included a complete systematic review. While Trevisan De Nardi et al [46] found no differences in Hb1Ac between two modalities of exercises, Liubaoerjijin et al [48] and Liu et al [47] observed greater improvement in HbA1c after HIIT intervention (WMD = -0.23 (95%CI -0.43 to -0.02), p = 0.03; − 0.37, (95%CI -0.55 to -0.19, P < 0.0001, respectively). Our meta-analysis is the largest one by including 19 studies and it revealed that subjects with T2DM underwent HIIT obtained reductions in glucose and HbA1c levels, which was statistically significant comparing to no exercise group. The results seemed to indicated that HIIT could have a slight benefit in glycemic control than the one produced by MICT; although, no statistical differences among two exercise protocols were found. However, it is interesting to highlight that any decrease in HbA1c concentrations has been widely related to a decrease in microvascular and macrovascular complications in T2DM specially in early phases of the disease [49,50]. In the Second Manifestations of Arterial Disease (SMART) trial, a 1%-HbA1c level increase was associated to a 27% higher risk of a cardiovascular event in patients with T2DM without vascular disease [51]. It is important to note that the non-difference between exercise protocols on glucose and HbA1c may be related to the small sample size of the studies.

The number of studies exploring the effect of HIIT on insulin and HOMA-IR in subjects with T2DM is quite limited. Just one meta-analysis including 5 trials has previously explored the effect of HIIT on insulin and HOMA-IR in subjects with diabetes by not showing statistical-ly significant differences between HIIT in control nor MICT groups [47]. Authors mentioned that the lack of benefit of HIIT on insulin resistance may be due to the different methods used to determine insulin sensitivity and glycemic control in different trials. Our meta-analysis showed that HIIT caused significant improvements in insulin and HOMA-IR concentrations with respect to not practicing physical activity, although predictive values were not significant for any parameter. This lack of significance could be due to the small differences observed after both interventions and the limited number of trials that reported fasting insulin (N = 8) and HOMA-IR (N = 11) levels after interventions. We observed no differences in the benefit obtained by HIIT and MICT interventions on insulin resistance markers.

The mechanisms responsible for the benefit of HIIT in glycemic control and insulin resistance in subjects with T2DM may entail a combination of improvements on beta cell function and, hepatic and peripheral insulin resistance [10]. HIIT has previously been demonstrated to increase receptor gamma coactivator 1-alpha (PGC-1a) which drives the expression of glucose transporter type 4 (GLUT 4) [52]. PGC-1a activity has been suggested to decrease glucose transport and mitochondrial fatty-acid oxidation; thus, incompletely oxidized fatty acid intermediates would increase by leading to insulin resistance [53]. On the other hand, Tjonna et al. showed increased circulating adiponectin after HIIT intervention whose concentrations have been widely and directly related to insulin sensitivity and T2DM development [54].

Previous meta-analysis has pointed out the superiority of HIIT for aerobic fitness by showing a higher increase in VO2max than MICT both in healthy and in subjects with T2DM [55,56]. In spite of it being a secondary outcome of our meta-analysis, we analyzed the cardiorespiratory fitness in those trials that were included by showing a significantly greater in-crease in VO2max compared with the no exercise group and MICT. However, the predictive value was not statistically significant, due to the limited number of trials and the small sample size. The

superiority of HIIT for cardiorespiratory fitness has important clinical implications since VO2max is a great predictor of cardiovascular risk and its improvement is associated with a decrease in cardiovascular disease morbidity and mortality and T2DM prevalence [57]. In fact, several researches point out that the improvement of functional capacity in T2DM pa-tients represents an important therapeutic task [57]. Moreover, HIIT interventions have demon-strated to have superior benefits than MICT in other factors with an essential impact on the management of T2DM and global cardiovascular risk: decreased in systolic and diastolic blood pressure, oxidative stress and inflammation and increased in high density lipoproteins, avail-ability of nitric oxide and cardiac function, among others [54,55,58–60].

Weight loss is also a key issue in the management of T2DM. Despite finding of a superior benefit on weight loss after HIIT intervention compared with MICT being not well established, a recent meta-analysis has reported that HIIT provided 28.5% greater reductions in total absolute fat mass than MICT [61]. Our meta-analysis revealed no significant decreases in BMI after HIIT intervention compared with control or MICT groups. However, the body composition is an essential factor that could interfere in the results and it was not assessed in the trials included in the meta-analysis. Researchers have previously proposed that the enhance-ability of HIIT on cardiorespiratory fitness could improve the hypoxia-induced necrosis of adipose tissue that occurs in overweight and obesity [62]. This could, in turn, lead to improvements in insulin resistance, inflammation and oxidative stress that could contribute to lower cardiovascular risk in subjects with T2DM.

