

Physical exercise in patients with diabetic neuropathy: systematic review and meta-analysis of randomized clinical trials

Exercícios físicos em portadores de neuropatia diabética: revisão sistemática e metanálise de ensaios clínicos randomizados

Ejercicios físicos en pacientes con neuropatía diabética: una revisión sistemática y del metaanálisis de estudios clínicos controlados

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ABSTRACT | The aim of this study was to systematically review the effects of treatment with aerobic, resistance or combined (resistance/aerobic/balance) exercises in the balance, muscular strength and glycemic index of patients with diabetic neuropathy. Searches were conducted in the electronic databases: MEDLINE (via PubMed), COCHRANE CENTRAL, LILACS (via Bireme) and PEDro of randomized clinical trials, which conducted aerobic, resistance or combined (resistance/aerobic/balance) exercises compared with the control group in individuals with diabetic neuropathy. The outcomes considered were: balance evaluated from ABC scale and glycemic index at fasting and at postprandial. Out of 389 studies, five were included, with a total of 292 individuals. We observed that the combined exercise (resistance/balance) compared with the control demonstrated significant improvement of balance (8; 95%CI). 1.12, 14.88; I2 = 0%). Two out of the five included studies evaluated the muscular strength of LL (Lower Limbs) (n=116), both studies with combined exercises (resistance/balance) versus control, but we could not conduct the meta-analysis of these studies as muscle strength was evaluated in different ways. Only one article evaluated the postprandial and fasting glycemic index (n = 87), which precluded meta-analysis. In this study, the postprandial and fasting glycemic index showed no significant difference when compared the

two groups. The data analyzed in this review demonstrated that the balance in individuals with diabetic neuropathy improved with combined exercise.

Keywords | Diabetic Neuropathies; Exercise; Clinical Trial.

RESUMO | O objetivo deste estudo foi revisar sistematicamente os efeitos do tratamento com exercícios aeróbio, resistido ou combinado (resistido/aeróbio/equilíbrio) no equilíbrio, força muscular e índice glicêmico de portadores de neuropatia diabética. A busca de ensaios clínicos randomizados que realizaram exercício aeróbio, exercício resistido ou exercício combinado em indivíduos com neuropatia diabética comparados com grupo controle foi realizada nas bases de dados eletrônicas MEDLINE (via PubMed), Cochrane CENTRAL, LILACS (via Bireme) e PEDro. Os desfechos considerados foram: equilíbrio, avaliado a partir da escala ABC, índice glicêmico, através da glicemia de jejum e pós-prandial, e a força muscular, avaliada pela dinamometria e pelo teste *Five-times-sit-to-stand*. Dos 389 estudos identificados, cinco foram incluídos, com um total de 292 indivíduos. Foi observado que o exercício combinado (resistido/equilíbrio) comparado com o controle demonstrou melhora significativa do equilíbrio (8; IC 95%: 1,12 a 14,88; I2=0%). Dois dos cinco

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estudos incluídos avaliaram a força muscular de MMII (n=116), ambos os estudos com exercícios combinados (resistido/ equilíbrio) vs. controle, porém não foi possível realizar a metanálise desses estudos, pois a força muscular foi avaliada de formas diferentes. Apenas um artigo avaliou o índice glicêmico pós-prandial e índice glicêmico de jejum (n=87), o que impossibilitou a metanálise. Nesse estudo, o índice glicêmico pós-prandial e o de jejum, quando comparados os dois grupos, não apresentaram diferença significativa. Os dados analisados nesta revisão demonstraram que o equilíbrio em indivíduos com neuropatia diabética melhorou com o exercício combinado.

Descritores | Neuropatias Diabéticas; Exercício; Ensaio Clínico.

RESUMEN | Este estudio tiene por objeto revisar sistemáticamente los efectos en el tratamiento con la práctica de ejercicios físicos aerobios, resistivos o combinados (resistido/aerobio/equilibrio) en el equilibrio, en la fuerza muscular y el índice de la glucemia de sujetos con neuropatía diabética. Se llevó a cabo una búsqueda de estudios clínicos controlados en los que fueron empleados ejercicio aerobio, ejercicio resistido o ejercicio combinado en sujetos con neuropatía diabética comparados con un grupo control en las siguientes bases de datos: MEDLINE (vía PubMed), Cochrane

