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REVIEW

Acute effects of physical exercise in type 2 diabetes: A review

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Abstract

The literature has shown the efficiency of exercise in the control of type 2 diabetes (T2D), being suggested as one of the best kinds of non-pharmacological treatments for its population. Thus, the scientific production related to this phenomenon has growing exponentially. However, despite its advances, still there is a lack of studies that have carried out a review on the acute effects of physical exercise on metabolic and hemodynamic markers and possible control mechanisms of these indicators in individuals with T2D, not to mention that in a related way, these themes have been very little studied today. Therefore, the aim of this study was to organize and analyze the current scientific production about the acute effects of physical exercise on metabolic and hemodynamic markers and possible control mechanisms of these indicators in T2D individuals. For such, a research with the following keywords was performed: -exercise; diabetes and post-exercise hypotension; diabetes and excess post-exercise oxygen consumption; diabetes and acute effects in PUBMED, SCIELO and HIGHWIRE databases. From the analyzed studies, it is possible to conclude that, a single exercise session can promote an increase in the bioavailability of nitric oxide and elicit decreases in postexercise blood pressure. Furthermore, the metabolic stress from physical exercise can increase the oxidation of carbohydrate during the exercise and keep it, in high levels, the post exercise consumption of O_2, this phenomenon increases the rate of fat oxidation during recovery periods after exercise, improves glucose tolerance and insulin sensitivity and reduces glycemia between 2-72 h, which seems to be dependent on the exercise intensity and duration of the effort.

Key words: Metabolic diseases; Hypertension; Nitric oxide; Blood glucose; Oxygen consumption

Core tip: Physical exercise is one of the best kinds of non-pharmacological treatments to prevent and control type 2 diabetes (T2D), being recommended by important medical associations, such as American College of Sports Medicine and the American Diabetes Association. In the literature, studies about the effects of a single exercise session on the population, its changes in blood pressure, glycemia, carbohydrate oxidation, fat oxidation, increase in nitric oxide and others are increasing exponentially. In this review, we report the most recent and important findings in the literature about the ef-

fects of acute exercise in T2D.

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INTRODUCTION

Physical exercise, along with a proper diet are central factors in the prevention and control of diabetes mellitus (DM), since their effects include appropriate values of blood pressure, glycemia and lipidemia[1]. Several studies have shown the efficiency of exercise programs in the control of DM, being suggested as one of the best types of non-pharmacological treatments to the population in question[2-5]. Aerobic, resistance or combined exercise programs can help in the control of glycemia of diabetes mellitus type 2 (T2D), mainly by the increase of the need of glucose consumption by skeletal muscle in activity and the hypoglycaemic effect after exercise has been performed[1,6-9].

Currently, the guidelines to physical exercise prescription by the American College of Sports Medicine and American Diabetes Association to T2D provide general information, such as exercise daily, accumulate 150 min of exercise in a moderate intensity or 75 min of high intensity exercise per week; resistance exercises should be included at least 2-3 times per week[1]. On the other hand, despite the advances made in discovering the effects of exercise in the treatment and control of T2D and associated diseases, still there is a lack of studies that have carried out a review on the acute effects of physical exercise on metabolic and hemodynamic markers and possible control mechanisms of these indicators in individuals with type 2 diabetes, not to mention that in a related way, these themes have been very little studied today. Mainly concerning the magnitude of different intensities and durations of exercise on glucose uptake, oxidation of macronutrients and blood pressure response after performing only one session of exercise (acute exercise) and biomolecular mechanisms involved in this phenomenon[1]. Hence, the aim of this study was to synthetize the current knowledge pertaining the acute effects of physical exercises in T2D; analyze the implications of exercise and determinate trends to future researches about this topic.

The method used in the present study was a review of the literature. As inclusion criteria and search of scientific articles, the following keywords were used: diabetes and exercise; diabetes and postexercise hypotension; diabetes and excess postexercise oxygen consumption; diabetes and acute effect of physical exercise, in the databases PubMed, Scielo and HIGHWIRE. The studies that have not addressed the acute effects of physical exercise on type 2 diabetes and did not show relevant results on the subject were excluded from the analysis.