Unquestionably, the success of an exercise intervention and the optimization of long-term benefits directly depend on the compliance to the recommendations. It has been previously demonstrated that adherence to HIIT protocol prescription is higher than the reported by other exercise like MICT and participants showed higher rates of enjoyment and greater improvements of quality of life with HIIT [6,55]. HIIT is also reported to be more time-efficient than MICT which is an essential issue since lack of time is often one the reasons why people do not practice sport. The compliance of both HIIT and MICT was very high in all trials that were included in

the meta-analysis and no differences were reported in safety, tolerability and compliance between the two protocols.

It is important to note that the trials included in the meta-analysis experiences methodological limitations that should be taken into account when interpreting the findings. Firstly, HIIT protocols are not fully standardized. The trials included in the meta-analysis consist of a variety of intervals, intensities and program durations. In this way, some authors have demonstrated that the intensity and duration of the recovery period in HIIT plays an essential role in cardiometabolic changes obtained with this exercise. Moreover, the mode and intensity of exercise protocol seems to have an essential role in benefits induced by HIIT since different studies have described that a 4x4 approach leads to higher improvements in cardiometabolic parameters when compared to other protocols. Secondly, most interventions were of short duration. Long-term interventions would be useful to explore the glycemic control, safety, tolerability and the adherence to this exercise protocol in subjects with T2DM.

5. CONCLUSIONS

In conclusion, this meta-analysis revealed that HIIT led to a greater improvement in glucose metabolism parameters (both glucose, HbA1c, insulin and HOMA-IR) in subjects with T2DM when compared with no practicing exercise. The benefits observed both in glycemic control, insulin resistance and the evolution of body mass index after the interventions with HIIT and MICT did not significantly differ. Importantly, the meta-analysis showed that HIIT caused higher significant VO2max increases than MICT in subjects with T2DM that would in-volve further clinical benefits beyond glycemic control. Based on these statements, future recommendations in the management of T2DM should consider including HIIT counselling at the same level as MICT is usually advised.

Author Contributions

Conceptualization, ILM and RMG; Methodology, ILM and RMG; Software ILM; Validation ILM, RMG and JGG; Formal Analysis ILM, RMG and LMN; Investigation, AMB, JGG, LMN,

LBR, LGT, SPC, ILM and RMG; Resources, FC.; Data Curation, ILM, RMG and LMN; Writing – Original Draft Preparation, ILM and RMG; Writing – Review & Editing, ILM and RMG; Visualization, AMB, JGG, SPC and LBR; Supervision RMG, ILM and FC; Project Administration, FC; Funding Acquisition, FC

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Data Availability Statement

The database generated as a result of the systematic review carried out will be fully available to replicate the results that are necessary at the request of the reviewers or editors.

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Conflicts of Interest

The authors declare no conflict of interest.

Figure Legend

Figure 1. Flow Chart

Figure 2. Forest plot of fasting glucose change depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure 3. Forest plot Hb1Ac change depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure 4. Forest plot insulin change depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure 5. Forest plot HOMA change depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure 6. Forest plot BMI change depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure 7. Forest plot Absolute VO 2max change depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure 8. Forest plot Relative VO 2max change depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Supplemental Figure

Figure S1. Funnel and bubble plot of fasting glucose depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure S2. Funnel and bubble plot of Hb1Ac depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure S3. Funnel and bubble plot of fasting insulin depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure S4. Funnel and bubble plot of HOMA depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure S5. Funnel and bubble plot of BMI depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure S6. Funnel and bubble plot of Absolute VO_2max depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

Figure S7. Funnel and bubble plot of relative VO_2max depending on exercise performed: HIIT vs non exercise (A) and HIIT vs CMIT exercise (B).

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Table 1. General information of articles included in the meta-analysis.

