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Review

Aerobic exercise improves HbA1c levels and sensory outcomes in diabetic peripheral neuropathy: A systematic review and meta-analysis

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Abstract. *Background and aim:* Diabetic peripheral neuropathy (DPN) is one of the complications of type 1 and type 2 diabetes. Some parts of the body experience damage to the nerves due to high blood sugar levels. Aerobic exercise is known to improve glycaemic control and nerve function. This meta-analysis aimed to evaluate the effect of aerobic exercise on sensory and haemoglobin A1c (HbA1c) in patients with DPN. *Methods:* Literature searches were conducted in ScienceDirect, Pubmed, Web of Science, and Scopus for eligible articles published from 2010 to 2024. Inclusion criteria were determined using the PICOS approach with a moderate-intensity aerobic exercise intervention. The primary outcomes were sensory scores (sural and peroneal NCV) and HbA1c with a randomised control trial (RCT) research design. *Results:* We found that the pooled effect analysis of aerobic exercise on HbA1c of the three studies were significant (SMD -0.53; 95% CI = -0.89-0.17; $P = 0.004$) however there was no significant effect of non-physical activity/standard care on HbA1c (SMD 0.08; 95% CI = -0.26-0.42; $P = 0.64$). Meanwhile, analysis shows a moderate effect of aerobic exercise on NCV-sural examination scores with a pooled standardised mean difference (SMD) 1.40 (95% CI = 0.44-2.36). *Conclusions*: Our findings highlight aerobic exercise could be an effective non-pharmacological intervention to improve sural nerve function in DPN. Aerobic exercise regimens should be structured in a comprehensive therapy strategy. Further research is needed to focus on identifying the more optimal and tolerable aerobic exercise to maximise therapeutic approaches. In addition, there is a need to develop analyses of the effect of various intensities and types of exercise on DPN management. (www.actabiomedica.it)

Key words: aerobic exercise, diabetic peripheral neuropathy, exercise therapy, haemoglobin A1c, glycemic control, meta-analysis, neuropathy complications, physical activity, sensory function, systematic review

Introduction

Diabetes is currently a global health issue. Various epidemiological studies have shown an increasing trend in the incidence and prevalence of type 2 diabetes in the world. Globally, the incidence of type 2 diabetes has increased from 2.8% in 2000 to an estimated 4.4% in 2030 (1). Chronic complications of diabetes can be in the form of macrovascular and microvascular disorders (2). In a study conducted on 1785 diabetes patients in Indonesia, 16% of diabetes patients had macrovascular complications, while 27.6% had microvascular complications. Of all patients with microvascular complications, 63.5% had neuropathy, 42% had retinopathy, and 7.3% had nephropathy (3). Diabetic peripheral neuropathy (DPN) is one of the most common long-term complications, affecting 40% of people with type 2 diabetes (4). The prevalence of peripheral neuropathy is estimated to be between 6% and 51% among adults with diabetes, depending on age, duration of diabetes, glucose control, and type 1 or type 2 diabetes (5). DPN is heterogeneous and affects various parts of the nervous system, so it has several different types depending on the location and type of nerve fibres involved. DPN is a neuropathic pain that is often found in diabetics due to damage to the central and peripheral nervous systems. More than 50% of the total adult population with type 1 and type 2 diabetes experience peripheral neuropathy (5). Neuropathic pain is known to affect a person's function and quality of life. Initial symptoms are usually characterised by sensory disturbances in the form of pain or tingling in the leg area (6, 7). Exercise can positively influence neuropathy-related pathological factors by promoting microvascular dilatation, reducing oxidative stress, and increasing neurotrophic factors. Previous studies have found that exercise interventions reduce neuropathic symptoms, nerve function, and skin innervation (8). As physical exercise has been shown to improve the management of diabetes and its complications, several previous studies have shown that aerobic exercise resulted in decreased HbA1c and improved muscle strength and glycaemic control. Exercise has also been shown to have an effect on glycaemic control in diabetes from weight control. Physical exercise also improves cardiovascular complications of diabetes by ameliorating endothelial dysfunction and arterial remodelling and stiffness through restoration of normal reduction-oxidation balance (9). In recent years, many studies have been conducted to extensively study physical exercise in patients with peripheral neuropathy. However, there are still study limitations and gaps in research results, so further research is needed, especially for sample characteristics (age, gender) and types of physical exercise, including exercise doses to prevent unwanted effects. This study's primary objective was to find out more about the effect of aerobic exercise on sensory scores and HbA1c levels in DPN patients. The study included age and gender variations in the DPN patient sample as well as specifics on the effect of aerobic exercise on sensory scores and HbA1c levels, which had never been examined in previous similar studies.

Methods

The present systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (10). Our study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the confirmed code CRD420H22330300.