ACUTE EFFECTS OF PHYSICAL EXERCISE ON GLYCEMIA AND INSULINEMIA

The control of glycemia is dependent of the activities of the neuroendocrine system. In resting conditions, the glucose uptake by the cells is mainly insulin dependent, where the glucose transporter 4 (GLUT-4) is translocated to the cell membrane, facilitating glucose entrance in the cell cytoplasm[10]. During exercise, an increase in the uptake and utilization of glucose occurs, and it seems to be dependent on the intensity and duration of the effort. The more intense the effort is, more carbohydrate will be metabolized[11,12]. Therewith, exercise promotes a reduction in glycemia, which is initially controlled by glucagon, epinephrine and norepinephrine. Afterwards, with the assistance of growth hormone and glucagon, production and release of glucose by the liver in the bloodstream is increased, thus, regulating again the glycemia[13].

This acute effect of exercise is benefic in euglycemic and T2D individuals. Exercise increases the concentration of GLUT-4 in the cell membrane, which leads to the increase in glucose uptake, even with low insulin levels[14]. On the other hand, the mechanisms surrounding this phenomenon are still inconclusive. Higher expression of key-proteins related to the insulin pathway, such as insulin receptor substrate 1 and phosphatidylinositide 3-kinases, and insulin independent mechanisms, such as the increase in the activity of AMP-activated protein kinase, the activation of the calcium-calmodulim pathway, and the kallikreins-kinins components can be involved in this process[10,15-20].

Furthermore, both exercise models, aerobic and resistance, promote improvements in glucose tolerance, insulin sensitivity and reduction in glycemia between 2-72 h, which seems to be dependent on the intensity and duration of the effort[1,21,22].

Although, there is some knowledge about the benefits of acute exercise in T2D, more studies are still made necessary to elucidate some questions, such as the effects of intense exercise in general population, since the most studies and exercise prescription to this population are of moderate intensity[1].

CARBOHYDRATE AND FAT OXIDATION DURING AND POST EXERCISE IN T2D

Insulin resistance, along with elevated oxidative stress, impairs energy metabolism at rest, as well as during and after exercising in T2D. At rest, the lowest availability of glucose and muscular glycogen in T2D increases the predominance of fat oxidation when compared to euglycemic individuals[1].

Although glucose uptake by insulin dependent pathways are impaired in T2D, exercise increases carbohydrate

oxidation, and this capacity seems to be preserved in T2D, since the glucose uptake during the effort occurs mainly by insulin independent pathways[23]. Nevertheless, T2D demonstrates lower capacity to utilize carbohydrate during exercise when compared to euglycemic individuals[24].

Other peculiarities occur during exercise in T2D, such as the decrease in rate of fatty acids oxidation when compared to euglycemic[25]. However, the effects of different lactate threshold intensities, during and after aerobic exercises, have been little studied and are yet inconclusive.

Ghanassia *et al*[25] observed that the predominance of carbohydrate oxidation in T2D during exercise seems to be independent of the intensity of effort. Nevertheless, the use of carbohydrate as substrate seems to be dependent of intensity, since it is available in the muscle (glycogen) and in the blood (glucose)[1].

Lima *et al*[26] observed an increase in fat oxidation after a cycle ergometer session, when compared to resting values in T2D. Furthermore, high exercise intensities extend this increase, and fat oxidation after exercise was higher in T2D in comparison to euglycemic.

The increase in carbohydrate oxidation during exercise, as well as fat oxidation during the post exercise recovery period can contribute to augment insulin sensitivity, and collaborate to reduce body fat percentage. It is noteworthy that the accumulation of intramuscular fat has a direct relation on insulin resistance, and consequently the appearance of T2D[27,28].

POST-EXERCISE HYPOTENSION IN T2D

Individuals with T2D present other impairments, such as endothelial dysfunction[3,29], increased sympathetic tonus and other cardiovascular diseases, including hypertension[30], which lead to the increase in morbidity and mortality.