CENTRAL, LILACS (vía Bireme) y PEDro. Se consideraron los términos: equilibrio, evaluación desde la escala AB, índice de la glucemia a través del valor de la glucemia en ayuno y después de la comida, y la fuerza muscular, evaluada según la dinamometría y el test Five-times-sit-to-stand. De los 389 estudios encontrados, se incluyeron cinco, con un total de 292 sujetos. Se observó que el ejercicio combinado (resistido/equilibrio) comparado con el del control presentó una significativa mejora en el equilibrio (8; IC 95%: 1,12 a 14,88; I²=0%). De estos cinco estudios incluidos, dos evaluaron la fuerza muscular de MMII (n=116), ambos estudios con ejercicios combinados (resistido/equilibrio) versus control, sin embargo no se realizó el metaanálisis, debido a que se evaluó la fuerza muscular de distintas formas. Solamente un estudio evaluó el índice de la glucemia después de la comida y en ayuno (n=87), por lo que impidió el metaanálisis. En dicho estudio, el índice de la glucemia después de la comida y en ayuno, cuando comparados en los dos grupos, no presentaron diferencias significativas. Los datos evaluados en esta revisión mostraron que el equilibrio en pacientes con neuropatía diabética presentó una mejora durante la práctica de ejercicios combinados.

Palabras clave | Neuropatías Diabéticas; Ejercicio; Ensayo Clínico.

INTRODUCTION

Diabetes mellitus (DM) is considered a public health problem of major significance with high social and economic burden. Blindness, kidney failure, nephropathy and peripheral neuropathy (PN) are among the most common complications. The PN seems to manifest as an autonomic and sensory disorder and as a progressive and irreversible motor disease, which depending on its stage (level of commitment), can interrupt the afferent and efferent functions of the lower extremities that are responsible for maintaining normal posture and normal walking and, consequently, cause the loss of proprioception¹.

Neuropathy can become chronic, being one of the major complications of type I and type II diabetes. It develops early in the disease and tends to get worse over time with a prevalence ranging from 5 to 80%. It is associated with pain, infection and loss of sensitivity in affected patients^{2,3}.

A systematic review, followed by meta-analysis, found that 150 minutes of aerobic exercise for at least 12 weeks reduced glycated hemoglobin in 0.5% in patients with DM.

However, there is an important limitation to the practice of physical exercise, since it is responsible for the greatest number of hyperglycemic crises. Therefore, the patient should always be guided before performing any physical activity⁴.

Interventions with physical exercises are associated with significant improvements in relation to muscle strength, functional capacity and muscle fatigue. Recently, the combination of aerobic and resistance exercises is recommended for people with diabetic peripheral neuropathy (DN)⁵, but its effects are still inconclusive.

Taking into account the different approaches of physical exercise in patients with DN, there is a scientific need to better evaluate types of physical exercise performed in this population to offer a better result in the treatment. Thus, the aim of this study

was to review systematically the effects of treatment with aerobic, resistance and combined exercises in the balance, muscular strength and glycemic index level of patients with DN.

METHODOLOGY

This study followed the recommendations proposed by the Cochrane Collaboration⁶ and by the Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA Statement⁷.

Eligibility criteria

We included randomized clinical trials (RCTs) with participants who fit the following criteria: (1) individuals with DN (DM type I and II); (2) age greater than or equal to 18 years; (3) who performed aerobic, resistance or combined (resistance/aerobic/balance) exercises compared with the control group (who performed no exercise or who performed any activity that did not

interfere in the exercise tested). To be eligible, we did not include studies with patients with other forms of PN in addition to that caused by DM.

The outcomes considered were: balance evaluated from ABC scale, fasting and postprandial glycemic index and muscular strength evaluated by dynamometry and Five-times-sit-to-stand (FTSTS).

Search strategy

Searches were conducted in the electronic databases: MEDLINE (via PubMed – Table 1), Cochrane CENTRAL, LILACS (via Bireme) and PEDro. The following terms were used: “Diabetic Neuropathies”, “Exercise”, “Randomized controlled trial”, as well as synonyms. For the search in the LILACS database, we used the terms in Portuguese. A sequence of words was also used according to each database, which produces a high sensitivity in the search for randomized clinical trials. There was no restriction in relation to language, date or publication status. The systematic search was conducted from October to December 2014.