Search strategy

The literature search was conducted using databases from Science direct, Pubmed, Web of science, and Scopus for articles up to. Study selection was limited to Randomised Control trial studies, English language, and available in full-text. The article search used keywords according to the previously formulated concepts of population, intervention and outcome based on the PICOS approach. The inclusion criteria for this study used the PICOS approach (11). Population: patients with diabetes neuropathy, diabetes peripheral neuropathy aged between 35 - 70 years; Intervention: moderate intensity aerobic exercise; Comparison: non-physical exercise; Outcome: sensory value (NCV) and HbA1c; Study design: randomised control trial (RCT). Inclusion criteria included studies involving subjects with a history of cardiovascular disease, patients with leg ulcers or amputations, patients with severe osteoporosis, studies without a control group, animal studies, and not RCTs. The main outcome parameters used for the analysis of this study were examination using the Michigan Diabetic Neuropathy Score (MDNS) and Michigan Neuropathy Screening Instrument (MNSI) scales to determine the degree of neuropathy, examination using the MAAS scale,

Table 1. Searching Strategy

Concept	Keyword	Boolean operator
Research related to Diabetic polyneuropathy	Diabetic Neuropathies, Diabetic Neuropathy, Diabetic Polyneuropaties,Diabetic Polyneuropathy, Diabetic Autonomic Neuropathy, Diabetic Complicaton, Asymmetric diabetic proximal motor neuropathy, Diabetic Asymmetric Polyneuropathy, Diabetic Peripheral Neuropathy, Diabetic Neuralgia, Diabetic Sensorimotor Polyneuropathy, Diabetic Neuropathies Painful	"Diabetic Neuropathies" OR "Diabetic Neuropathy" OR "Diabetic Polyneuropaties" OR "Diabetic Polyneuropathy" OR "Diabetic Autonomic Neuropathy" OR "Diabetic Complicaton" OR "asymmetric diabetic proximal motor neuropathy" OR "Diabetic Asymmetric Polyneuropathy" OR "Diabetic Peripheral Neuropathy" OR "Diabetic Neuralgia" OR "Diabetic Sensorimotor Polyneuropathy" OR "Diabetic Neuropathies Painful"

Toronto Clinical score (TCSS) to determine nerve damage and nerve dysfunction and examination of blood samples to determine HbA1c levels. Based on these keywords, Boolean operators will be added to simplify and specify the search. To search more specifically, the keywords were assigned the boolean operator (Table 1).

Criteria and study selection

Study selection was limited to Randomised Control Trial (RCT) studies, English language and available in full-text. The article selection process uses guidelines based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 diagram. Based on the PRISMA 2020 diagram, articles that have been identified will then be selected based on the previously formulated inclusion and exclusion criteria. In the selection process, researchers also reduced duplicated articles using the Mendeley desktop reference manager. Data extraction was carried out by compiling a summary related to the description of study characteristics (such as author, year of publication), sample characteristics (such as type of diabetes, age, gender, BMI), exposure characteristics (duration, type of exposure, type of physical activity), as well as research results data that met the inclusion and exclusion criteria to be entered and analysed using the Revman 5 application.

Quality assessment

This study used the Revised Cochrane Collaboration Tool for Risk of Bias (RoB 2.0) to systematically assess the risk of bias in the studies included in this review. There are five domains assessed by RoB, which are 1) randomization process, 2) deviation from the intended intervention, 3) missing outcome data, 4) outcome measurement, and 5) selection of reported results (12). The results of each study's risk of bias assessment will be recorded in tabular format (.xlsx) and visualised using robvis (13). The authors assessed the risk of bias of each study. Disagreements between reviewers were resolved through discussion to reach a consensus.

Data analysis

A heterogeneity test to test whether the studies used have similar or different characteristics. In meta-analysis, fixed effects for low heterogeneity of effects (Chi Square: $P \geq 0.05$/ $I^2 < 50\%$) and random effects for high heterogeneity of effects (Chi Square: $P < 0.05$/ $I^2 \geq 50\%$) are known for heterogeneity tests. The selection of the two tests can use the help of the Cochrane Q statistical test or the intuitive index (I^2). In this process, a publication bias analysis with funnel plots will also be conducted. A subgroup analysis to broaden and deepen the analysis was also conducted in this study. The next step was to analyze the amount of publication bias in each article using Cochrane's RoB 2 (Risk of Bias 2) tool. It was used as a recommended critical review to ensure the quality of the articles/primary studies used. The risk of bias was assessed as "low", "high", and "some concerns". Subsequently, the results fr ni om all studies were combined to analyze the effect of the intervention. Standardised Mean Difference (SMD) with forest plot output is used to determine the effect size or intervention effect.