One session of aerobic or resistance exercise can promote postexercise hypotension (PEH). The exercise-induced mechanical stress on the wall of the arteries, can increase the release of vasodilating substances by the endothelium (*e.g.*, nitric oxide, bradykinin), augments baroreflex sensitivity, and decreased sympathetic nervous activity in the solitary tract nucleus caused by the release of substance P by skeletal muscles[31-34]. This adaptation can bring benefits to health, because it helps to keep low levels of blood pressure, avoiding and controlling blood pressure increase at rest. However, the magnitude of this effect seems to be diminished in T2D individuals, since this population presents endothelial dysfunction, which collaborates to a decrease in the capacity of nitric oxide (NO) release when compared with euglycemic individuals[35-37]. Increased sympathetic tonus and other cardiovascular diseases are also observed in T2D[30].

Studies have demonstrated that the occurrence of PEH in T2D can be intense depending on the effort. Lima *et al*[4] demonstrated that T2D individuals seem to be more responsive to high intensity exercise sessions, since exercise above lactate threshold (LT) (110% of the LT) resulted in a significant decrease in systolic blood pressure (SBP) values up to 90 min after the session, whereas exercise performed below lactate threshold (90% of the LT) only reduced SBP during 45 min post exercise.

Simões *et al*[38] comparing two resistance training exercise intensities (23% and 43% of 1RM), observed that only the higher session (43%) promoted PEH. Similar results were found by Motta *et al*[29], when studying the effects of a 20 min high intensity cycle ergometer (90% of lactate threshold) in individuals with and without T2D. Both studies only observed significant blood pressure decreases in non T2D individuals.

Although the physiological mechanism responsible by this process still remains inconclusive, it is known that high intensity exercise promotes increases the activity of the kallikrein-kinin system, and consequently, augments the synthesis and release of nitric oxide[29]. However, more studies are still made necessary to elucidate this question.

EXCESS POSTEXERCISE OXYGEN CONSUMPTION IN T2D

Exercise increases oxygen consumption after exercising and during rest, this phenomenon is known as excess postexercise oxygen consumption (EPOC), which has a fast component (2-3 min), and a slow component which can persist for more than 30 min. The duration and magnitude of EPOC depends on the intensity and duration of the effort[39-42].

The need to resynthesize creatine phosphate, restore intramuscular oxygen, body temperature and muscular glycogen, increased activity of the sodium-potassium pump, clearance of lactate, high levels of epinephrine and norepinephrine are factors that can lead to EPOC[40,41].

However, T2D individuals present metabolic impairments, such as lower capacity to utilize carbohydrate, due to lower enzymatic regulation and intracellular signalling and gene transcription[43]. Thus, these modifications can change the pattern of metabolic and respiratory alterations elicited during and after exercise[4]. Therefore, it decreased the benefits of EPOC when compared to euglycemic individuals.

Studies about EPOC in T2D are scarce. Therefore, determining which intensity and duration could be more beneficial to promote this event in T2D is important to increase post-exercise fat oxidation, once the accumulation of intramuscular fat has been associated to the development of T2D[43].

NITRIC OXIDE AND EXERCISE IN TYPE 2 DIABETES

NO is a gaseous, inorganic and colorless free radical, which has seven electrons of nitrogen and eight of oxygen, having an unpaired electron[44]. NO is synthetized from oxidation one of the two guanidine nitrogens of

L-arginine, which is converted to L-citrulline[45].

NO produced by endothelial cells has an essential function in the process of relaxing of blood vessels. In physiological conditions, vascular relaxing occurs when the membrane receptors of endothelial cells are activated by soluble stimulus, which include: acetylcholine, bradykinin, adenosine diphosphate, substance P, serotonin and others, or when there is an increase of friction exerted by circulating cells in the endothelial layer (shear stress), generating the activation of endothelial NO synthases (eNOS) present in these cells, causing an increase of synthesis and release of NO[46].

