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SYSTEMATIC REVIEW

The effects of high-intensity training on glycated hemoglobin A1C and insulin resistance compared to moderate-intensity training in patients with type 2 diabetes: a systematic review and meta-analysis

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) typically can be managed through lifestyle changes, including physical activity. Several studies have examined the effects of high-intensity training (HIT) and moderate-intensity training (MIT) on the reduction of glycated hemoglobin type A1C (HbA1c) and the improvement of insulin resistance (IR) in T2DM. **Objective**: This meta-analysis study aims to investigate the effects of high-intensity and moderate-intensity training on reducing HbA1C and improving IR in T2DM patients. **Materials and Method**: A comprehensive search of online databases, namely PubMed, ScienceDirect, and Cochrane Library, was conducted to identify relevant studies that assessed the effects of HIT in T2DM patients. A random effects model was employed to compare the mean difference and standard deviation (SD) with a 95% confidence interval (CI) to evaluate the findings of these studies. **Conclusion**: The analysis revealed that HIT led to a significantly greater improvement in reducing HbA1C. This can be attributed to HIT's ability to recruit more muscle fibers and deplete muscle glycogen levels, thereby improving glucose control. However, HIT did not show a significant improvement in IR compared to MIT.

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Highlights

1. Physical activity (PA) is an essential component of T2DM management.
2. High-intensity training is more effective in reducing HbA1C levels in T2DM patient.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) remains a major global healthcare concern (Chung et al., 2020). The World Health Organization (WHO) and the World Diabetes Federation (WDF) have reported that more than 537 million people were diagnosed with T2DM. In Indonesia, the WHO predicts that T2DM cases will increase to 21.3 million by 2030 (International Diabetes Federation, 2021). Consistent with the WHO's statement, the Baseline Health Research (2018) projected an increase in T2DM prevalence in both urban and rural areas of Indonesia. This is concerning as not only is the prevalence increasing, but also the onset of T2DM occurs more rapidly than in previous decades (Kumar et al., 2019).

T2DM is a metabolic disease characterized by a decline in pancreatic function and insulin resistance in the body's cells (Pedrosa et al., 2023). Multiple mechanisms contribute to reduced pancreatic function, including genetic predisposition and abnormalities, epigenetic processes, insulin resistance (IR), autoimmunity, concurrent illnesses, inflammation, and environmental factors (Petersen and Shulman, 2018). Common risk factors in T2DM patients include being overweight, a lack of physical activity, a family history of diabetes, a history of gestational diabetes, and ethnicity (WHO and IDF, 2020). These conditions can lead to premature mortality and morbidity related to cardiovascular disease, kidney disease, cerebrovascular disease, and peripheral vascular disease (Pedrosa et al., 2023; WHO and IDF, 2020), all of which impact the quality of life (QoL) of T2DM patients (Kumar et al., 2019).

T2DM patients require strict dietary intervention and physical activity management (Sami et al., 2017). Guidelines strongly recommend physical activity as a lifestyle modification. Patients are advised to engage in at least 150 minutes of moderate-intensity training (MIT) or vigorous-intensity continuous aerobic exercise per week, divided into three sessions, with intervals at 40-60% of their maximum aerobic capacity (Colberg et al., 2016). Physical activity encompasses all energy expenditure through movement defined as any body movement resulting in energy expenditure above the resting level (Manz and Krug, 2013). Meanwhile, exercise is planned or structured movement with specific intent to improve aerobic and/or muscular fitness (Dasso, 2019). Several studies indicated that high-intensity interval training (HIT) can serve as an alternative therapy with positive impacts on IR markers. HIT is defined as 75 minutes of aerobic exercise per week, spread over three sessions, with a minimum of 70% aerobic capacity (Pedrosa et al., 2023). Exercise provides substantial energy expenditure for T2DM patients, which enhances insulin action through insulin-independent glucose transport. As a result, exercise improves glycemic control, reduces fasting insulin by 45%, and stimulates glucose disposal (Kirwan et al., 2017).