Results

The search results produced a total of 11,342 articles with details for each database, namely: Pubmed (592 articles), Web Of Science (735 articles), ProQuest (98 articles), Science Direct (7,934 articles) and Scopus (1,983 articles). The remaining articles (n=19) were selected by reading in detail the full-text of the articles. From this step, 15 articles were excluded with the following details: Compare with healthy participants (n = 2), Compare with other exercise (n = 1), Combine with other exercise (n = 4), Have no NCV/Hba1c score (n = 2), Not moderate aerobic exercise (n = 2), Not DPN (n = 1), Have no control group (n = 2), Have the same sample and outcome with other articles (n = 1). This left only four articles that met the inclusion and exclusion criteria. This selection process was described in detail in PRISMA Flow

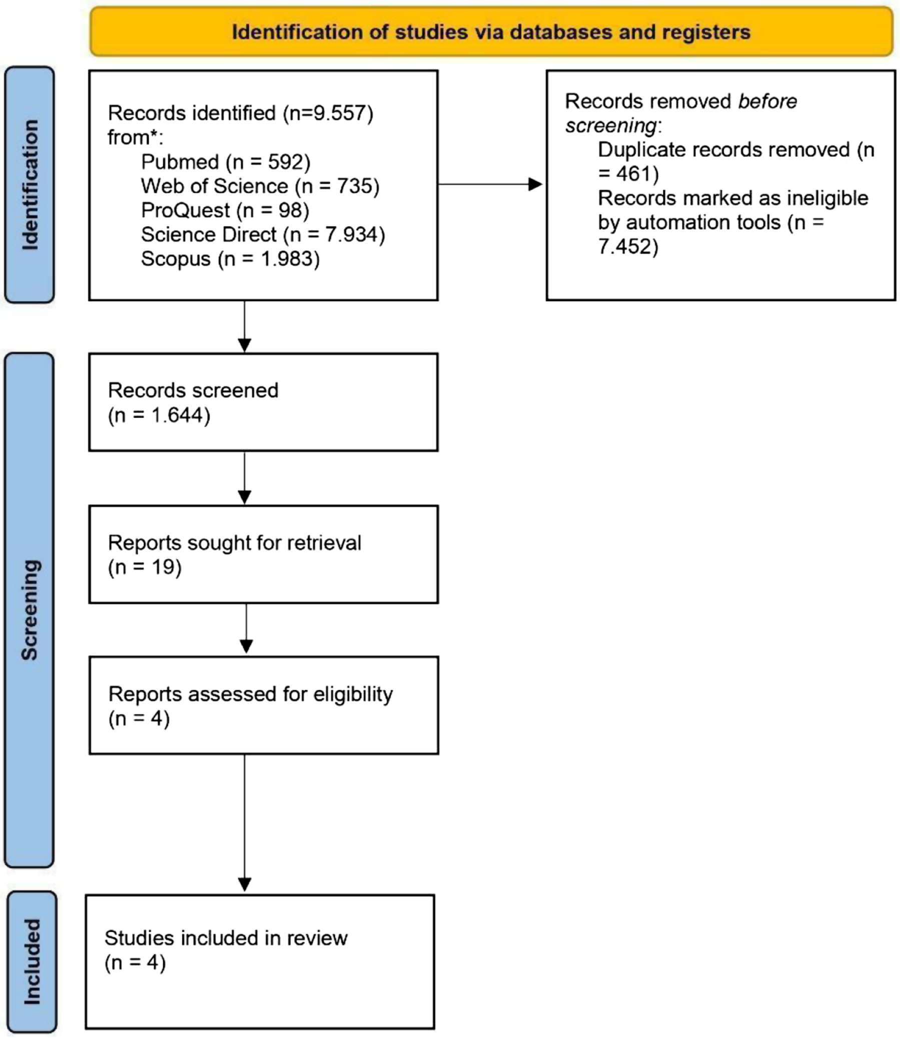

Figure 1. PRISMA flow diagram of study selection process for the review, detailing identification, screening, eligibility, and inclusion stages.

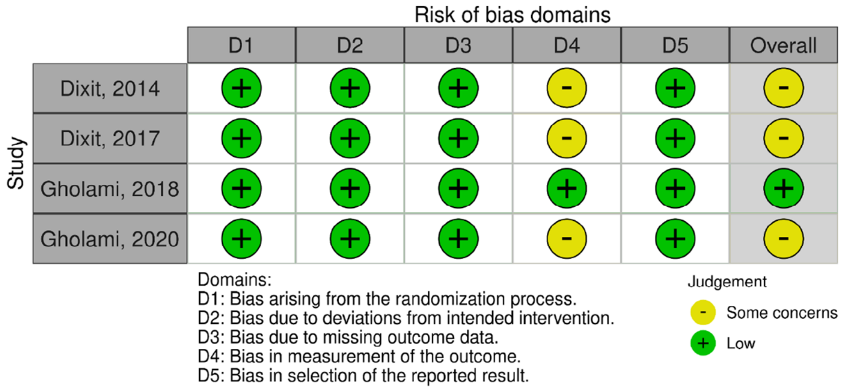

Figure 2. Risk of Bias (RoB) 2 Tools.

2020 (Figure 1). Analysis of the magnitude of publication bias in each article using RoB 2 (Risk of Bias 2) Tools from Cochrane. The results of the bias analysis on the four selected articles showed that three articles had some concerns and 1 article was of high quality as indicated by low publication bias (Figure 2). The overall study characteristics are summarised in Table 2. The studies used were from two countries: two articles from Iran and two articles from India. The selected articles were published from 2010 to 2024, all of which used RCT study design, with two articles using single blinding, while the other two were not described.

