

Influence of the Exercise on Autonomic Nervous System in Diabetics: A Literature Review

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ABSTRACT

Diabetes mellitus remains a serious problem of public health and also have the autonomic neuropathy as one of the most frequent

complications. In this sense, it is important early identify and prevent changes induced by diabetes mellitus. Physical exercise is known by their positive influences on autonomic modulation so, in order to provide an update of published findings on the topic over the past thirteen years related to this issue the objective of this study was gather information about the influence of physical exercise on autonomic nervous system in individuals with diabetes mellitus, using heart rate variability as a tool of measurement. The search for studies was conducted in the following electronic databases: MedLine/Pubmed, PEDro, SciELO, Lilacs and Cochrane using diabetes mellitus, physical exercise, exercise therapy, autonomic nervous system, sympathetic nervous system, parasympathetic nervous system and heart rate as standard descriptors. Additionally, heart rate variability and diabetic autonomic neuropathy were included due to the wide use as keyword. The results included 10 articles which, in general, showed the physical training promotes positive influence on autonomic nervous system of patients with diabetes mellitus; exercise has different responses on autonomic nervous system in diabetes mellitus when associated with other variables as cardiac autonomic neuropathy, hypertension, obesity and ventricular dysfunction; the positive influence of exercise could be observed through hear rate variability and depends on the characteristics of the exercise as frequency, intensity and type of training.

Key words: Diabetes mellitus; Physical exercise; Autonomic nervous system

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INTRODUCTION

Diabetes mellitus (DM) remains a serious problem of public health due to the increase in prevalence, morbidity and mortality in developed and developing countries^[1]. Nowadays, it is estimated

382 million of individuals with diabetes in the world, being 11.9 million in Brazil^[1,2]. DM is characterized by hyperglycemia arising from insulin secretion injuries, insulin action injuries or both factors^[1,3].

That factors leads to several complications such as carbohydrates, fat and protein metabolism damages^[3,4]; typical symptoms like thirst, polyuria, blurred vision and weight loss^[5]; in case of poor glycemic and blood pressure control, high prevalence of micro and macrovascular complications as retinopathy with potential blindness, kidney failure, risk of foot ulcers and also diabetic autonomic neuropathy (DAN)^[6,7].

In general, DAN initially affects the cardiovascular system, triggering cardiovascular autonomic neuropathy (CAN)^[8,9]. It is related to clinical signs of tachycardia at rest, syncope, exercise intolerance, changing in the central and peripheral region of the vascular dynamics, ischemia, asymptomatic myocardial infarction and an increased risk of stroke, decreasing quality of life^[10,11].

The autonomic changes induced by DM may represent an important negative factor, since autonomic function modulates some of the internal functions of the body and, in this sense, deserves attention. One way to access the autonomic nervous system (ANS) is thought the heart rate variability (HRV), tool that describes the oscillation of intervals between consecutive heart beats (RR intervals) and provides information about the diagnosis and prognosis of several diseases^[12,13]. It has a potential to generate knowledge regarding to how neuropathy starts and in which pathway they can change sympathetic and parasympathetic branches.

In addition to the information cited above, chronic complications induced by DM are the main responsible for morbidity and mortality, being the cardiovascular disease a leading cause of death in diabetic patients. To treat patients with DM is very important^[14]. Drug therapy and physical exercise are, between others, known therapies which may improve the quality of life in these patients^[15].

Specially regarding to physical exercise, it may provide cardiovascular, metabolic and autonomic benefits in individuals with DM, leading to decreased insulin resistance and improved glycemic control in the blood^[16]. Also, studies showed that physical exercise improves cardiac autonomic function in diabetic subjects^[17,18,19].

In this context, to provide an update of published findings on the topic over the past thirteen years related to this issue and also given the matter of early identification and prevention of changes induced by DM on ANS, this review aimed at gather information about the influence of physical exercise on the ANS in individuals with DM, using HRV as a tool.