In general, aerobic exercises are favored in T2DM lifestyle management due to their engagement of more muscles and increased energy metabolism. In the short term, aerobic exercises increase glucose availability, contributing to higher glucose consumption and improving insulin sensitivity within 72 hours. In addition, they enhance glucose transporter (GLUT) sensitivity on the cell membrane (Kirwan et al., 2017). In the long term, physical exercises enhance β-cell function, reduce fat storage, preserve lean body mass, and improve cardiovascular health, lipid metabolism, and low-density lipoprotein cholesterol (LDL-c) (Amanat et al., 2020). Nevertheless, the question remains as to which specific physical activities have the greatest impact on T2DM patients.

Moreover, global health expenditures due to T2DM are estimated to be twice as high as for individuals without diabetes. In the United States alone, the cost increased from $232 billion in 2007 to $966 billion in 2021 for adults with T2DM. The increasing prevalence of T2DM will further increase the direct costs of this disease. To curb the rapid growth of medication costs, it is important to manage already diagnosed T2DM patients so that complications can be prevented and the severity of T2DM can be reduced (Cho et al., 2018). Many T2DM patients with uncontrolled glucose levels require comprehensive lifelong treatment. Early prevention through lifestyle modification is one of the cost-effective strategies to mitigate T2DM's impacts.

OBJECTIVES

This meta-analysis aims to investigate the effects of high-intensity and moderate-intensity training on reducing HbA1C and improving insulin resistance in T2DM patients.

MATERIAL AND METHODS

Search strategies

This systematic review was conducted following the PRISMA 2020 Guidelines and involved online database searches conducted in February 2023. The databases searched were PubMed, ScienceDirect, and Cochrane Library. The literature search only projected studies assessing the effects of high-intensity training (HIT) in comparison to moderate-intensity training (MIT) on patients with type 2 diabetes mellitus. The following search string used was "("High-intensity training" OR "High-intensity interval training" OR "High-intensity aerobic interval training") AND "Type 2 Diabetes", which was limited to human studies. In addition, a bibliographic search of included papers was done by the authors independently. Disagreements were resolved through consensus or by involving a third reviewer.

Inclusion criteria

The inclusion criteria for this study encompasses the following criteria: (1) randomized controlled trial (RCT) studies involving (2) adult populations with T2DM; (3) the intervention group that received a high-intensity training program; (4) the control group that received a moderate-intensity training program; (5) providing training duration lasting more than four weeks; and (6) having outcomes that must include changes in HbA1C.

Exclusion criteria

Excluded studies consisted of those involving patients with secondary acute or chronic diseases or patients with heart failure. Studies were also excluded if they had a total population of fewer than 40 patients, or if the full-text articles were unavailable.

Data collection

The extracted publications that met the inclusion criteria were analyzed. The analysis encompasses the study title, authors, publication year, number of patients, patients' primary diagnoses, intervention treatment, control treatment, number of patients in each treatment group, duration of treatment, and reported outcomes. For statistical analysis, the intervention group included studies with high-intensity training, which was defined as a training program with a target heart rate (HR) of ≥75% of the maximum heart rate (maximum heart rate = 220 – age) or ≥75% of the maximum VO_2. The control group consisted of studies with moderate-intensity training, which was defined as a training program with a target HR of 50-70% of the maximum heart rate or 40-70% of the maximum VO_2 regardless of the training duration.

Data analysis

Each study included in this systematic review was described with baseline characteristics, and continuous variables were presented as mean ± standard deviation (SD), while categorical variables were summarized as percentages (%). The primary outcomes of this study were glycated hemoglobin type A1C (%) and IR (measured by the Homeostatic Model Assessment for Insulin Resistance or HOMA-IR). All continuous data were summarized as mean differences, while statistical significance was assessed using a standard χ^2 test (with a significance level of $p < 0.05$) and I^2 (>50%). If I^2 was

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<50%, fixed effects, and random effects models were applied. In cases where these analyses yielded similar results, the results of the random effects models were assessed for heterogeneity. In addition, Funnel plots, Egger's test, and Begg's tests were used to assess publication bias quantitatively with visual inspection. All variables were considered significant at $p < 0.05$. Finally, a forest plot analysis was performed using Review Manager 5.4 (Cochrane.org), while a funnel plot analysis was performed using MedCalc 20.217 (MedCalc Software Ltd.).