First author, year of publication	N	Age	Gender (men, n (%))	Type of article	Participants	Groups	Training description	Training frequency and duration	Study duration (w)
Backx, 2011	10	59.6 [44.0–69.0]	15 (78.9)	Randomized controlled trial	T2DM subjects diagnosed in the previous 3 months without oral anti-diabetic drugs or insulin, and severe complications of DM.	SEP	Cycle ergometer: 10-min warm-up + interval periods at intensity of 40–50% or 80-90% HR_{max} + 5-min cool-down. W1-2: 1-2 min at 40-50% HRmax + 1,2 or 3 min at 80-90% HRmax (until 20 min of PA) W 3-12: 1–2 min at 40–50% HR_{max} + 1, 2 or 3 min at 80–90% HR_{max} (until 20–40 min of PA)	5 d/w; Consisted of three 60-min supported + 2 unsupported exercise sessions per week	12
	9					SCP	No specific exercise intensities indicated. SCP participants were telephoned every other week, as advised by the ethics committee, to check on progress.	5 d/w; 30 min/session	
Karstoft, 2012	12	57.5± 2.4	7 (58.3)	Randomized controlled trial	T2DM subjects with stable weight (<2 kg/6 months), sedentary habits (<150 min/w) and no associated disease.	IWT-HIIT	IWT-HIIT: 3 min of fast walking (>70% of the peak energy-expenditure rate) + 3 min of slow walking	5 d/w; 59±2 min/day	4 months
	8	57.1± 3.0	5 (62.5)			Control	CON subjects were instructed to continue their habitual lifestyle	-	4 months
	12	60.8± 2.2	8 (66.6)			CWT	Continuous walking: >55% of the peak energy-expenditure rate	5 d/w; 59±2 min/day	4 months
Terada T, 2013	7	62±3	4 (57.1)	Randomized controlled trial	T2DM subjects, aged 55-75 years, and non-smokers	HIIT	Cycling and walking training: 1-min exercise at 100% VO2R (as many intervals as possible) + 3-min recovery intervals at 20% VO2R.	5 d/w; W 1-4: 30 min/session, W 5-8: 45 min/session, W 9-12: 60 min/session.	12
	8	63±5	4 (50)			MICT	Cycling and walking training: continuous exercise at 40% VO_2R.		
Mitranun, 2014	14	61.7 ± 2.7	5 (35.7)	Randomized controlled trial	T2DM subjects without nephropathy, retinopathy, severe diabetic neuropathy, and severe CVD or stroke disease	CON	CON exercise had 3 phases: Phase 1: 5 min warmed up (50% of the VO_{2peak}) + 20 min (50% of the VO_{2peak}) + 5 min cool down. Phase 2: 5 min warmed up (60% of VO_{2peak}) + 20 min (60% of VO_{2peak}) + 5 min cool down. Phase 3: 5 min warm up (65% of VO_{2peak}) + 30 min (65% of VO_{2peak}) + 5 min cool down	3 d/week; Phase 1 (w 1–2): 30 min, Phase 2 (w 3–6): 30 min Phase 3 (W 7–12): 40 min.	12
	14	61.2± 2.8	5 (35.7)			INT	INT exercise had 3 phases: Phase 1: Equal to CON phase 1. Phase 2: 5 min warmed up (50% of VO_{2peak}) + 4 interval x 1min at 80% of VO_{2peak} interspersed by 4-min at 50% VO_{2peak} + 5 min cool down. Phase 3: 5 min warn up (60% of VO_{2peak}) + 6 interval x 1-min 85% VO2peak interspersed by 4-min at 60% VO_{2peak} + 5-min cool down.	3 d/week; Phase 1 (w 1–2): 30 min, Phase 2 (w 3–6): 30 min Phase 3 (W 7–12): 40 min.	12
	15	60.9 ± 2.4	5 (33.3)			SED	SED control group were instructed to remain sedentary.	-	12

