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Resistance training in the treatment of diabetes mellitus II: a narrative review

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Abstract Diabetes Mellitus is defined as a condition in which glucose levels in the bloodstream are present in high concentrations. Type II Diabetes Mellitus (DMT2) is the most common and develops in the long term, being mainly associated with the individual's lifestyle. It is characterized by the cellular situation of insulin resistance, and treatment is recommended through pharmacological, nutritional, and resources and regular exercise. Therefore, the objective of the study was to review the literature on the influences of the practice of Resistance Training (RT) in patients with Diabetes Mellitus Type II. The increase in the activation of the AMPK pathway induced by muscle contraction seems to be the most important mechanism of action since there is an increase in the translocation of GLUT4 to the cell membrane, which allows a greater uptake of glucose from the bloodstream in an insulin-independent manner, establishing a balance in glucose levels. RT, in addition to promoting serum glucose homeostasis, also reduces the risk factors for the disease, thus becoming an effective strategy for the prevention and treatment of T2DM.

Keywords: glucose, insulin, muscular contraction

1. Introduction

Diabetes Mellitus (DM) is one of the most challenging public health problems in the world due to its high and increasing prevalence. In 2019 the *International Diabetes Federation* (IDF) estimated that 463 million adults aged between 20 and 79 years had diabetes. The expectation is that these numbers will grow considerably in the coming decades, reaching, by the year 2045, 693 million people diagnosed with the disease (Cho et al 2018). Currently, approximately 6% of the entire world population lives with some type of DM (WHO 2021). For this, the World Health Organization (WHO) has spared no resources to contain the advance of DM, presenting strategies and recommendations aimed at its prevention, diagnosis, and control, as well as the management and care of risk factors for the development of DM disease, such as obesity.

DM has reached epidemic proportions worldwide and is associated with several mortality risks. From this perspective, strategies that can mitigate the risks of developing the disease are extremely important. In this sense, many epidemiological studies have reported the importance of regular physical exercise in the prevention, control, and treatment of patients diagnosed with Type 2 Diabetes Mellitus (DMT2) (ACSM 2010; Lavie et al 2014; Aune et al 2015; Sawada et al 2019; Jansson et al 2022). It is known that DMT2 is responsible for about 90% of cases of diabetes worldwide (Jansson et al 2022).

Historically, aerobic exercise was considered the main method to control T2DM. Although aerobic exercise alone can improve glycemic levels, guidelines responsible for DM have consistently recommended resistance training (RT) for patients diagnosed with T2DM, as an important non-pharmacological therapeutic strategy (Pan et al 2018). In order to understand the effectiveness of RT in the control and prevention of T2DM, the present study aims to review the influences of the practice of resistance training in patients with Type II Diabetes Mellitus.

2. Methodology

The study is a narrative literature review that used the following databases to collect journals: PubMed, Scielo, and Google Scholar. The years of publication of the studies for the search were not filtered, and only the studies that dealt with the specific theme (Resistance Training and Type 2 Diabetes Mellitus) were selected. Figure 1 shows a flowchart with the steps for selecting the studies in this review.

3. Diabetes Mellitus

According to the IDF (2019) DM can be basically defined as a serious and long-term (or chronic) condition in which the individual has high blood glucose levels as a result of a deficit in the production or ineffectiveness in the use of the hormone insulin by the body. The *American Diabetics Association* (ADA) classifies DM as a metabolic disease characterized by blood hyperglycemia resulting from dysfunction in insulin secretion or insulin action (ADA 2019). In general, diabetes is characterized as a serious and chronic disease, determined by the failure of the pancreas to produce enough insulin to regulate blood glucose levels (McArdle et al 2013).