NO produced by eNOS in endothelial cells spreads out to smooth muscle cells and vascular lumen. In the smooth muscle, NO interacts with the iron from heme group of enzyme guanylate cyclase (GC), causing an alteration in the structure of this enzyme, becoming activated (GCa). GCa catalyzes the departure of two phosphate groups from the molecule guanosine triphosphate, similar to the adenosine triphosphate (ATP), forming the cyclic guanosine monophosphate (cGMP). An increase in the levels of cGMP occurs when NO activates GC inside the cells[47], resulting in: (1) maintenance of vascular tonus; (2) blood pressure regulation; (3) prevention of platelet aggregation (by increase of cGMP and decrease in Ca^{2+}); (4) inhibition in adhesion of monocytes and neutrophils in the vascular endothelium; (5) anti-proliferative effect; and (6) anti-oxidant effect decreasing the production of peroxynitrite anion (ONOO-)[36]. Recent studies have shown that having a physically active lifestyle can contribute to maintain the functional capacity of the vascular endothelium, measured by the preservation of ability to produce NO[48-50].

The acute effects of exercise in the bioavailability of NO in physical performance and health, mainly in endothelial function, have been previously studied. Studies have demonstrated that exercise promotes an increase in NO levels after a single session. This acute effect of exercise in NO can induce positive adaptations in the cardiovascular, hepatic, esqueleto muscle systems and others[35,51].

This effect can influence health parameters, such as the control of blood pressure (BP). Faria *et al*[52] induced spontaneously hypertensive rats to one session of exercise (squat), using vests as load. They observed a decrease in BP, lower vascular reactivity, and endothelium-dependent vasodilatation mediated by the NO after exercising.

Augeri *et al*[53] examined the influence of the T786C gene of eNOS in post-exercise hypotension (PEH) and NO after a low (40% VO_2max) and moderate intensity exercise (60% VO_2max) in the cycle ergometer in prehypertensive individuals. The individuals, who carried the TT genotype, demonstrated less PEH than heterozygous individuals 9 h after exercising.

On the other hand, Long *et al*[54] determined the preventive effects of exercise in the coronary blood flow and macrovascular atherosclerosis in aerobic trained Yucatan pigs, which passed by a high cholesterol and fat concentrated diet. The short aerobic training kept the endothelium independent relaxation (adenosine) and increased the coronary endothelium-dependent relaxation through the action of bradykinin, that is a mediator of NO production, and decreased the developing of atheromatous plaques in the aerobic trained pigs.

In the venous system, Chies *et al*[55] evaluated the effects of angiotensin Ⅱ in the portal vein and vena cava of trained rats. The exposition of trained animals to consecutive sessions of acute aerobic exercise in a treadmill improved the portal vein response in the presence of angiotensin Ⅱ. This upgrading seems to be specific in portal vein, once the researches didn't observe this phenomenon in vena cava. The authors concluded that these adaptations are influenced by NO, endothelin and prostanoids.

Regarding vascular damage, Cubbon *et al*[56] studied the association of NO induced by exercise in the proliferation and mobilization of circulating progenitor cells (CPC), which are potential mediators of cell repair. The mobilization of CPC is critically dependent of NO, and south Asians are associated with low CPC levels. The mobilization of CPC was measured during a moderate-intensity exercise session. Mediators of vasodilatation and CPC were lower in the Asian group than in Europeans. During the exercise, the CPC also was lower in Asians. A decrease in the release of NO can contribute to inappropriate balance between vascular damage and muscular repair in the population.

The acute effects of exercise in NO have also been studied in other tissues. In the skeletal muscle, Lee-Young *et al*[57] observed that in mice without eNOS, ATP is reduced (40%), in sedentary conditions exercise tolerance is markedly impaired during a 30 min session. The researchers observed that a partial reduction of eNOS expression is enough to induce physiological changes in ATP and NO production, and consequently, reducing the tolerance to the effort.

Besides exercise, diet also seems to influence the availability of NO. Bailey *et al*[58] administrated oral L-arginine in nine healthy individuals and performed "step" exercise in two intensities (moderate and high) one hour after ingestion. Plasma nitrite was significantly higher in the group that consumed L-arginine, resulting in a decrease in SBP. Submaximal VO_2max was 7% lower in the moderate intensity exercise, while in the high intensity exercise the slow component was reduced and the time to exhaustion delayed with L-arginine supplementation. As a conclusion, the authors stated that diet with L-arginine showed similar results with nitrite, increasing the bioavailability of NO, and reducing the cost of O_2 in the moderate exercise and time to exhaustion in the maximal exercise.