Maillard F, 2016	8	61-80	0	Randomized controlled trial	Postmenopausal T2DM women, BMI 25-40 kg/m², stable eating habits and physical activity ≥ 3 months.	HIIT	Cycling training: 60 cycles x 8 s (77-85% HR_{max}) + pedaling slowly (20–30 rpm) x 12 s + 5-min cool down.	2 d/w; 20 min/ session.	16
	8	61-80	0			MICT	Cycling training: 40 min at 55–60% of their individual HRR+ 5-min cool down.	2 d/w; 40-min/ session.	
Hollekim-Strand SM, 2016	24	58.6± 5.0	12 (60)	Randomized controlled trial	T2DM subjects, aged 20-65 years, without insulin treatment and with diastolic dysfunction. CON subjects were matched by gender, age and BMI.	HIIT	Walking or jogging on an inclined treadmill: 10-min warm up at 70% HR_{max} + 4 intervals x 4-min work bouts at 90-95% HR_{max} + 3-min intervals of recovery at 70% HR_{max} between work bouts + 5-min cool-down.	3d/w; 40 min/session	12
	23	54.7± 5.3	13 (64.7)			MICT	Home-based exercise training: 210 min/w including exercise bouts ≥ 10-min in duration.	210 min/w; No frequency indicated.	
	37	51	NR			Control	No training	-	
Ramos JS, 2016	66	57± 10	36 (55)	Randomized controlled trial	Subjects with metabolic syndrome; a sub analysis of subjects with T2DM was performed	4HIIT	10-min warm up at 60-70% of HR_{peak} + 4 intervals x 4-min exercise at 85-95% of HR_{peak} + 3-min intervals of recovery at 50-70% of HR_{peak} between work intervals + 3-min cool-down at 60-70% of HR_{peak}.	3 d/w; 38 min/session	16
	12	58± 7	6 (61)			1HIIT	10-min warm up at 60-70% of HR_{peak} + 4-min exercise at 85-95% of HR_{peak} + 3-min cool-down at 60-70% of HR_{peak}.	3 d/w; 17 min/session	
	6	57± 9	4 (71)			MICT	30-min exercise at 60-70% of HR_{peak}.	5 d/w; 30 min/session	
Cassidy S, 2016	12	61± 9	8 (72.7)	Randomized controlled trial	T2DM subjects with stable diet or metformin treatment for ≥ 6 months.	HIIT group	Ergocycle training: 5-min warm-up at 9-13 of RPE + 2-min (increasing up to 3-min in 12 w) x 5 intervals at >80 rev/min by reaching 16-17 of RPE) + 3-min of recovery periods + 3-min cool down.	3d/w	12
	11	59± 9	10 (83.3)			Control	No training	-	
Ruffino S, 2016	16 (Cross -over)	55± 5	16 (100)	Clinical trial	Subjects with T2DM for ≥ 6 months, not under insulin treatment or more than 2 anti-diabetic drugs.	Redu-ced exer tion HIIT	Cycling: 10-min of exercise at 25 W+ 10-s (sessions 1-4) / 15-s (sessions 5-12) / 20-s (remaining 12 sessions) x 1 (first session) or 2 (remaining sessions) intervals of cycle-sprints against a constant torque of 0.65 Nm·kg/ lean mass.	3d/w; 10 min+10-40 s/session	8
						Control	Walking: 30-min of exercise at 40% (w 1-2), 50% (w 3-4) and 55% (w 5-8) of HRR.	5d/w; 30-min/session	
Bellia, 2017	11	58.8 ± 7.9	9 (81.8)	Randomized controlled trial	T2DM Subjects aged 40-60 years, BMI <30 with stable body weight, HbA1c <7.5%, without comorbidities associated, sedentary habits and ability to perform PA	HIIT-AIT group	Treadmill: Warm up: 10 'at 40-60% of HR_{max} + 4 min walk at 75-80% of the HRmax repeated 2 to 4 times per training session interspersed with active 3 min recovery to 45-50% of the HRmax. Workload (speed, incline and serial number) was gradually adapted to the level of efficiency achieved by the subject. Cool down: 10' at 40-50% of HRmax.	34, 41 and 48 min (2, 3 or 4 intervals); w 1-2: 2 d/w x 2 intervals, w 3-4: 3 d/w x 2 intervals, w 5-6: 3 d/w x 3 intervals and w 7-12: 3 d/w x 4 intervals.	12
	11	56.3 ± 6.4	7 (63.6)			SOC group	SOC group received a pedometer and asked to make at least 10,000 steps per day or 70,000 steps per week.	NA	