METHODS

The search for studies was conducted between March and April 2016 in the following electronic databases: Medical Literature Analysis and Retrieval System Online (MedLine/Pubmed), Physiotherapy Evidence Database (PEDro), Scientific Electronic Library Online (SciELO), *Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs)* and Cochrane focusing on papers published between January 2003 and March 2016.

To our search strategy the codes diabetes mellitus, physical exercise, exercise therapy, autonomic nervous system, sympathetic nervous system, parasympathetic nervous system, heart rate were used in Portuguese according the health descriptors (DeCS) and their correspondents pairs in English according to the Medical Subject Headings (MeSH). Additionally, heart rate variability and diabetic autonomic neuropathy were included due to the wide use as a

keyword.

The codes were crossed using “diabetes mellitus and physical exercise” against autonomic nervous system, sympathetic nervous system, parasympathetic nervous system, heart rate and diabetic autonomic neuropathy. Also, “diabetes mellitus and exercise therapy” were used at the same way.

One review author performed the searches. Initially, the studies were reviewed by the title considering potentially relevant articles addressing the main idea of this paper which is the influence of ANS in patients with DM who regularly exercises using HRV as toll of measurement. After this, the results were filtered to exclude repetitions, since the search was conducted in several databases. In sequence, the titles selected had their abstracts verified. At the end, the abstracts selected had the full texts read. In addition, the references of full texts selected were analyzed independently to identify relevant studies that had not been identified in the electronic search. All types of papers published in Portuguese, English and Spanish were included, with exception of Letters to Editor, dissertations and thesis.

Data were described qualitatively and organized according to author, year of the study, clinical and physical features, objective of the study, indexes of HRV evaluated and conclusions.

RESULTS

The initial record identified 2484 titles using keywords described on methods section as well as the described databases. After the screening of titles and remove duplicates, 2418 titles were excluded. The remained studies going on to the next step of selection which considered abstracts and 39 of them were removed. The 25 remained texts had their full text accessed to verify the eligibility and excluded 17 articles, resulting at the end in 10 studies included to this review.

Table 1 was organized according to authors and year of publication, population, indexes evaluated, training program and results. It contains 4 articles resulting of the search, which addresses the influence of physical exercise on ANS in individuals with DM.

While, in spite of Table 2 is also organized according to authors and year of publication, population, indices evaluated, training program and results, it considers the 6 articles resulting from the search, that address the influence of physical exercise on ANS in individuals with DM associated with another following variable: obesity, hypertension, ventricular dysfunction and CAN.

DISCUSSION

In general, the selected texts of this review showed: (1) physical training promotes positive influence on ANS of patients with DM; (2) exercise has different responses on ANS in DM when associated with other variables as CAN, hypertension, obesity and ventricular dysfunction; (3) the positive influence of exercise could be observed through HRV and depends on the characteristics of the exercise as frequency, intensity and type of training.

The ANS changes arising from exercise in individuals with DM is targeted of several authors. Bhagyalakshmi *et al*^[17] performed a study to compare individuals with type 2 DM who underwent to an aerobic training program for nine months, for five days per week versus no intervention. They showed significant benefits on ANS, observed by an increase in global HRV values in subjects who underwent the program. Patients with type 2 DM who did not undergo the training program presented a reduction in overall HRV, which can be justified by changes in autonomic modulation induced by the natural course of the disease.

Table 1 Description of the studies according to the authors, year of publication, population features, indexes evaluated, training program and results.