Table 1. Search strategy conducted in the Pubmed tool

#1	“Diabetic Neuropathies”[Mesh]or “Diabetic Neuropathies” or “Diabetic Neuropathy” or “Neuropathies, Diabetic” or “Neuropathy, Diabetic” or “Diabetic Polyneuropathy” or “Diabetic Polyneuropathies” or “Polyneuropathies, Diabetic” or “Polyneuropathy, Diabetic” or “Asymmetric Diabetic Proximal Motor Neuropathy” or “Diabetic Asymmetric Polyneuropathy” or “Asymmetric Polyneuropathies, Diabetic” or “Asymmetric Polyneuropathy, Diabetic” or “Diabetic Asymmetric Polyneuropathies” or “Polyneuropathies, Diabetic Asymmetric” or “Polyneuropathy, Diabetic Asymmetric” or “Diabetic Autonomic Neuropathy” or “Autonomic Neuropathies, Diabetic” or “Autonomic Neuropathy, Diabetic” or “Diabetic Autonomic Neuropathies” or “Neuropathies, Diabetic Autonomic” or “Neuropathy, Diabetic Autonomic” or “Symmetric Diabetic Proximal Motor Neuropathy” or “Diabetic Amyotrophy” or “Amyotrophies, Diabetic” or “Amyotrophy, Diabetic” or “Diabetic Amyotrophies” or “Diabetic Neuralgia” or “Diabetic Neuralgias” or “Neuralgias, Diabetic” or “Diabetic Neuropathy, Painful” or “Diabetic Neuropathies, Painful” or “Neuropathies, Painful Diabetic” or “Neuropathy, Painful Diabetic” or “Painful Diabetic Neuropathies” or “Painful Diabetic Neuropathy” or “Neuralgia, Diabetic” or “Diabetic Mononeuropathy” or “Diabetic Mononeuropathies” or “Mononeuropathies, Diabetic” or “Mononeuropathy, Diabetic” or “Diabetic Mononeuropathy Simplex” or “Diabetic Mononeuropathy Simplicies” or “Mononeuropathy Simplex, Diabetic” or “Mononeuropathy Simplicies, Diabetic” or “Simplex, Diabetic Mononeuropathy” or “Simplicies, Diabetic Mononeuropathy”
#2	“Exercise”[Mesh] or “Exercise” or “Exercises” or “Exercise, Physical” or “Exercises, Physical” or “Physical Exercise” or “Physical Exercises” or “Exercise, Isometric” or “Exercises, Isometric” or “Isometric Exercises” or “Isometric Exercise” or “Exercise, Aerobic” or “Aerobic Exercises” or “Exercises, Aerobic” or “Aerobic Exercise”
#3	Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]
#4	#1 AND #2 AND #3

Selection of studies and data extraction

The titles and abstracts of all articles identified by the search strategy were reviewed independently by two investigators. All abstracts that did not provide enough information about the inclusion and exclusion

criteria were evaluated in full, and selected according to the eligibility criteria. Both reviewers conducted data extraction individually regarding methodological features of the studies, patients’ characteristics, characteristics of the interventions and outcome. Disagreements were resolved by consensus or by a third reviewer.

Methodological quality assessment

The methodological quality assessment of included studies was conducted in a descriptive way and with the following characteristics: random sequence generation, allocation concealment, blinding of outcome assessors, use of intention-to-treat analysis and description of loss and exclusions.

Studies without a clear description of a proper sequence generation were considered as not having fulfilled these criteria. We considered that the lack of a description of how the allocation list was conducted indicated absence of this characteristic. The use of intention-to-treat analysis was considered as: confirmation on the assessment of study that the number of participants randomized and analyzed was identical, except for patients who lost follow-up or who withdrew their consent to participate in the study. We considered that studies without this characteristic did not fulfill this criterion.

The methodological quality assessment was conducted independently by two reviewers.

Data analysis

Meta-analysis was conducted using the random effects model, and effect measures were obtained from post-intervention values. Studies were analyzed separately according to the type of exercise performed. We considered, as statistically significant, an alpha value = 0.05 and a 95% confidence interval. Statistical heterogeneity of treatment effects among studies was assessed by Cochran's *Q* Test and inconsistency by *I*-Test², in which values above 25% and 50% indicated moderate and high heterogeneity, respectively. All analyses were conducted using the Review Manager software version 5.1 (Cochrane Collaboration).

RESULTS

Description of studies

We found 389 studies in the database. From these, 30 articles were considered of potential relevance for a complete review of studies. However, five studies met the eligibility criteria for the systematic review. Figure 1 shows the flowchart of included studies in this review and Table 2 shows the characteristics of these studies.