Støa EM, 2017	19	59± 11	15 (39.5)	Clinical trial	T2DM subjects, overweight and sedentary habits	HIIT	~15-min warm up at ~52% VO_{2max} + 4 intervals × 4-min exercise at 85–95% at HR_{peak} + 3-min recovery between intervals + ~12-min cool down at ~52% VO_{2max}	3 d/w; 52 min/session	12
	19	59± 10				MICT	Continuously exercise at 70–75% HR_{peak}.	3 d/w; 60 min/session	
Winding KM, 2018	13	54± 6	7 (53.8)	Randomized controlled trial	T2DM subjects, no under insulin treatment, with stable body weight and non-smokers.	HIIT	Cycling training: 5-min warm up + 1-min x 10 intervals of exercise at 95% of Wpeak + 1-min recovery intervals at 20% W_{peak}	3 d/w; 135 min/session	11
	12	58± 8	7 (58.3)			END	Cycling training: 5-min warm up + 40-min of exercise at 40% of W_{peak}	3d/w; 75 min/session	
	7	57± 7	5 (71.4)			Control	No training	-	
Ghardashi Afousi A, 2018	17	54.2± 5.61	9 (52.9)	Clinical trial	T2DM Subjects for ≥ 2 years, aged 45-60 years, pre-HTA or treated HTA, and no exercise training in the previous 6 months.	Low-volume HIIT	Ergocycle training: 10-min warm-up (walking, running and stretching) at 40% HR_{max} + 1.5 min x 12 intervals of exercise (85%-90% HR_{max}) + 2-min active recovery intervals (55%- 60% HR_{max}) + 10-min cool-down (40% of HR_{max})	3d/w; 62 min/session	12
	18	54.8± 6.19	9 (50.0)			MICT	Ergocycle training: 10-min warm-up at 40% HR_{max} + 42-min cycling at 70% HR_{max} + 10-min cool-down (40% of HR_{max})	3d/w; 62 min/session	
	17	53.1± 4.84	7 (41.2)			Control	Encouraged to maintain the same daily activities without physical training throughout the study	-	
Wormgoor SG, 2018	12	52.2± 7.1	12 (100)	Clinical trial	T2DM subjects, aged 35–59 years.	HIIT	Introductory stage (3 ws): 10-min MICT cycling (50%eWLmax) at RPE of ~13. Intermediate stage (4 w): 3 bouts x 3:30-min (75% eWLmax), at RPE of ~16. Advanced stage (5 w): 2 alternative 28-min trainings, a) 12 x 1-min bouts (95% eWLmax) + 1-min recovery bouts (40% eWLmax) at RPE of ~18; b) a sprint interval training session including 8 x 30 s bouts (120% eWLmax) + 2:15-min recovery bouts (30% eWLmax). 2-min warm-up + 3-min cool-down.	3 d/w	12 w + 6 months follow-up
	11	52.5± 7.0	11 (100)			MICT	Introductory stage (3 w): 10-min MICT cycling (50%eWLmax) at RPE of ~13. Intermediate stage (4 ws): 17:30-min MICT cycling (55% eWLmax) at RPE of ~13. Advance stage (5 ws): 26-min MICT cycling (55% eWLmax) at RPE of ~14. 2-min warm-up + 3-min cool-down	3 d/w	
Mortensen SP, 2018	11	53± 7	6 (54)	Randomized controlled trial	Subjects with T2DM	HIIT	Cycling training: 5-min warm-up (40% Wpeak) + 20-min cycling (10 x 1 min at 95% Wpeak) + 1-min of active recovery (20% Wpeak).	3 d/w; 25-min of exercise/ session	11
	10	57± 9	7 (70)			MICT	Cycling training: 5-min warm-up (40% Wpeak) + 40-min cycling (50% Wpeak).	3 d/w; 45-min of exercise/ session	
Magalhaes JP, 2019	25	56.7± 8.3	15 (60)	Randomized controlled trial	Subjects with T2DM, aged 30-75 years, BMI < 48 kg/m² and no major micro or macro vascular complications.	HIIT	Cycling training: Phase 1 (w 1–4): continuous exercise at 40-60% of HRR; Phase 2 (w 5–8): 2-min bouts at 70% (w 5-6) or 80% of HRR (ws 7-8) of HRR + 1-min at 40-60% of HRR; Phase 3 (ws 9-52): 1-min exercise at 90% of HRR+ 1-min at 40-60% of HRR. After aerobic component, participants completed a whole-body resistance training with increasing weight.	3d/w; Exercise duration calculated based on VO_{2max} of each participant + weekly target of 10 kcal/kg, 33.1±6.4 min (average)	52

	28	59.7± 6.5	13 (46.4)			MICT	Cycling training: continuous exercise at 40-60% of HRR. After aerobic component, participants completed a whole- body resistance training with increasing weight.	3d/w; Exercise duration calculated based on VO_{2max} of each participant + wly target of 10 kcal/kg, 45.0±7.1 min (average)	
	27	59.0± 8.1	14 (51.9)			Control	No structured exercise sessions, participants were invited to a baseline orientation session and monthly meetings by including general PA counselling.	-	
Suryanegara J, 2019	13	61.1± 8.6	3 (23)	Randomized controlled trial	T2DM subjects, well-controlled previous 6 months, absence of DM complications, and non-smokers	HIIT	Ergocycle training: 5-min warm up at 9-13 of RPE + 5 intervals with pedal rate > 80 rev/min (16-17 of RPE) x 2-min (first w by increasing 10 s for every w until reached 3-min) + 3-min recovery cycle (90s passive recovery).	3d/w; 30-35 min/session	12
	13	59.8± 8.6	3 (23)			Control	No training	-	12
Hwang CL, 2019	18	65± 2	9 (50.0)	Randomized controlled trial	T2DM subjects, aged 30–79 years, with sedentary habits.	HIIT	Ergocycle training: 10-min warm-up at 70% HR_{peak} + 4-min × 4 intervals at 90% of HR_{peak} +3-min x 3 intervals of active recovery at 70% of HR_{peak} + 5-min cool down at 70% of HR_{peak}.	4d/w; 40 min/session	8
	16	62± 2	10 (62.5)			MICT	Ergocycle training: 10-min warm-up + 32-min of exercise at 70% HR_{peak} + 5-min cool down at 70% of HR_{peak}.	4d/w; 47 min/session	8
	16	61± 2	8 (50.0)			Control	No training	-	8
Abdelbasset WK, 2019	16	55.2± 4.3	9 (56.2)	Randomized controlled trial	T2DM Subjects, obesity, nonalcoholic fatty liver disease and aged 45-60 years.	HIIT	Ergocycling training: 5-min warm-up (cycling without resistance) + 4-min x 3 intervals of exercise at 80-85% of VO_{2max} + 2-min active recovery intervals at 50% of VO_{2max} + 5-min of cool down.	3d/w; 40 min/session	8
	16	54.4± 5.8	10 (62.5)			Control	No training	-	8