Authors / Year	Population	Indices Evaluated	Training Program	Results
Loimaala <i>et al.</i> 2003 ^[20]	49 individuals with DM2 divided into two groups: GC ($n = 25$; 54.0 ± 5.0 years) and GE ($n = 24$; 53.6 ± 6.2 years)	SDNN, pNN50, LF, HF, VLF, LF/HF ratio	TA and TF for 12 months modified every 2 months; TA: walking or running 2 to 3 times a week at 65% - 75% of peak VO ₂ ; TF: twice per week performing 8 exercises for large muscle groups from 70% to 80% of 1RM	No significant changes in the indices of HRV were observed
Bhagyalakshmi <i>et al.</i> 2007 ^[17]	48 individuals with DM2 divided into two groups: GC ($n = 20$; 59.45 ± 2.75 years) and GE ($n = 28$; 61.78 ± 3.8 years)	Baseline of HRV.	45 minutes of exercise for 9 months, 5 days per week, being 5 minutes warm-up, 30 minutes of aerobic exercise and 10 minutes of relaxation	Supervision Regular exercise program showed improve HRV on GE in comparison with GC
Zoppini <i>et al.</i> 2007 ^[18]	12 individuals with DM2 (65.7 ± 5.6 years).	LF, HF and LF/HF ratio: lying and standing at the beginning and end of the 6 month program	Aerobic exercise twice per week with intensity of 50% to 70% of RFC for 6 months. The program was composed of 10 minutes warm-up, 40 minutes of aerobic exercise and 10 minutes of relaxation	The program improved the HRV indices with a reduction in LF and increase in HF. The change was most significant when standing
Simmonds <i>et al.</i> 2012 ^[25]	15 women with DM2 were divided in two groups G1 ($n = 8$; 68.9 ± 2.8) and G2 ($n = 7$; 69.3 ± 2.5).	SDNN, RMSSD, LH, HF and LF/HF ratio	Duration: 12 weeks; G1: twice for 60 minutes and G2: four times for 30 minutes. Intensity determined by VO _{2max} and readjusted after 6 weeks. Sessions with 3 minutes of warm-up and 3 minutes of recovery with a speed of 3.0 km/ hours	No change in HRV was observed in G1. For the G2 several HRV indices improved (SDNN, RMSSD and HF)

DM2: Diabetes mellitus type 2; DM1: Diabetes mellitus type 1; GC: Control group; GE: Exercise group; HRV: Heart rate variability; SDNN: Standard deviation of all normal RR intervals; pNN50: Percentage of adjacent RR intervals with difference of duration greater than 50 ms; PT: Total power; LF: Low frequency component; HF: High frequency component; LF/HF: Ratio between the low and high frequency components; VLF: Very low frequency component; RMSSD: Square root of the mean of the square of differences between adjacent normal RR intervals; TA: Aerobic training; TF: Strength training; VO₂: Volume of oxygen; RM: Repetition maximum; RFC: Reserve heart rate; G1: Group 1; G2: Group 2.

Table 2 Description of the studies in patients with diabetes mellitus associated with other variables as obesity, hypertension, cardiac autonomic neuropathy and ventricular dysfunction, according to the authors, year of publication, population features, indexes evaluated, training program and results.