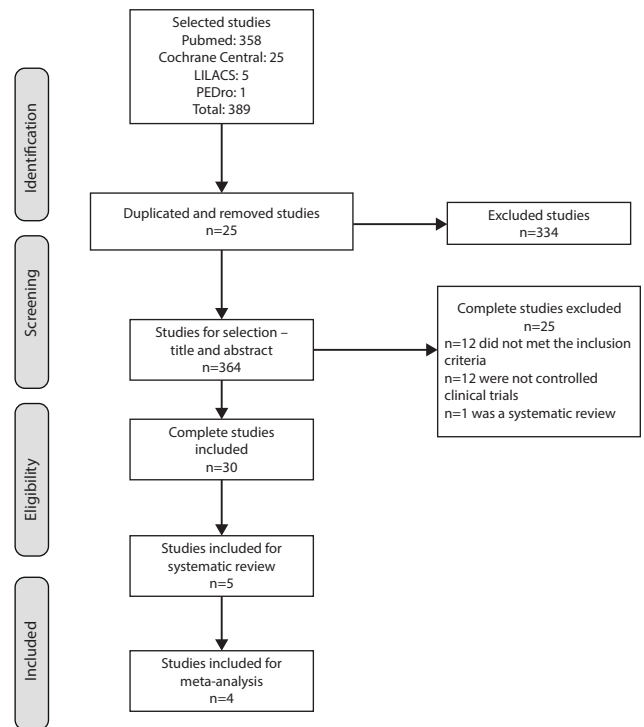


Figure 1. Flowchart of identified studies

Risk of bias

The studies included had 80% of adequate random sequence and 80% showed allocation concealment; in 40% of the studies, participants were blinded, and in 60% the assessor was blinded; 100% described the number of participants' losses and 40% of the studies showed the intention to treat.

EFFECTS OF THE INTERVENTION

Balance

Two articles evaluated the balance by the ABC Scale. Both evaluated the combined exercise (resistance/balance) versus (vs.) control^{8,9} (n=71) (Figure 2).

We observed that the combined (resistance/balance) exercise compared with the control demonstrated significant improvement of balance (8; 95%CI). 1.12, 14.88; *I*² = 0%).

Two articles evaluated the balance by the Berg Balance Scale. Both evaluated the combined (resistance/balance) exercise versus control^{10,11} (n=116) (Figure 3).

Table 2. Characteristics of included studies

Authors	n	Average age	Group	Gender F/M	Supervision	Modality	Exercises		Length	Outcome
							Prescription/Intensity/Frequency			
Richardson; Sandman; Vela, 2001	16	64.0±6.3	Intervention (n=9)	F/M	No	CE	Heating Strengthening of the triceps surae muscle, ankle invertors and evertors, and quadriceps. 1x 10 repetitions up to 3 x10. Balance.	3 weeks	Balance (ABC Scale)	
		63.3±7.6	Controle (n=7)		No		Strengthen upper limbs in the sitting position. 5x each exercise.	3 weeks		
Kruse; LeMaster; Madsen, 2010	79	66.3±10.6	Intervention (n=41)	F/M	Yes	CE	Part 1: 1-3 months, 8 sessions with the physiotherapist, strengthen LL and balance, then 3x a week for one hour at home and a walking program monitored with pedometer. Part 2: 4-12 months, phone calls by nurses every two weeks, minimum length 10 minutes to encourage the LL strengthening exercises, balance and walking.	6 and 12 weeks	Muscle strength (dynamometer) Balance (Berg Balance Scale)	
		64.8±9.4	Control (n=38)		Yes		Part 1: Instructions for health care. 8 physiotherapist visits Part 2: They received calls in the same frequency as the IG to report their recent activities, but did not receive the nurse's motivation.	6 and 12 weeks		
Lee; Lee; Song, 2013	55	76.3±4.7	Intervention WBV (n=19)	F/M	Yes	CE	Balance exercise (vibrating platform), combined with progressive strengthening, balance and functional mobility. 60 min 2x a week	6 weeks	Balance (Berg Balance Scale) Muscle Strength (FTSTS-time)	
		74.0±5.4	Intervention BE (n=18)	F/M	Yes		Balance exercise - 10 min heating, 40 min balance training, 10 min cooldown activities	6 weeks		
		75.7±5.6	Control (n=18)	F/M			No activity performed			
Dixit; Maiya; Shastry, 2014	87	54.0±1.16	Intervention (n=40)	F/M	Yes	AE	Moderate intensity exercise on a treadmill with 40% -60% HR. From 3-6 days a week, minimum 150 min/week and maximum 360 min/week. Diet for diabetics (instructions).	8 weeks	Gycemic index	
		59.45±1.24	Control (n=47)		Yes		Lectures on diabetic foot and diet instructions with nutritionists and doctors	8 weeks		
Sartor et al., 2014	55	60±12	Intervention (n=26)	F/M	Yes	CE	(a) foot and ankle ROM, (b) strengthen foot and ankle muscles, (c) increase foot and ankle performance through functional exercises, and (d) increase foot skills. The patient was exposed to progressive difficulty. 2x/week. 40-60 min per session	12 weeks	Balance (ABC Scale)	
		59±4	Control (n=29)		Yes		No activity performed, the patient continued receiving drug and medical care and instructions for foot care.	12 weeks		