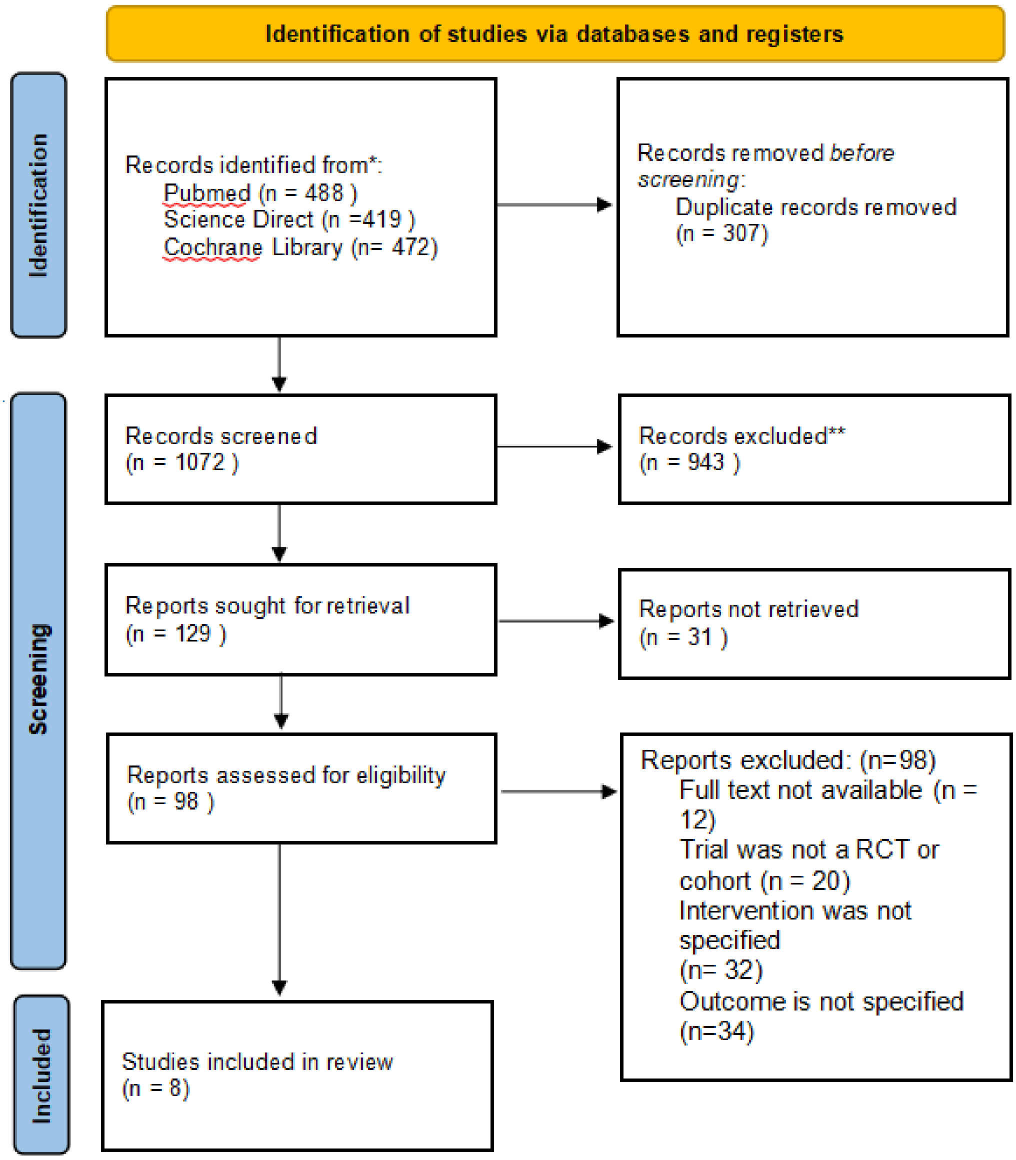

Figure 1. Study selection process diagram for meta-analysis

RESULTS

Description of studies

The initial search on PubMed, Cochrane Library, and Science Direct yielded a total of 1,379 articles. After the removal of 307 duplicates, 1,072 articles were reviewed by their titles and abstracts. Subsequently, 943 articles were excluded, leaving 98 potentially eligible articles for further assessment to determine whether they met the inclusion or exclusion criteria. Ultimately, eight articles were found to meet the inclusion criteria (**Figure 1**). The characteristics of studies investigating the effects of high-intensity interval training versus moderate-intensity training on glycated hemoglobin type A1C and insulin resistance in patients with type 2 diabetes are presented in **Table 1.** The number of participants in each trial ranged from 15 to 20 patients, with a total population of 246 participants across all studies. These studies were published between 2009 and 2023, and the duration of each study ranged from 8 weeks to 4 months.

Table 1. Characteristics of studies included in this systematic review

Author Name	Year of Publication	Type of Patients	Sample Size	Type of Intervention	Duration of Intervention