Authors / Year	Population	Indices Evaluated	Training Program	Results
Pagkalos <i>et al.</i> 2008 ^[19]	DM2 with CAN ($n = 19$; 56.2 ± 5.8 years) and DM2 without CAN ($n = 19$; 55.8 ± 5.6 years)	SDNN, pNN50, RMSSD, HF, LF and LF/HF ratio	Aerobic exercise of 70% to 80% of RFC three times per week; 6 months; 3 initial months: 45 minutes per session and 3 final months: 75 minutes per session	The training improved ANS function in DM2 with more favorable effects in DM2 with CAN
Kanaley <i>et al.</i> 2009 ^[22]	156 obese individuals; GO: ($n = 34$; 49.0 ± 0.9 years and $BMI \geq 30$ kg/m ²); GODM2: ($n = 22$; 50.0 ± 1.6 years; $BMI \geq 30$ kg/m ² ; fasting glucose ≥ 126 mg/dL)	HF, LF, VLF, LF/HF ratio	Duration: 16 weeks. Aerobic exercises at 65% of VO _{2max} , in treadmill walking supervised four times per week, evaluated by HR and perceived exertion; 30 minutes in 8 initial weeks reaching 45 minutes in the final 6 weeks	Training improved parasympathetic modulation (HF) in obese but not in obese with DM2
Goulopoulou <i>et al.</i> 2010 ^[23]	GO: ($n = 36$; 49.0 ± 1.0 years and $BMI \geq 30$ kg/m ²); GODM2: ($n = 26$; 50.0 ± 1.0 years; $BMI \geq 30$ kg/m ² and fasting glucose ≥ 126 mg/dL)	PT, HF, LF, LF/HF ratio	Duration: 16 weeks. Aerobic exercises at 65% of VO _{2max} , in treadmill walking supervised four times per week, evaluated by HR and perceived exertion; 30 minutes in 8 initial weeks reaching 45 minutes in the final 6 weeks	Training improved HRV in obese individuals but not in obese diabetics. An increase in LF and reduction in HF in response to an oral glucose load in both groups
Figueroa <i>et al.</i> 2007 ^[24]	28 obese women GO: ($n = 18$; 48.0 ± 2.0 years and $BMI \geq 30$ kg/m ²); GODM2: ($n = 10$; 50.0 ± 1.0 years, $BMI \geq 30$ kg/m ² and fasting glucose ≥ 126 mg/dl)	HF, LF, LF/HF ratio	Duration: 16 weeks. Aerobic exercises at 65% of VO _{2max} , in treadmill walking supervised four times per week, evaluated by HR and perceived exertion; 30 minutes in 8 initial weeks reaching 45 minutes in the final 6 weeks	HF increased during recovery from acute exercise, but not at rest in both groups
Shidhar <i>et al.</i> 2010 ^[25]	105 individuals with DM2 were divided in 2 groups: GC ($n = 50$; 59.45 ± 2.75 28 DM2+H and 22 DM2); and GE ($n = 55$; 61.78 ± 3.1 years 25 DM2+H and 30 DM2)	HRV was recorded with deep breathing	Duration: 12 months. GE: 5 minutes warm-up, 30 minutes aerobic exercise and 10 minutes relaxation	Regular physical exercise increased HRV in diabetic patients with and without hypertension, being higher benefits in those who hypertension
Sacre <i>et al.</i> 2014 ^[21]	47 individuals with DM2 and subclinical ventricular nonischemic dysfunction. GE ($n = 22$); GC ($n = 25$)	RR mean, SDNN, RMSSD, PT, LF, HF, LF/HF ratio	Duration: 6 months. GE: 75 minutes of exercise twice per week; 20'-40' minutes of aerobic exercise; 6-12 resistance exercises. Intensity controlled by perceived subjective exertion with intermittent verification using HR monitors	An overall improvement in HRV (SDNN and PT), was found in addition to a favorable change in the sympathetic-vagal balance

DM2: Diabetes mellitus type 2; CAN: Cardiovascular autonomic neuropathy; GO: Obese group; GODM2: Obese group with diabetes mellitus type 2; GE: Exercise group; GC: Control group; GN: Normotensive exercise group; GH: Hypertensive exercise group; GCN: Normotensive control group; GCH: Hypertensive control group; SDNN= Standard deviation of all normal RR intervals; pNN50: Percentage of adjacent RR intervals with difference of duration greater than 50ms; RMSSD: Square root of the mean of the square of differences between adjacent normal RR intervals; LF: Low frequency component; HF: High frequency component; LF/HF: Ratio between the low and high frequency components; VLF: Very low frequency component; PT: Total power; RR mean: mean of RR intervals; HRV: Heart rate variability; RFC: Reserve heart rate; SNA: Autonomic nervous system; VO_{2max}: Maximum volume of oxygen; HR: heart rate.

In agreement with this study, Zoppini *et al.*^[18] observed a significant improvement in autonomic modulation in patients with DM when they were evaluated in the standing position, characterized by a decrease on sympathetic activity (LF) and increase on parasympathetic activity (HF). They performed an aerobic training with lower intensity and lower frequency than the study above, for twice a week during six months and even so they found benefits.

In contrast, Loimaala *et al.*^[20] accessed the effects of a combined aerobic and resistance training on autonomic modulation versus no intervention for 12 months, being 2 times per week of aerobic training and 2 times of resistance training. They observed there are no important changes on HVR indexes despite of benefits on baroreflex sensibility, glycemic control, muscle strength, VO₂ peak. The authors suggest more frequency of training could improve also HRV in type 2 DM patients.