AE - aerobic exercise; CE - combined exercise; ROM - range of motion; HR - heart rate; IG - intervention group; FTSTS - Five-times-sit-to-stand; LL - lower limbs; WVB - wholebody vibration; BE - balance exercise.

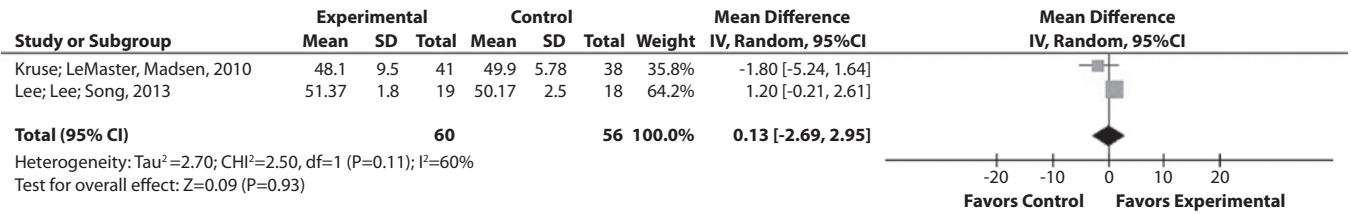


Figure 2. Balance Berg Scale – combined (resistance/balance) exercise vs. control

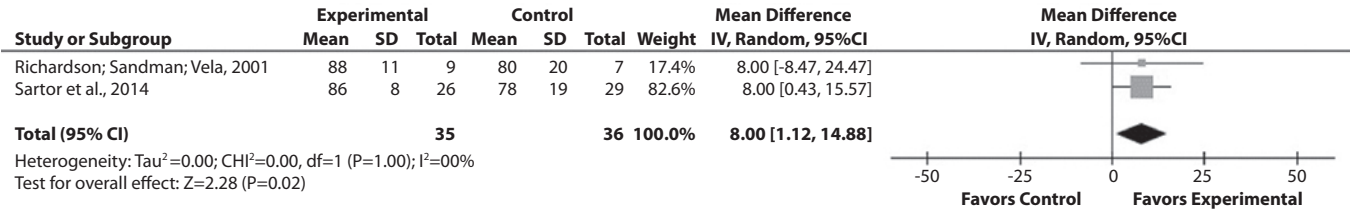


Figure 3. ABC Scale – combined (resistance/balance) exercise vs. control

We observed that the combined exercise (resistance/balance) compared with the control demonstrated significant improvement of balance (0.13;8; 95%CI). -2.69, 2.95; I²=60%) by the Berg Balance Scale. This comparison showed high heterogeneity. Studies by Kruse et al.¹⁰ presented an important difference in the time of the intervention, which occurred for up to 12 months. However, the data used in this meta-analysis was of the six-month evaluation, for being closer to the six-week intervention of the article by Lee et al.¹¹

Muscular strength

Two out of the five studies included evaluated the muscular strength of lower limbs (LL)^{10,11} (n=116), both studies using combined (resistance/balance) exercises versus control, but it was not possible to perform a meta-analysis of these studies because muscular strength was evaluated in different ways.

The article by Lee et al.¹¹ evaluated muscle strength by the Five-times-sit-to-stand Test considered suitable for older adults, which resulted in a significant improvement of strength compared to the WBC group vs. control (p=0.02), on the other hand, the authors Kruse et al.¹⁰ evaluated muscle strength by ankle dynamometry, which showed no significant improvement when compared with the intervention group vs. control even after six months of intervention (p=0.11) and even after 12 months of intervention (p=0.22).

Glycemic index

Out of the five included studies, only one article evaluated the postprandial and fasting glycemic indexes¹² (n=87), which precluded meta-analysis. In this study, postprandial and fasting glycemic index showed no significant difference when comparing the two groups.