The total number of subjects included in the four primary studies was 187 with the following breakdown: Two studies used a total of 66 subjects aged ≥ 50 years who met the criteria of having been diagnosed with DPN with a minimum Michigan Diabetic Neuropathy Score (MDNS) score of 7 or mild score (8). One study utilised 24 subjects who met the criteria of being diagnosed with DPN and having a Michigan Neuropathy Screening Instrument (MNSI) score ≥ 3 (14). One study used 31 people who had been diagnosed with DPN and had Michigan Diabetic Neuropathy Score (DPN) scores of 13-29 or classified as moderate scores (15).

The interventions in all selected studies were moderate aerobic exercise performed by walking or running on a treadmill (8, 14, 15) and stationary cycling (15). The determination of exercise dose was described as follows: two studies were conducted 3-6 times per week with exercise duration of 150-360 minutes per week, intensity of 40-60% of HRR and duration of the study was for 8 weeks (8, 16). One study was conducted 3 times per-week for 60 to 135 min/week at an intensity of 50-70% of HRR, and the duration of the study was 12 weeks (14). One study was conducted 3 times per week for 90 to 135 minutes/week at an intensity of 50-70% of HRR and a study duration of 12 weeks (15). All studies compared moderate aerobic exercise interventions with standard medical care and maintained the subjects' usual physical activity habits.

The results of the heterogeneity test showed that this analysis had high variation (Heterogeneous) as indicated by the intuitive index (I^2) value = 78% and a *P* value of 0.05 (P = 0.01), so a random effects analysis was performed. The results of the overall effect analysis of the 3 studies showed that there was no significant effect of both groups after treatment on HbA1c as indicated by the pooled SMD value = -0.82 (95% CI = -1.69-0.06; P = 0.07) (Figure 3). However, the results of further analysis of the effects of the 3 studies on this group showed that there was a significant effect of the pre- and post- test analysis on the aerobic exercise group indicated by a pooled SMD value = -0.53 (95% CI =-0.89-0.17; P = 0.004) and there was no significant effect on the non-physical exercise/standard care Pre and post -test with a pooled SMD value = 0.08 (95% CI =-0.26-0.42; P = 0.64) (Figure 4).

A total of 2 studies have been analyzed regarding the improvement of NCV-sural size in people with DPN by comparing the effect of moderate aerobic exercise with standard care/no exercise. The results of the overall effect analysis of the 2 studies showed that there was a significant effect of both groups as indicated by

Table 2. Primary Study Characteristics

Author, year	Title	Study Design	Subject	Age	Sample Size	Intervention	Intervention Duration	Outcome
Dixit, 2014 (8)	Effect of aerobic exercise on peripheral nerve functions of population with DPN in type 2 diabetes: A single blind, parallel group randomised controlled trial	RCT - Single Blinding	Type 2 Diabetes with DPN (MDNS Mild Score/ minimum 7)	≥ 50 y.o	Exc: 29 Non: 37	Type: Aerobic Moderate / treadmill Frequency: 3-6 times/week Duration: 150-360 min/ week Intensity: 40-60% HRR	8 weeks	NCV (Peroneal & Sural)
Dixit, 2017 (16)	Effect of moderate-intensity aerobic exercise on glycosylated haemoglobin among elderly patients with type 2 diabetes & peripheral neuropathy	RCT - Single Blinding	Type 2 Diabetes with DPN (MDNS Score minimum 7)	≥ 50 y.o	Exc: 29 Non: 37	Type: Aerobic Moderate / treadmill Frequency: 3-6 times/week Duration: 150-360 min/ week Intensity: 40-60% HRR	8 weeks	HbA1c
Gholami, 2018 (14)	Effect of aerobic training on nerve conduction in men with type 2 diabetes and peripheral neuropathy: A randomised controlled trial	RCT	Type 2 Diabetes with DPN (MNSI Score ≥ 3)	-	Exc: 12 Non: 12	Type: Aerobic Moderate - walking / jogging on treadmill Frequency: 3 times/week Duration: 60-135 min/week Intensity: 50-70% HRR	12 weeks	NCV (Sural, peroneal, tibial), HbA1c
Gholami, 2020 (15)	Cycle Training improves vascular function and neuropathic symptoms in patients with type 2 diabetes and peripheral neuropathy: A randomised controlled trial	RCT	Type 2 Diabetes with DPN (MDNS Moderate Score/ 13-29)	-	Exc: 16 Non: 15	Type: Aerobic Moderate / cycling exercise Frequency: 3 times/week Duration: 90-135 min/week Intensity: 50-70% HRR	12 weeks	Vascular measures of FMD, intima media thickness (IMT) and baseline vessel diameter in superficial femoral artery, MDNS, BGC, HbA1C

Abbreviations: Exc (exercise); non (non-exercise); DPN (diabetic peripheral neuropathy); RCT (randomised controlled trial); MDNS (The Michigan Diabetic Neuropathy Score); MNSI (Michigan Neuropathy Screening Instrument); HRR (heart rate reverse); NCV (nerve conduction velocity); HbA1c (haemoglobin A1c); FMD (flow-mediated dilatation); BMI (body mass index); BGC (blood glucose concentration.