It is known that the clinical condition of type 2 DM, in most cases, is associated with other diseases; therefore some studies have evaluated this association regarding to the physical training.

Shidhar *et al.*^[15] evaluated the effects of twelve months of aerobic training in patients with DM and hypertension or in normotensive condition and found that aerobic training significantly increase global HRV values in these patients, being higher in those with hypertension. The authors point out that this may be due to the decrease response of the physical training on blood pressure and blood glucose, which could influence autonomic changes.

Another study verified the condition in which type 2 DM is associated or not with CAN, and performed aerobic training three times a week for six months in those patients. This study found increases on SDNN, RMSSD, pNN50, LF ms² and HF ms² indexes, indicating benefits on autonomic modulation. The group with type 2 DM associated with CAN presented more significant improvements when compared to individuals with type 2 DM without CAN^[19].

Regarding to the effects of physical training in type 2 DM with ischemic subclinical left ventricle dysfunction it was evaluated after a program of six months and there was increase in global HRV (TP and SDNN) but changes were not found in the parasympathetic modulation (RMSSD and HFms²). Also, there was improvement on sympathetic-vagal balance (RR mean), showing a decrease of resting HR, which implies a relative bradycardia induced by exercise^[21].

Kanaley *et al.*^[22] performed an aerobic training for obese individuals with and without type 2 DM and found increase on global HRV and increase on parasympathetic modulation (HF) in just obese individuals but the same result was not found in obese individuals with type 2 DM. The authors suggest there is a decrease in ANS responsiveness in individuals with type 2 DM which implies that if obese individuals progress to type 2 DM, the autonomic dysfunction may irreversible or requires a more aggressive training program.

Also, Gouloupoulou *et al.*^[23] observed increase in global HRV in just obese individuals but not in obese diabetics as a result of the training. In that study, the authors investigated the effects of aerobic training for sixteen-weeks on cardiac autonomic modulation after oral ingestion of glucose and found after glucose intake an increase of sympathetic (LF) and decrease of parasympathetic modulation (HF) in obese patients, independent of the presence or absence of the DM. This study suggests that insulin can stimulate the sympathetic nervous system through hypothalamic regulation, or indirectly, by baroreflex-mediated sympathetic stimulation in response to the vasodilation induced by insulin.

Differently to the studies described above, Figueroa *et al.*^[24] observed sixteen weeks of aerobic exercise training in obese women with or without diabetes and found no differences in autonomic

modulation at rest, but the parasympathetic control (HF) increased in both groups during recovery after acute exercise. The authors suggest that a longer period of physical training could also lead to significant improvements at rest.

The different responses observed in autonomic modulation induced by physical training in individuals with DM may be related to the different prescriptions used (e.g., type of exercise, frequency, intensity)^[21]. Then, the above studies included different exercise protocols, and although most studies contained aerobic training, they changed regarding to the type of exercise, frequency and intensity, which may have influenced the results.

Simmonds *et al.*^[25] investigated the effects of frequency and duration of aerobic training for twelve weeks on HRV in women with type 2 DM, while one group performed 30 minutes of exercise four times a week, another group performed 60 minutes twice a week. The authors observed an increase in the values of SDNN, RMSSD and HF only in the group that performed physical activity more frequently and concluded that changes in autonomic modulation are sensitive to the frequency of physical training.

Considering the studies analyzed in this review, in general, the ages ranged from 50 to 65 years old and the studies were conducted in patients with type 2 DM. This type of DM represents 90% of the DM cases^[5,26]. During the search, only one study addressed the effects of physical training and autonomic function in individuals with type 1 DM, this is the second most common type of DM. It affects younger population and generally does not present associated comorbidities. Then, the information of physical exercise looking this outcome for type 1 DM are little known, which represents an area of opportunities to research on next studies.

CONCLUSION

The studies demonstrated that aerobic physical exercise, in general, improve autonomic condition of patients with DM, however some factors has influence this improvement, such as the duration, the intensity of exercise and associated comorbidities.

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