One exercise session seems to increase the bioavailability of NO, collaborating with the regulation of vascular tonus, balance between damage and muscle repair and preventing diseases such as atherosclerosis and hypertension[59]. Studies related to the bioavailability of NO in different exercise intensities are inexistent. The production

Table 1 Summary of human studies about acute effects of physical exercise in type 2 diabetes

Ref.	Sample	Exercise intervention	Results
Lima *et al*[4]	T2D = 11	20 min of cycle ergometer at 90% and 110% LT, and control session	Higher intensity exercise (110% LT) was more effective than lower intensity (90% LT)
Sriwijitkamol *et al*[5]	Obese T2D = 12 Obese CG = 8 Lean CG = 8	40 min of cycle ergometer at 50% and 70% VO_{2max}	Obese and T2D had attenuated exercise-stimulated AMPK activity and AS160 phosphorylation. T2D had reduced basal *PGC-1* gene expression but normal exercise-induced increases in PGC-1 expression
Borghouts *et al*[12]	T2D = 8 CG = 8	1 h of cycle ergometer at 40% VO_{2peak} and control session	Muscle glycogen oxidation was lower in T2D than in CG. Plasma glucose contributed more to energy expenditure in T2D than CG
Braun *et al*[24]	Insulin-resistant = 6 Insulin-sensitive = 6	50 min of treadmill walking at 45% VO_{2max}	Carbohydrate oxidation and estimated muscle glycogen use were significantly lower in the insulin-resistance group
Ghanassia *et al*[25]	T2D = 30 CG = 38	Increasing exercise intensity in cycle ergometer	Lipid oxidation was lower in T2D. Maximal lipid oxidation point and the crossover point were lower in T2D
Lima *et al*[26]	T2D = 9 CG = 11	20 min of cycle ergometer at 90% LT, increasing exercise intensity and control session	T2D have a better fat oxidation after high-intensity exercise than moderate exercise. T2D had less fat oxidation than CG after moderate exercise
Motta *et al*[29]	T2D = 10 CG = 10	20 min of cycle ergometer at 90% LT and control session	CG presented PEH, but not in the T2D. Plasma kallikrein activity increased postexercise in the CG, but not in the T2D
Simões *et al*[38]	T2D = 10 CG = 10	Resistance exercise circuit at 43% and 23% 1RM (approximately 25 min), and control session	43% 1RM promoted PEH, whereas the 23% did not
Asano *et al*[60]	T2D = 11	20 min of cycle ergometer at 80% and 120% LT, and control session	Exercise above LT (120% LT) increase nitric oxide and decrease SBP post-exercise, but about 80% LT not

T2D: Type 2 diabetics; LT: Lactate threshold; CG: Control group; VO_{2max}: Maximal oxygen uptake; VO_{2peak}: Peak oxygen uptake; PEH: Post-exercise hypotension; 1RM: 1-repetition maximum; AMPK: AMP-activated protein kinase; PGC-1: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

of knowledge about this important topic is essential to define better exercise strategies to increase the bioavailability of NO in individuals with T2D after one exercise session.

A summary of acute effects of physical exercise in T2D, along with the reference, number of volunteers and the kind of intervention, can be observed in Table 1.

CONCLUSION

A single session of exercise can promote beneficial effects regarding blood pressure control, glycemia, carbohydrate oxidation during exercise and fat oxidation after exercise. Evidence has shown that exercise, especially at intense domains, can increase the bioavailability of nitric oxide, promoting a decrease in blood pressure after exercising. Furthermore, metabolic stress from exercising is able to increase the oxidation of carbohydrates during exercise, keeping an elevated O_2 consumption after exercising. This, in consequence, increases fat oxidation during at rest and improves glucose tolerance, insulin sensibility and can reduce glucose levels between 2 to 72 h depending of intensity and duration of the effort.

These acute effects of physical exercise are important to T2D, because they help to improve conditions such as high blood pressure, hyperglycaemia and lipidemia.

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