Walid Kamal et al.	2019	T2DM, non-alcoholic fatty liver	47	HIT, MIT, control	8 weeks
Chueh-Lung et al.	2019	T2DM, sedentary, 30-79 y.o	50	HIT, MIT, control	8 weeks
Siri Hollekim et al.	2014	T2DM with diastolic dysfunction	37	HIT, MIT	12 weeks
Hansen et al.	2009	T2DM min 12 months w/ oral OAD	50	HIT, MIT	6 months
Paulo et al.	2023	T2DM, > 40 y.o	52	MIT, L-HIT, S-HIT	8 weeks
Eva Maria et al.	2017	T2DM , 20-70 y.o	38	HIT, MIT	12 weeks
Tasuku Terada	2012	T2DM, 55-75 y.o	15	HIT, MIT	12 weeks
Mailar et al.	2016	T2DM, post menopause	16	HIT, MIT	16 weeks

Sources: (Gentil et al., 2023; Hansen et al., 2009; Hollekim-Strand et al., 2014; Hwang et al., 2019; Maillard et al., 2016; Støa et al., 2017; Terada et al., 2013)

The effects of HIT and MIT on T2DM patients

To assess the effects of HIT and MIT on HbA1C levels in T2DM patients, data from eight RCTs were analyzed. The results showed that HIT led to a significant reduction in HbA1C levels compared to MIT (WMD -0.21; $I^2 = 94\%$; 95% CI [-0.37; -0.06] $p < 0.006$) (**Figure 2)**. However, HIT did not significantly improve IR compared to MIT (WMD -0.72; $I^2 = 99\%$; 95% CI [-1.68; 0.24] p = 0.14) **(Figure 3).**