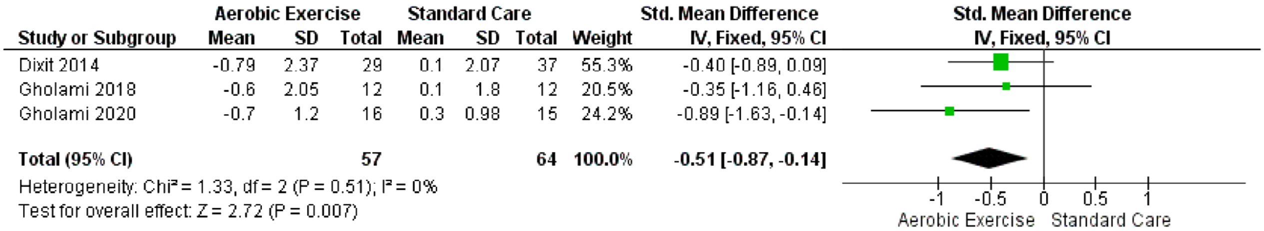

Figure 3. Results of analysis and Forest plot of HbA1c levels after moderate aerobic exercise and without exercise/standard care.

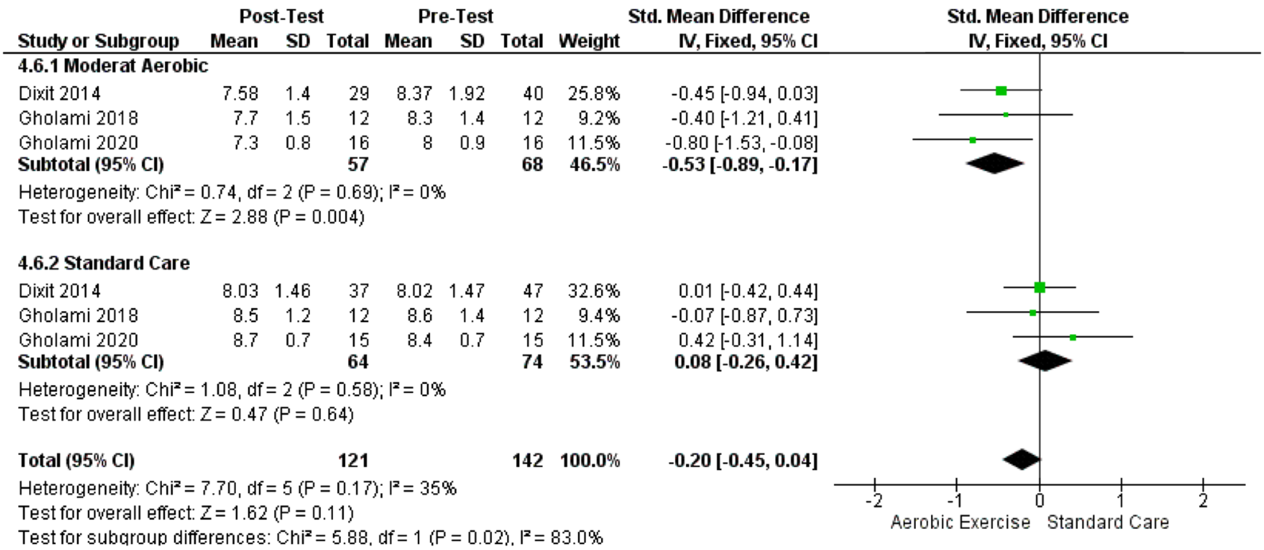

Figure 4. Results of analysis and Forest plot of HbA1c levels at pre- and post-test in the moderate aerobic exercise group and without exercise/standard care.

the pooled SMD value = 1.40 (95% CI = 0.44-2.36; *P* = 0.004) and the diamond image on the forest plot that did not touch the vertical centre line (Figure 5). Meanwhile, the results of the effect analysis on NCV-peroneal showed that there was a non-significant effect of the two groups as indicated by the pooled SMD = 2.66 (95% CI = -3.21-8.54; *P* = 0.37) (Figure 6). Our study also analyzed the NCV-peroneal changes before and after in the moderate aerobic exercise group and the no physical exercise/standard care group. The results of the effect analysis of the moderate aerobic exercise group showed that there was no significant effect from the pre- and post-test analysis as indicated by the pooled SMD value = 1.41 (95% CI = -0.66-3.47; *P* = 0.18) (Figure 7). Similarly, the results of the effect analysis in the non-physical exercise/standard care group showed that there was no significant effect from the pre- and post-test analysis as indicated by the pooled SMD = -0.10 (95% CI = -0.48-0.28; *P* = 0.61) (Figure 8).