DDP-4 I: DPP-4 inhibitor; GLP-1 A: GLP-1 analogues; HRmax: Heart rate max; HRR: heart rate reserve; HRpeak: Heart rate peak; HTA: Hypertension; Min: minutes; NR: not reported; PA: physical activity; pre-HTA: pre-hypertension; RPE: Borg Rating of Perceived Exertion; S:seconds; T2DM, type 2 diabetes mellitus; W: week; Bs: Baseline; SEP: Supported exercise programme; SCP: Standard care programme; DM: Diabetes Mellitus; IWT-HIIT: Interval-walking training-High Intensity Interval Training ; CON: Continuous exercise training; CWT: continuous-walking training; HIIT: High-intensity Interval Training; MICT: Moderate intensity continuous training; CVD: Cardiovascular Disease; INT: Interval exercise training ; SED: Sedentary control ; BMI: Body Mass Index; HIIT-AIT: High intensity interval training- aerobic interval training; SOC: unsupervised physical activity; HbA1c: Glycated haemoglobin; NA: Not applied; Wpeak: peak workload; END: endurance training; eWLmax: maximum estimated workload.

Table 2. Results of the main outcomes, intervention adherence and quality score of all articles included in the meta-analysis.

First author, year of publication	Glucose (mg/dL)		Glycated hemoglobin(%)		Insulin (μIU/mL)		HOMA-IR		$VO_{2\ max}$ (L/min)		BMI (kg/m²)		Intervention adherence	Quality score
	Bs	Final	Bs	Final	Bs	Final	Bs	Final	Bs	Final	Bs	Final		
Backx, 2011	130 [103 – 162]	119 [95.5– 135]	6.40 [5.70 – 8.50]	6.00 [5.50– 7.10] **	14.5 [2.88– 34.7]	11.7 [7.2– 18.86]	3.0 [1.4– 4.1]	2.1 [1.2– 3.8]*	NR	NR	30.0 [25.3– 40.1]	28.7 [23.1 – 39.4]	63.0%	0.69
	144 [115– 202]	153 [97.3– 238]	6.60 [5.60 – 7.90]	6.70 [5.70– 9.70]	20.1 [4.17– 29.8]	17.8 [0.43– 42.2]	3.5 [1.7– 7.4]	3.1 [1.3– 6.1]	NR	NR	32.3 [26.4– 40.5]	32.0 [25.0– 41.2]	69.0%	
Karstoft, 2012	153± 14.4	151± 18	6.90± 0.20	6.80± 0.30	13.2± 2	10.6± 1.4 *	NR	NR	2.28± 1.56	2.52± 2.04**	29± 1.3	27.6± 1.1 */**	100%	0.80
	132± 14.4	148± 16.2	6.40± 0.2	6.80± 0.30	11.8 ± 1.54	16.9± 2.26**	NR	NR	2.20± 1.89	2.23± 1.81	29.7± 1.9	29.8± 1.9	100%	
	133± 7.2	139± 12.6	6.60± 0.20	6.60± 0.30	12.7 ± 1.6	13.1± 1.84	NR	NR	2.27± 1.18	2.28± 1.26	29.9± 1.6	29.6± 1.6	100%	
Terada T, 2013	123± 14.4	121± 14.4	6.6± 0.6	6.5± 0.5	NR	NR	NR	NR	22.8± 5.4[2]	24.3± 7.4[2]	28.4± 4.1	28.1± 4.0	97.2 ± 2.7%	0.69