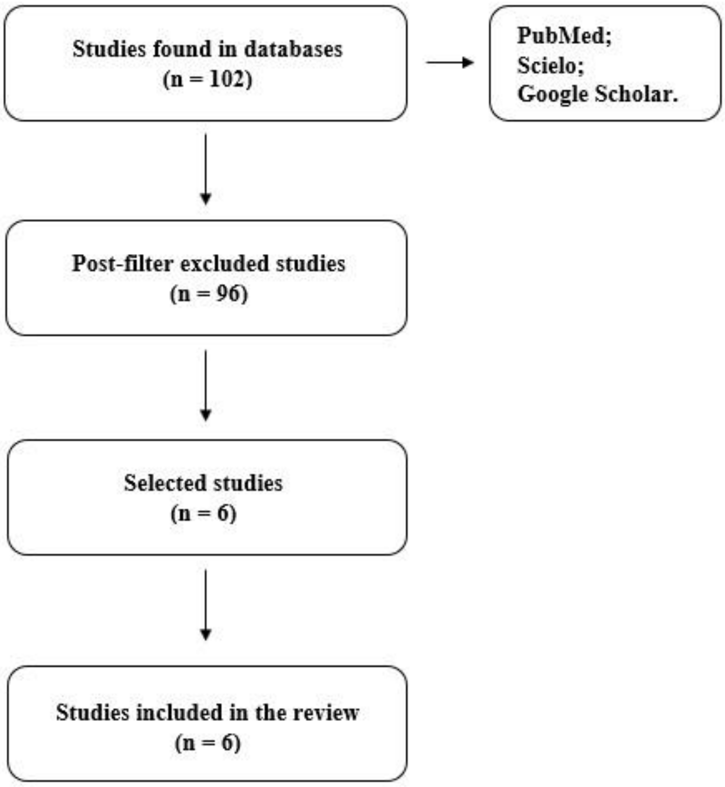

Figure 1 Study selection flowchart.

More broadly, in the development of diabetes, the pancreas is the central organ since it produces and secretes hormones that are responsible for controlling blood glucose, such as insulin, which is secreted from β cells and glucagon by α cells. After a meal, insulin acts by capturing blood glucose that is in high concentration so that it can be stored in the cell as a source of energy substrate. Thus, insulin basically has a hypoglycemic effect by reducing blood glucose concentrations (McArdle et al 2013). Therefore, insulin mainly stimulates glycogenesis and inhibits gluconeogenesis (Costa and Porto 2015). Glucagon, on the other hand, promotes glycogenolysis and increased gluconeogenesis since it is secreted in states of hypoglycemia and has the function of returning blood glucose to normal levels (Costa and Porto 2015).

Considered by the WHO as one of the four priority non-communicable diseases (NCDs), DM has become an important public health problem. According to the ADA (2005), there are four types of classifications for diabetes: type 1, type 2, gestational and secondary to other pathologies. Despite the different types, glycemic control and early treatment are extremely important to prevent the development of other complications, such as: cardiovascular diseases, retinopathies, autonomic and peripheral neuropathies, nephropathy, peripheral vascular disease, atherosclerosis, cerebrovascular disease, hypertension, susceptibility to periodontal infections and diseases (Arsa et al 2009).

The IDF (2019) classifies T2DM as the most common type, and is mainly correlated with the individual's lifestyle, and may be referred to as non-insulin-dependent diabetes, type 2, or adult-onset diabetes (ADA 2005). This type of DM is due to a situation called "insulin resistance", where the body's cells are unable to respond to insulin, causing the hormone to become ineffective and high concentrations of serum glucose to remain unchanged. In the long term, this disorder can lead to the overloading of pancreatic beta cells since they cannot keep up with the body's demands (IDF 2019).

The mechanism of action of insulin occurs through a cascade of enzymatic reactions in the cellular cytoplasm when the hormone binds to its transmembrane receptor (IR) (Arsa et al 2009). When activated, the IR promotes the phosphorylation of some substrates (IRS-1 and IRS-2). This mechanism allows the creation of binding sites for a cytosolic protein called phosphatidylinositol 3-kinase (PI3K). PI3K plays a fundamental role in the transport of glucose since its activation promotes the phosphorylation of protein kinase B (AKT), which, in turn, allows the translocation of the GLUT4 protein to the cell membrane, allowing glucose uptake by facilitated diffusion (Pauli et al 2009).