Discussion

Effect of aerobic exercise on HbA1c

Diabetes is one of the main problems in metabolic syndrome characterised by loss of carbohydrate tolerance, causing hyperglycemia. Chronic complications of diabetes can be macrovascular and microvascular disorders (17). Diabetes cases in Indonesia in 2003 were 13.7 million people and increased to 20.1

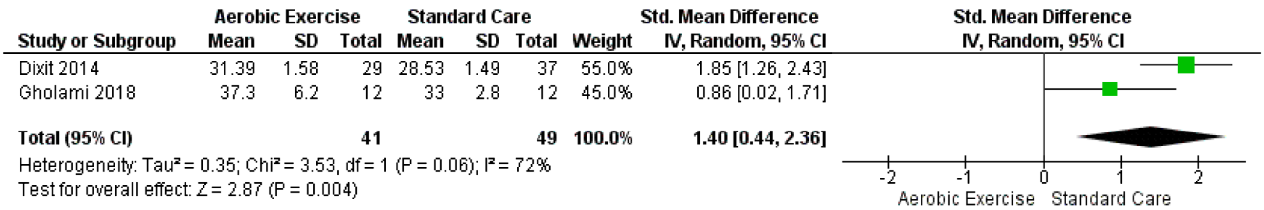

Figure 5. Standardised mean effects of aerobic exercise and standard care on NCV-sural after moderate aerobic exercise and no exercise/standard care.

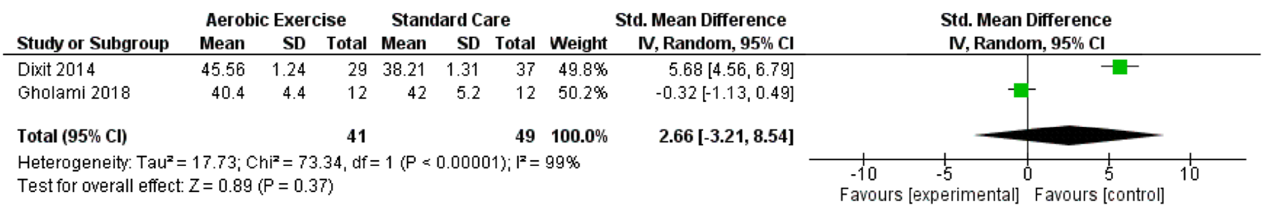

Figure 6. Standardised mean effects of aerobic exercise and standard care on NCV-peroneal after moderate aerobic exercise and no exercise/standard care.

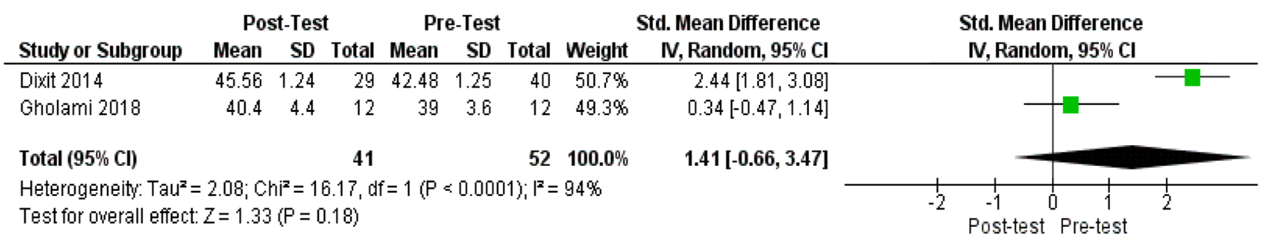

Figure 7. Standardised mean effects of NCV-peroneal at pre- and post-test in moderate aerobic exercise group.

million people in 2030 due to population growth, and the prevalence is higher in urban areas (14.7%) compared to rural areas (7.2%). Globally, the incidence of type 2 diabetes increased from 2.8% in 2000 to an estimated 4.4% in 2030 (18). In a study conducted on 1785 diabetes patients in Indonesia, 16% of diabetes patients experienced macrovascular complications, 27.6% microvascular complications. Of all patients who experienced microvascular complications, 63.5% experienced neuropathy, 42% diabetic retinopathy, and 7.3% nephropathy (3). This study specifically aimed to analyze the effect of moderate intensity aerobic exercise on sensory scores and HbA1c levels in patients with DPN. A total of 4 primary studies with a total of 187 subjects were meta-analyzed in this study. Previous study showed a difference in HbA1C between the moderate aerobic exercise group and the non-physical exercise/standard care group after 8 weeks with a change from 8.37% ± 1.92% to 7.58% ± 1.4% in the moderate aerobic exercise group. While in the non-exercise/standard care group there was no change in HbA1C, from 8.02 ± 1.47% to 8.03 ± 1.46% (16). Another study showed that the moderate aerobic exercise group experienced a significant decrease in HbA1C, namely a decrease of 0.80 (95% CI = -1.53, -0.08). Meanwhile, it was found that the non-exercise / standard care group actually experienced an increase in HbA1c of 0.42 (95% CI = -0.31, 1.14). The results of this comparison showed a decrease in HbA1c in all groups with moderate aerobic exercise, while in the non-exercise/standard care group there was a tendency to increase HbA1C (15). While several other