	132± 32.4	121± 23.4	6.6± 0.9	6.7± 0.8	NR	NR	NR	NR	18.1± 2.7[2]	18.9± 4.1[2]	33.1± 4.5	32.6± 4.3	97.3± 3.7%	
Mitranun, 2014	138± 504	120± 360**	7.70± 2.30	7.50± 2.40	NR	NR	NR	NR	23.8±1.00[3]	27.1± 1.20[3] **/*	29.4± 0.70	29.2±0.60	80%	0.77
	138± 396	119± 414**	7.60± 2.30	7.10± 2.30**/*	NR	NR	NR	NR	24.2±1.60[3]	30.3± 1.20[3] **/*	29.6±0.50	28.5±0.30 **	80%	
	133± 396	131± 360	7.80± 2.30	8.10± 2.30	NR	NR	NR	NR	24.4± 1.30[3]	23.9 ± 1.00[3]	29.7± 0.40	29.4± 0.60	NR	
Maillard F, 2016	175± 12.6	180± 14.4	7.4± 0.3	7.3± 0.3**	NR	NR	NR	NR	NR	NR	32.6± 1.7	32.4± 1.6	100%	0.78
	151± 12.6	159± 19.8	7.6± 0.3	7.4± 0.3**	NR	NR	NR	NR	NR	NR	29.7± 1.2	29.9± 1.3	89%	
Hollekim-Strand SM, 2016	NR	NR	7.0± 1.2	6.6± 0.9**	NR	NR	2.7±0 .7	2.7±1.0	2.96± 0.57	3.29± 0.68 */**	30.2± 2.8	29.7± 2.4*	94%	0.81
	NR	NR	6.7± 0.7	6.5± 0.6	NR	NR	2.6±1 .0	2.5±0.9	2.96± 0.81	3.0± 0.79 */**	29.7± 3.7	29.4± 3.8	94%	
	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-	
Ramos JS, 2016	142± 30.6	148± 52.3	7.6± 2.8	7.6±3.0	15.3± 5.47	13.1± 5.62	2.1± 0.8	1.9± 0.6**	2.4± 0.7	2.7± 0.8**	NR	NR	NR	0.85
	141± 36.0	142± 41.4	7.0± 1.4	6.7±0.8	15.4± 8.06	14.3± 9.22	2.3± 1.4	2.1± 1.5	2.4± 0.6	2.6± 0.6**	NR	NR	NR	
	132± 25.2	123± 20.0	6.2± 0.9	6.0±0.7	16.4± 9.94	12.8± 8.35**	2.3± 1.6	1.7± 0.9**	2.7± 0.6	2.7± 0.4	NR	NR	NR	
Cassidy S, 2016	122± 28.8	122± 28.8	7.1± 1.0	6.8±0.9*	9.43± 5.69	9.43± 4.72	1.3± 0.8	1.4± 0.6	NR	NR	NR	NR	89%	0.64
	126± 18.0	137± 25.2**	7.2± 0.5	7.4±0.7*	11.7± 6.68	12.7± 5.69	1.6± 0.9	1.8± 0.8	NR	NR	NR	NR	-	
Ruffino S, 2016	178± 54.1	166± 39.6	NR	NR	16.0± 11.6	16.1± 13.6	7.1± 5.2	6.6± 5.4	2.60± 0.44	2.79± 0.47*	NR	NR	99%	0.76
	178± 50.4	175± 41.4	NR	NR	13.7± 10.1	17.7± 13.9	6.2± 4.8	7.5± 5.3	2.64± 0.45	2.66± 0.49*	NR	NR	97%	
Bellia, 2017	1(-14; 15) †		-0.3 (-0.4; -0.7)		0.3 (-3.5; 4.2)•		NR	NR	-1.9 (-0.3;-3.5) kg$^{\phi}$		NR	NR	>80%	0.59
	10 (-6; 27) †		-0.4 (-0.07; -0.8) ‡		2.8 (-3.8; 4.6)•		NR	NR	1.7 (-0.2; -3.3) $^{\phi}$		NR	NR	>80%	
Støa EM, 2017	NR	NR	7.78±1.39	7.19 ± 1.10 */**	NR	NR	1.75± 0.94	1.91±1.0	2.39 ±0.55	2.84± 0.66 */**	32.0± 4.7	31.4± 4.7 */**	NR	0.75
	NR	NR	6.84± 0.88	6.83± 0.84	NR	NR	1.83± 0.73	1.79± 0.77	2.29± 0.61 */**	2.25± 0.58	31.1± 4.5	31.2± 4.1	NR	
Winding KM, 2018	157± 34.2	144± 27.0**	6.8± 3	6.7± 3**	17.3± 18.9	15.0± 14.7	2.38± 2.24	1.79± 1.47**	2.4± 0.5	2.8± 0.5	28.1± 3.5	27.8± 3.5**	91± 18	0.62