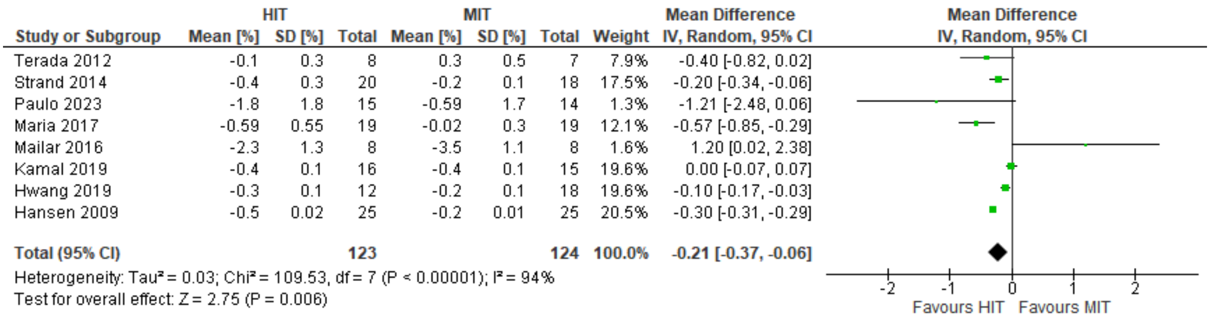

Figure 2. Forest plot for analysis of glycated hemoglobin type A1C

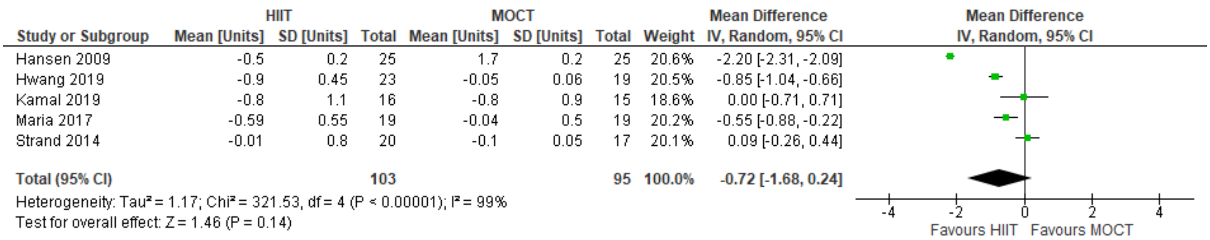

Figure 3. Forest plot for IR analysis

Publication bias

In this systematic review, a funnel plot was employed to assess publication bias and heterogeneity in the studies included in the analysis. For the comparison between MIT and HIT regarding changes in IR, a symmetric inverted funnel shape was identified, indicating that publication bias is unlikely. In contrast, an asymmetric funnel shape and a different redistribution pattern were identified, indicating the presence of publication bias regarding changes in glycated hemoglobin type A1C (HbA1C). To further quantify funnel plot asymmetry, statistical measures, Egger's test and Begger's test, were employed (Ali et al., 2019; Simmonds, 2015).

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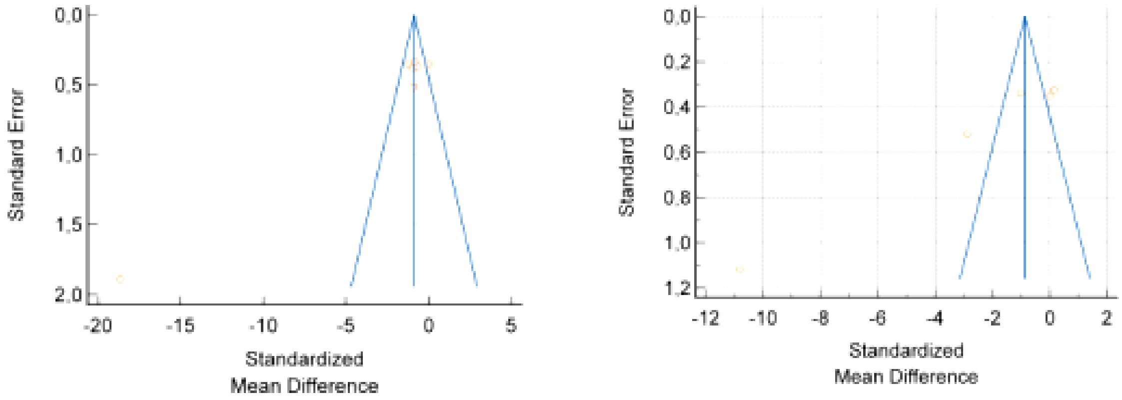

Figure 4. Funnel plot for analysis of IR and glycated hemoglobin type A1C

Table 2. Egger's Test and Begg's test for publication bias

	Intercept	Egger's test 95% CI	P value	Begg's test	
				Kendall's Tau	P value
HbA1C %	-10.4182	-15.8517 to -4.9847	0.0044	-0.3333	0.0092
HOMA-IR	-13.6021	-20.0179 to -7.1864	0.0066	-0.8000	0.0500