The guideline of the Brazilian Society of Diabetes (2019-2020) indicates that levels of insulin resistance can be characterized in a physiological or pathological condition, as in more severe conditions. The pathological state of insulin resistance is mainly the result of bad habits, such as excessive caloric intake combined with low levels of physical activity, thus favoring the development of excess body weight (Guedes et al 2019). The literature (Pauli et al 2009; Guedes et al 2019) points to obesity as one of the main causes of the development of insulin resistance since the excessive accumulation of triglycerides and the release of free fatty acids lead to inflammation. These inflammatory substances produced react with the substrate of the insulin receptor (IRS-1 and IRS-2); once phosphorylated, they can no longer react to contribute to the action of the hormone, thus establishing resistance.

4. Diagnosis of Diabetes Mellitus

The diagnosis of DM is performed mainly through laboratory tests that identify glucose and insulin levels after periods of fasting or after glycemic loads through the oral route. Basically, three levels of glucose concentration are indicated, when it is normal (< 110 mg/dl), when it presents an altered variation (between 110 and 125 mg/dl) or when diabetes is suspected (> 125 mg/dl) (McArdle et al 2013; SBD 2019). The main risk factors for the development of diabetes are: altered glucose and insulin metabolism (fasting glucose ≥ 110 mg/dl), overweight with abdominal fat distribution (waist circumference: men > 102 cm; women > 88 cm), mild dyslipidemia (triacylglycerols ≥ 150 mg/dℓ; high-density lipoprotein cholesterol: men < 40 mg/dℓ; women < 50 mg/dℓ), and hypertension (≥ 130/ ≥ 85 mmHg) (McArdle et al 2013).

The IDF (2019) also highlights the difficulty of diagnosing T2DM, as it is a long-term condition and is often asymptomatic. However, the most common symptoms of the disease are: polyuria, polydipsia, polyphagia, sudden weight loss, blurred vision, and lack of energy.

5. Treatment of Diabetes Mellitus

The means of treatment and prevention of DM can be established according to the classification of the disease. DMT2 can be developed during life, and the means of treatment can be diversified (Costa and Porto 2015). It is possible to control the glycemic index of DMT2 from medications, physical exercises, and nutritional strategies, knowing that pharmacological resources are indispensable in the treatment and prevention of the disease, as well as diet and physical exercise. Improving the action of insulin in the body, decreasing the release of free radicals, and avoiding hypoglycemia and weight gain, are some of the responses achieved by the proposed treatment strategies (Kelley et al 1993; Pfeiffer and Klein 2014).

6. Resistance training in the treatment of T2DM

Physical exercise, in general, is able to promote hormonal changes in response to imposed stress, whereas RT directly helps in the prevention and treatment of pathologies such as osteoporosis, obesity, diabetes and hypertension (Calvinho and Lira 2008; Kraemer et al 2002). Among the various cascades of reactions triggered by exercise, there are pathways that are independent of insulin action, which have the ability to capture circulating glucose in the blood (Arsa et al 2009). The American Heart Association (AHA) classifies as the maximum level that the regular practice of RT has a great role in decreasing the concentration of glycated hemoglobin (Hb1Ac) (Marwick et al 2009). This effect is related to the stimulation of GLUT4 translocation to the cell membrane, which allows greater glucose uptake, consequently reducing its concentration in the bloodstream. Muscle contraction becomes the main signaling agent for this reaction to occur, causing the uptake of blood glucose regardless of the action of the insulin hormone (Pauli et al 2009). This mechanism reveals the physiological potential that physical exercise or RT itself has for the regulation of glucose levels in patients with T2DM.

In this perspective, RT promotes the activity of P13K/AKT/mTOR pathways that are directly related to the anabolic effects that insulin has on protein metabolism (Pacheco et al 2017). In this way, RT promotes the activation of a key enzyme in response to muscle contraction, AMP-activated protein kinase (AMPK) (Pauli et al 2009). Studies suggest that the AMPK signaling pathway participates in important metabolic actions, such as lipolysis in adipose tissue and lipid and glycogen metabolism in the liver and muscle. AMPK also stimulates glucose transport in muscle and adipose tissue (Barnes and Zierath 2005). Activated at times of decreasing cellular energy levels, phosphorylated AMPK activates pathways that generate an increase in ATP, such as activation of mitochondrial biogenesis and inhibition of pathways that consume ATP, including glycogen synthesis (McGee et al 2008).