										*/**				
	144± 39.6	151± 46.8	6.9± 3.1	6.9± 3	9.07± 3.60	11.1± 5.04	1.28± 0.56	1.58± 0.72	2.3± 0.6	2.5± 0.7**	27.4± 3.1	27.1± 3.2	94± 9	
	160± 43.2	169± 37.8	7± 3.3	6.9± 3.2	15.5± 10.8	15.1± 9.22	2.18± 1.32	2.18± 1.16	2.3± 0.5	2.3± 0.4	28.0± 3.5	28.3± 3.2	-	
Ghardashi Afousi A, 2018	183± 43.8	143± 35.1 */**	NR	NR	9.31± 2.88	6.80± 1.87 */**	4.21± 1.84	2.38± 0.93 */**	22.9± 4.16[2]	29.1± 4.28[2] */**	29.4± 0.93	29.2± 0.88		
	186± 33.3	155± 29.9 */**	NR	NR	9.32± 2.85	7.32± 1.88 */**	9.32± 2.85	7.32± 1.88 */**	23.5± 4.18[2]	26.5± 4.07[2] */**	28.9± 1.02	28.7± 0.98	70%	0.70
	188± 36.0	182± 35.7	NR	NR	8.94± 2.37	8.80± 2.33	4.24± 1.68	4.03± 1.62	24.4± 3.93[2]	23.1± 3.29[2] *	29.3± 1.30	29.4± 1.24		
Wormgoor SG, 2018	NR	NR	7.9 (7.2. 8.2)	7.4 (7.3. 8.1)	NR	NR	NR	NR	20.4± 6.6[2]	24.3± 6.3[2]	39.2± 9.4	39.0± 9.2	91.2± 9.9 %	
	NR	NR	7.5 (7.1. 8.4)	6.7 (6.5. 7.5)	NR	NR	NR	NR	22.7± 5.3[2]	27.3± 5.5[2]	35.0± 6.1	34.4± 5.5	90.4± 6.8 %	0.66
Mortensen SP, 2018	NR	NR	6.8± 0.9	6.6± 0.9	NR	NR	NR	NR	2.5± 0.5	2.8± 0.7	NR	NR	100%	
	NR	NR	6.9± 0.9	6.8± 0.8	NR	NR	NR	NR	2.4± 0.5	2.6± 0.5	NR	NR	100%	0.84
Magalhaes JP, 2019	159± 59.5	151± 64.8	6.9± 1.1	7.1± 3.5	NR	NR	1.9± 1.0	1.9± 1.7	27.1± 6.3[2]	26.5± 6.0[2] */**	30.1± 5.7	29.7± 5.7	52%	
	166± 73.8	166± 75.7	7.4± 1.9	7.3± 3.5	NR	NR	1.7± 1.1	1.9± 1.2	24.1± 3.2[2]	24.9± 4.1[2] */**	31.1± 5.0	30.6± 5.1	57.1%	0.96
	159± 73.8	150± 45.0	7.4± 1.8	7.4± 3.3	NR	NR	4.8± 12.3	2.4± 1.7	25.9± 5.5[2]	24.4± 5.4[2]	30.7± 5.0	30.7± 4.9	81.5%	
Suryanegara J, 2019	119± 28.8	123± 30.6	7.1± 3.1	*P*>0.05 vs. Bs	NR	NR	NR	NR	1.4± 0.4	1.4± 0.3	31.3± 5.4	-	NR	
	123± 14.4	137± 25.4 **[2]	7.2± 2.7	*P* >0.05 vs. Bs	NR	NR	NR	NR	1.4± 0.2	1.35± 0.17	31.9± 5.3	-	-	0.82
Hwang CL, 2019	133± 9	127± 9	7.1± 0.3	6.8± 0.2	NR	NR	3.65± 0.90	2.75± 0.46	2.06± 0.15	2.25± 0.17 */**	31.7± 1.3	31.5± 1.2	83± 4%	
	140± 10	139± 7	7.2± 0.3	7.0± 0.2	NR	NR	4.13± 0.84	4.08± 0.78	1.96± 0.12	2,11± 0,13 */**	31,8± 1,4	31,7± 1,5	84± 4%	0.83
	147± 16	152± 17	7.4± 0.4	7.5± 0.4	NR	NR	3.97± 0.45	4.39± 0.70	1.96± 0.12	1,92± 0,12	33,9± 1,4	33,9± 1,4	-	
Abdelbasset WK, 2019	112± 32.4	95.5± 21.6 */**	6.6± 0.4	6.2± 0.3 */**	NR	NR	4.9± 1.7	4.1± 0.6 */**	19.6± 2.6[2]	24.8± 2.5[2] */**	36.3± 4.5	34.1± 3.1 */**	NR	0.70
	106± 25.2	110± 30.6*	6.7± 0.6	6.5± 0.5*	-	-	4.8± 1.5	4.98± 1.8*	20.2± 2.3[2]	21.1± 2.4[2]*	36.9± 5.3	36.2± 5.5*	-	

[1] Values are expressed as mean ± SD or mean ± SE. [2] VO2max expressed as relative values (mL/kg/min). [3] Authors indicate that pooled data are included in statistical analysis. *Denotes p< 0.05 between groups. **Denotes p< 0.05 within each group. NR: not reported