Study or Subgroup	Post-Test Mean	Post-Test SD	Post-Test Total	Pre-Test Mean	Pre-Test SD	Pre-Test Total	Weight	Std. mean difference IV, Fixed, 95% CI
Dixit 2014	38.21	1.31	37	38.4	1.36	47	77.5%	-0.14 [-0.57 , 0.29]
Gholami 2018	42	5.2	12	41.8	4.4	12	22.5%	0.04 [-0.76 , 0.84]
Total			**49**			**59**	**100.0%**	**-0.10 [-0.48 , 0.28]**

Test for overall effect: Z = 0.52 (P = 0.61)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%

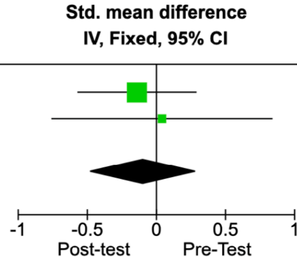

Figure 8. Standardised mean effects of NCV-peroneal at pre- and post-test in no exercise/standard care group.

studies have also found that moderate intensity aerobic exercise can improve glycaemic control and reduce HbA1c levels in elderly patients with type 2 diabetes and DPN (16). The results of the meta-analysis of this study showed no effect of moderate aerobic exercise on HbA1c, which is in line with a previous study where aerobic exercise 2 times a week combined with 1 time a week resistant exercise had no effect on changes in HbA1c. This is associated with the duration of exercise performed during the week, where exercise of 150 minutes or less per week has a lower HbA1c reduction compared to higher exercise volumes (19, 20). In addition, the lack of significance of the association in this meta-analysis was due to the limited number of studies combined for analysis. These mixed findings suggest that while aerobic exercise may have a positive impact on DPN, its effect on HbA1c levels specifically may vary. The lack of change in HbA1c with aerobic exercise may be due to individual variability and the need for higher adherence. In addition, the insignificant effect of moderate intensity aerobic exercise on HbA1c can be influenced by the initial HbA1c levels before intervention in each group (21). Based on a meta-analysis conducted before, showed that there was a significant relationship between initial HbA1c levels and the effect of the intervention. The higher the initial HbA1c level, the higher the intervention effect (20). Moderate and high-intensity aerobic exercise is proven to improve insulin sensitivity and directly reduce blood glucose levels. These mechanisms are thought to be related to increased GLUT-4-mediated glucose uptake, increased nitric oxide production, and sympathetic nervous system activation (22). The reduction in HbA1c with moderate aerobic exercise is mediated by several mechanisms related to a combination of improved pancreatic beta cell function and hepatic and peripheral insulin resistance (23). The occurrence of exercise-induced improvement in insulin sensitivity will increase the expression of GLUT 4 receptors and thus increase glucose uptake (22). Meanwhile, aerobic exercise reduces HbA1c through two pathways. Aerobic exercise does not require PI3K to drive GLUT-4 translocation so that insulin-resistant tissues will still take up glucose during exercise. This helps to lower high blood glucose concentrations and evidently may mediate the decrease in HbA1c. Another possible mechanism underlying the decrease in HbA1c is that exercise decreases adiposity and BMI, this allows insulin to work more effectively in providing glycaemic control and could be an additional explanation for the decrease in HbA1c (24).