Therefore, this increase in AMPK activation through muscle contraction promotes a greater need for ATP, causing the translocation of GLUT4 to the membrane to increase and, consequently, greater transport of glucose into the cell. This process is similar to what occurs in the insulin signaling pathway. However, AMPK causes this entire procedure to occur independently of the hormone (Entezari et al 2022). Figure 2 shows a schematic showing how muscle contraction promotes the uptake of glucose into the bloodstream.

Corroborating these concepts, Pádua et al (2009) demonstrated that the increase in AMPK phosphorylation induced by physical exercise can cause a decrease in hepatic glucose and increase glucose uptake in the muscle of diabetic animals. Consequently, increased exercise-induced activation of the AMPK pathway proves to be a potential non-pharmacological treatment method for glucose control in T2DM patients. In addition, RT also promotes positive effects through other processes, such as, through increased muscle mass that induces greater capillarization in muscle cells (Ishii et al 1998; Souza and Toigo 2018) and, according to Marwick et al (2009), an increased capillary-to-muscle ratio further favors blood glucose control.

However, despite the positive effects of RT on the reduction of blood glucose caused by a greater expression of GLUT-4 proteins, evidence on chronic adaptations is still lacking. Host et al (1998) reported that GLUT-4 concentration and glucose transport via insulin increased approximately two-fold in rats that underwent either 5 days or 5 weeks of resistance training. However, within 40 hours after the last exercise session there was a rapid decrease in GLUT-4 content, a finding that is related to the short half-life of the protein (8 to 10 hours).

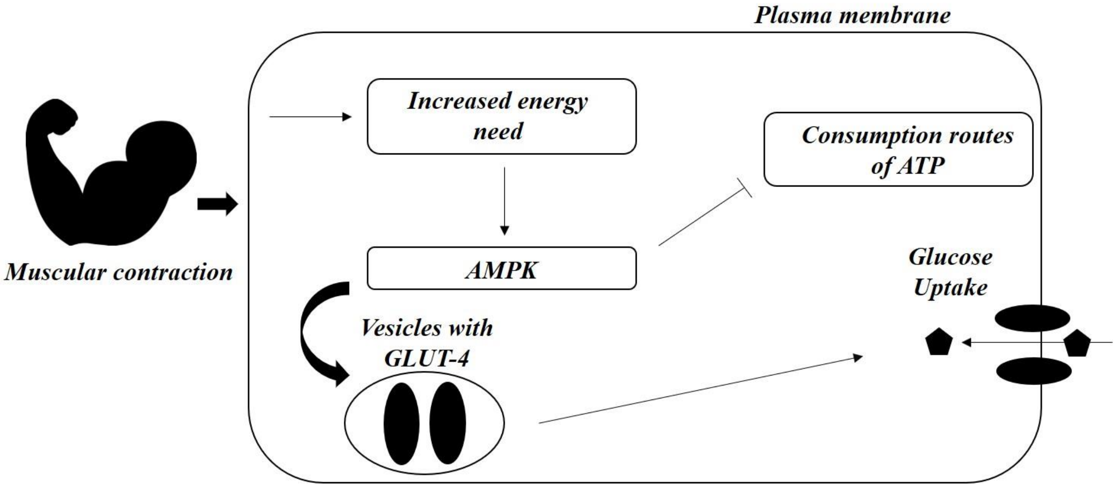

Figure 2 Insulin-independent glucose uptake pathway.

7. Resistance training variables in the treatment of T2DM

The mechanisms in which RT influences the treatment of patients with T2DM are already well established. However, RT training has many variables and ways of being systematized that will influence the responses caused to patients with T2DM. A summary of the main findings of the analyzed studies is presented in Table 1.