DISCUSSION

This study includes five RCTs, the frequency of intervention was of at least three and at most 12 months, containing a total of 274 randomized participants, out of whom 135 were part of the intervention group and 139 were part of the control group.

We analyzed five studies, two RCTs that compared combined exercises versus control evaluated the balance by ABC scale^{8,9}, two RCTs that compared combined exercises versus control that evaluated the balance by Berg Balance Scale and evaluated the muscle strength of LL^{10,11}, and one RCTs that compared aerobic exercise versus control evaluated the postprandial and fasting glycemic indexes¹².

According to Richardson et al.⁸, previous studies described that older adults with DN had a higher risk for falls compared to older adults with healthy peripheral nerves, as well as had a decrease in balance, thus more conducive to suffer falls.

Analyzing the studies with combined (resistance+balance) exercises vs. control, evaluated

by the ABC Scale, there was no significant change in the groups for the study of Richardson et al.⁸, but a significant improvement was shown in the intervention group for isolated activities, such as up and down stairs, activities such as standing up to pick up an object, staying on tiptoe, among others.

In the analysis of the study of Sartor et al.⁹, we can observe that there was significant improvement in the balance between the intervention and control groups after 12 weeks of intervention. The results suggest that after an intervention with combined exercises proposed for patients with DN, foot positioning was altered slightly, with improvement in the distribution of the dynamic pressure, in ankle extension and a better functional condition of the ankle and foot muscles.

The evidence available from the meta-analysis of these two RCTs (71 individuals), which compared exercise combined (resistance/balance) versus control, maintains that the combined exercise significantly improved the balance of individuals with DN^{8,9}.

The balance was also evaluated by Berg Balance Scale by two RCTs^{10,11} (116 individuals), of which the meta-analysis had no significant improvement after a combined intervention (resistance/balance) vs. control. The muscular strength of LL (Lower Limbs) was also evaluated by these studies, however the meta-analysis was not possible due to the different evaluation way in both studies.

In the article by Lee et al.¹¹, when compared intervention group vs. control group after intervention, a significant improvement was not found in the scores of balance of the Berg Balance Scale. In addition, they evaluated the muscular strength of LL (FTSTS test), which verified the time in which participants sat down and stood up from a chair five times. This test is suitable for evaluating older adults, as a result it found significant improvement of the LL strength, which indicated low risk of falls.

In the article by Kruse et al.¹⁰, participants with DN had no improvement in balance and in muscle strength of LL (evaluated by dynamometry). They reported that the extent of muscle strength of LL and balance may not be sensitive enough to detect changes in people with DN and the intervention carried out was not intense enough to achieve improvements in balance and strength of LL, especially in the population with sedentary DN.

The fasting and postprandial glucose is used to check the amount of glucose in the blood for diabetes

monitoring. Only one study with aerobic exercise versus control examined glycemic index, which did not observe significant decrease in the postprandial and fasting examination after the follow-up.

Glycemic control is an important factor to control DN because hyperglycemia leads to inactivation of the production of nitric oxide, which is an important mechanism of endothelial dysfunction in DN, thus it causes a hypoxic state in the nerves. Adjustments due to moderate-intensity aerobic exercise can lead to restoration of peripheral nerve functions by the activation of endothelial derived nitric oxide⁹.

However, it is clear that there are a few points to clarify, so that we can understand the behavior of DN compared to aerobic, resistance and combined exercises.

Strengths and limitations of the study

The study had some strengths: comprehensive and systematic literature search. It used explicit and reproducible eligibility criteria. The meta-analysis was conducted to quantitatively express the result obtained.

Weaknesses of the clinical trials found: few controlled randomized clinical trials were found on this subject in accordance with the eligibility criteria. Only 40% of the included studies had blinding of participants and 40% had the intention to treat. We found limitation in the analysis of the glycemic index and muscle strength outcome, which precluded meta-analysis.

Physical exercises are extremely important for patients with diabetes, since they help improving balance, endurance and muscular strength. We observed that there is need for more studies to prove the importance of these exercises compared to patients with DN, but which are essential to their quality of life.

CONCLUSION

The data analyzed in this review showed that the balance in individuals with diabetic neuropathy improved with combined (resistance/balance) exercise. We could not conduct the meta-analysis regarding muscle strength, because only two studies with different ways of assessment were presented and, regarding the glycemic index, only one study was presented. We need more scientific evidence regarding the muscle strength and glycemic index compared to physical exercise in general.

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