DISCUSSION

Exercising effectively reduces HbA1C levels in T2DM, a marker of long-term glycemic control associated with T2DM complications (Van Dijk and Van Loon, 2015; Yun et al., 2022). While HbA1C reflects average blood glucose concentrations over an extended period, it provides limited information about daily fluctuations in blood glucose levels (Van Dijk and Van Loon, 2015). Exercise affects glucoregulation through both weight-loss and weight-loss-independent mechanisms (Syeda et al., 2023), including a reduction in visceral fat, which improves metabolism (Najafipour et al., 2017). Some studies suggest that HIT is required to effectively improve glycemic status in T2DM patients (Kirwan et al., 2017; Park and Lee, 2015; Syeda et al., 2023; Van Dijk and Van Loon, 2015). The rationale for the advantage of MIT and HIT in glycemic control for T2DM patients lies in the fact that exercise leads to similar energy expenditure. Endurance-type exercise is generally recommended for glycemic control in T2DM patients as it reduces body fat mass and maximizes the oxidation of skeletal muscle fat (Dunstan et al., 2005). HIT has been shown to reduce trunk fat mass, which is associated with higher oxidative capacity of skeletal muscles, potentially lowering the risk of obesity. However, the greater loss of trunk fat mass is not necessarily accompanied by improvements in IR in T2DM patients (Mulla et al., 2000).

In this study, eight studies with a total 246 participants were analyzed. The effects of physical exercise on T2DM patients, comparing HIT and MIT, showed variations among the studies. While not all studies focused on reducing HbA1C levels and changes in IR, some studies provided data on HbA1C levels before and after exercise. Some studies also showed improvements in IR as a secondary outcome (Gentil et al., 2023; Hansen et al., 2009; Hollekim-Strand et al., 2014; Hwang et al., 2019; Maillard et al., 2016; Støa et al., 2017; Terada et al., 2013).

The results suggested that HIT has a greater impact on reducing HbA1C levels compared to MIT. Although the forest plot in this study showed statistical heterogeneity, differences in population, interventions, duration, and settings were implied. To account for this heterogeneity, a random-effects method for statistical analysis was used. The data showed a statistically significant difference (WMD -0.21; $I^2 = 94\%$; 95% CI [-0.37; -0.06] p =< 0.006). For instance, the study by Gentil et al. (2023) yielded similar results. When comparing HIT and MIT over eight weeks with twice-weekly sessions, HIT led to greater reductions in HbA1C, blood glucose levels, and other risk factors than MIT (Gentil et al., 2023). This may be related to the increase in glucose transporter 4 (GLUT 4) protein with high calcium concentrations, which is found to increase with training intensity, resulting in protein translocation to the cell membrane and increasing glucose uptake by muscle cells (Schnurr et al., 2015). In addition, the study by Eva in 2017 showed that HIT improved the maximum rate of Vo2 (Vo2 max) to a greater extent than MIT. Improved Vo2 max is known to reduce cardiovascular events and contribute to weight reduction as a result of increased energy expenditure (Stoa, 2017).

Abdelbasset et al. (2020) found that MIT was as effective as HIT in reducing HbA1C levels with no significant difference between them (Abdelbasset et al., 2020). However, this study lacked supervision during exercise training. A six-month exercise training program observed by Hansen et al. (2009) also found no significant difference between MIT and HIT, but it revealed that HIT was significantly more effective in improving metabolism in certain populations (Hansen et al., 2009). According to Terada et al. (2012), although both HIT and MIT did not significantly reduce HbA1C levels, both exercises were feasible and provided satisfaction to all participants over 12 weeks (Terada et al., 2013).

Limitations

This study had several limitations. It included all available clinical data, and the quality of the included studies varied from intermediate to excellent levels. However, the results of this systematic review are considered reliable based on the findings of the sensitivity analysis and the assessment of publication bias. Another limitation is the relatively small sample size, which can reduce the statistical power of the analysis. In addition, this study only included short-term studies despite diabetes being a chronic disease. Future research needs to encompass long-term studies comparing different exercises interventions. Furthermore, variations in interventions and exercises across the studies may contribute to some heterogeneity.

CONCLUSION

This study has shown that high-intensity training significantly reduces serum HbA1C levels compared to moderate-intensity training. However, high-intensity training has no significant difference in the reduction of insulin resistance compared to moderate-intensity training.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Clearance

Not applicable.

Author Contribution

Conceptualization, SES., M.W., D.W., G.W.; Methodology, S.S., M.W., D.W., G.W., Software, M.W., G.W., Searched and extracted data, S.S., M.W.,; Validation D.W., G.W., writing -original fradt preparation S.S., M.W., ; writing review and editing D.W., G.W. All authors have read and agreed to published version of the manuscript.

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