Effect of aerobic exercise on Sensory

The meta-analysis of the effect of moderate aerobic exercise on NCV-surreal found no articles that crossed the number 1 with the confidence interval of the combined effect of the two studies not crossing the number 1, while it found articles that crossed the number 1 in the NCV-peroneal analysis results. Aerobic exercise can train nerve conduction velocity in the sural sensory nerve but has no significant effect on nerve action potential (14). In contrast to the results of a study that found moderate aerobic exercise for 8 weeks increased sural and peroneal NCV while the non-physical exercise/standard care group experienced a slight increase in sural NCV and a decrease in peroneal NCV. Even a slight increase in NCV-sural in the non-physical exercise/standard care group was influenced by the insulin dose which also increased at the end of the study in the control group (8). In line with previous study that found moderate intensity aerobic exercise for 8 weeks can increase sural sensory nerves and increase muscle action potential (25). The group who performed moderate aerobic exercise had a significant increase in distal peroneal velocity by 3.08 m/s, while the group without physical activity/standard care had a decrease of 0.192 m/s (8). However, the specific impact of aerobic exercise on peroneal nerve function in DPN remains unclear. Previous study found no significant relationship of time x group interaction on NCV-peroneal, while there was a significant difference in NCV-peroneal before and after the intervention (pre: 39.0 m/s ± 3.6 m/s; post: 40.4 m/s ± 4.4 m/s) (14). NCV-Sural was used to evaluate sensory nerve conduction, while NCV-Peroneal was used to evaluate motor nerve conduction especially in the lower extremity (14). Combined analysis of peripheral nerves both dorsal sural, peroneal may increase the sensitivity in detecting neuropathy and allow earlier diagnosis. However, compared to other nerves, the sural nerve is not susceptible to mechanical trauma so it can determine easier and more sensitive sensory examination results (26). Peripheral neuropathy is a complication responsible for decreased muscle strength, atrophy of distal segments of the lower limbs caused by motor axon loss combined with insufficient reinnervation (27). In other words, neuropathy occurs when the rate of axon loss exceeds the regenerative capacity, as seen from histological analysis of sural nerve tissue of early diabetic patients that showed regeneration among unmyelinated nerves. However, this regeneration is unable to compensate for the progressive axon loss (28). Therefore, early DPN may be more responsive to treatments that promote nerve regeneration. Moderate intensity aerobic exercise will inhibit aldose reductase leading to NADPH sparing which in turn participates in NO synthesis thereby alleviating the hypoxic state of the nerves due to the role of NO to increase blood flow as well as amplify vasodilatation (8). This may be beneficial in preventing diabetes-induced changes in the polyol pathway. Exercise-affected nerve function is also associated with increased Na/K ATPase activity in muscle. In addition, K(ATP) channel openers exert positive effects on nerve perfusion and function in DPN (29). Exercise will also reduce changes in Ca2+ channels activated by high and low voltage, thus delaying the onset of tactile hypersensitivity in neurons (21). Physical exercise will also increase blood supply to meet metabolic needs and induce the growth of nerve collaterals and thus increase electrical activity (27). This indicates a significant contribution of moderate intensity aerobic exercise to blood flow for the improvement of sensory function in patients with DPN (14, 31). Based on these findings, clinicians should consider prescribing structured, moderate-intensity aerobic exercise (e.g., treadmill walking, cycling) for 150–300 minutes per week at 40–70% of heart rate reserve to improve sural nerve function and glycaemic control in patients with DPN (32). This regimen aligns with the American Diabetes Association's guidelines for physical activity in diabetes management (33). Aerobic exercise may not be able to improve peroneal nerve function due to factors such as nerve entrapment and nerve compression. Another study also found that although physical activity and fitness were positively associated with peripheral nervous system function, this may not directly translate into improved peroneal nerve function (34). The role of nerve entrapment and nerve compression can be exacerbated by certain types of aerobic exercise (35). These factors may limit the potential benefits of aerobic exercise on peroneal nerve function. Chronic hyperglycaemia will damage vascular endothelial cells and impair the expression of NO. This condition will cause impaired vascular vasodilatation due to decreased endothelial function, so that these macro and micro vascular abnormalities will cause oxygen supply to nerve cells to be disrupted and result in nerve dysfunction. Diabetes is known to increase the sensitivity of nerve function to ischaemia and it was reported that adrenergic-mediated ischaemia decreased sensory but not motor nerve conduction velocity in type 2 diabetic subjects. These findings suggest a significant contribution of blood flow to nerve conductive function, especially in sensory nerves (31). Any change in glycaemic status will affect the sensory nerves first, so a short duration of exercise intervention with better glycaemic control is sufficient to observe a significant increase in suralis nerve conduction velocity. Meanwhile, to observe significant changes in motor nerve function, longer duration interventions may be required (30). Given the variability in HbA1c responses, exercise programs should be tailored to individual patient factors, including baseline HbA1c levels, neuropathy severity, and comorbidities. Patients with higher baseline HbA1c (>8%) may require longer or more frequent sessions to achieve clinically meaningful reductions.

Strength and limitation

This study was the first meta-analysis that assessed the effects of aerobic exercise on sensory score and haemoglobin A1c (HbA1c) in patients with DPN only includes studies in the form of Randomised Controlled Trial (RCT), which a study that measures the effectiveness of a new intervention or treatment. Although it has limitations, this meta-analysis is one of the studies that only focuses on analyzing one physical exercise that focuses on reducing Hba1c levels and sensory nerves in DPN sufferers. Compared to other meta-analysis studies that examine or compare several physical exercises to find out which is more effective in treating DPN. This meta-analysis is limited by the small number of studies that met the inclusion criteria. The available randomised controlled trials provided minimal details on research methods, incomplete results, and subjects who did not fully meet the inclusion criteria. Additionally, some studies lacked clear descriptions of the treatments used, and certain data were unavailable in a usable format, further restricting the analysis.

Conclusion

Our findings indicate that aerobic exercise is a promising non-pharmacological intervention for reducing the risk of complications in individuals with diabetes, particularly DPN. This study suggests that moderate aerobic exercise can improve sensory nerve function and lower HbA1c levels in individuals with DPN. However, further randomised controlled trials with larger sample sizes are necessary to validate these findings and establish definitive clinical recommendations.

Ethic Approval: Not Applicable

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