In view of this, Dunstan et al (1998) sought to evaluate the effects of RT in the circuit on the glycemic control of sedentary men and women not trained with DMT2. Consequently, after 8 weeks of training, the volunteers who performed the circuited RT showed improvement in glycemic control. This response was justified by the decrease in serum glucose concentration and an improvement in insulin action on glucose concentrations, thus resulting in a better balance of your levels.

Cambri and Santos (2006) analyzed the effect of 12 weeks of RT with progressive volumes in patients with T2DM. The authors found that in addition to the decrease in capillary blood glucose levels (Pre-test 191.79 ± 77.30; Post-test 153.70 ± 73.08; $p<0.05$), the percentage of body fat was also significantly reduced ($p<0.05$). Thus, RT proved to be efficient in the treatment by controlling blood glucose levels and in the prevention of T2DM by reducing the risk factors for the disease.

Castaneda et al (2002) sought to analyze the effect of high-intensity progressive resistance training on glycemic control, metabolic syndrome abnormality, body composition, and muscle glycogen levels in the elderly. After the interventions, it was concluded that high-intensity RT (70-80% 1MR) was a viable and effective treatment for elderly people with T2DM. Since the results showed a decrease in glucose levels (Hb1Ac = from 8.7 ± 0.3 to 7.6 ± 0.2%), an increase in muscle glycogen stores and mainly a large reduction in the prescription of drugs for the treatment of T2DM. In contrast, Kwon et al (2010) investigated the effects of low-intensity RT on body fat, muscle mass and strength, cardiovascular fitness, and insulin sensitivity in overweight women with T2DM. The intervention was performed with elastic bands that represented 40-50% of the participants' 1MR for 12 weeks, 3 sessions were performed per week with 3 sets of 10 to 15 repetitions per exercise. Finally, the authors concluded that low-intensity RT was effective in decreasing fat mass and increasing muscle mass and strength. However, there was no change in the participants' insulin sensitivity (Intervention group = 1.8 ± 1.0 versus Control group = 2.0 ± 0.8 %/min; $p = 0.49$).

Contrasting with Kwon et al (2010), Ishii et al (1998) found improvement in insulin sensitivity of T2DM patients submitted to low-intensity training (40-50% of 1MR). However, in the study by Ishii et al (1998), the participants performed a greater total training volume, where 4-6 weeks of RT were performed with 5 sessions per week, consisting of 9 exercises structured in 2 series of 10 repetitions for exercises of upper limbs and 20 for lower limb exercises. Considering that RT is dose-dependent, that is, the magnitude of adaptive gains is directly related to the volume performed in the session (Suchomel et al 2018), it is possible that the contrasting results of the cited studies are explained by the large difference in training volume, so that the stimulus imposed by Kwon et al (2010) may not have been enough to generate adaptive responses to RT.

Still in this sense, Dunstan et al (2002) investigated the effect of high-intensity progressive RT combined with moderate weight loss in elderly patients with DM2. The intervention lasted 6 months, with 3 non-consecutive RT sessions per week; during the first two weeks, the intensity was maintained at 50-60% of 1MR, being increased in the following weeks to 75-85%

of 1MR, in all, they have performed 9 exercises with 3 sets of 10 repetitions for 90-120 seconds of rest. Both during and at the end of the intervention, Hb1Ac values decreased significantly ($p < 0.05$), as well as fasting glucose and insulin concentration. Consequently, the conclusion proposed by the authors is that progressive RT of high intensity, in combination with moderate weight loss, is an effective plan to improve glycemic control in elderly patients with T2DM, corroborating the findings of the studies cited throughout the text, which point mainly to the control of risk factors, levels of serum glucose and insulin resistance.

Table 1 Characteristics of the analyzed studies.

Study	Participants	Training protocol	Main outcomes
Dunstan et al (1998)	17 untrained males and 10 females with a mean age of 51 years.	10 resistance exercises alternated per segment and performed in a circuit format. Frequency: 3 non-consecutive times a week. Intensity: Progressive over the weeks Volume: 1-2 (2x 15-20 reps), 3-8 (3x 10-15 reps). Duration: 8 weeks	↑Strength ↓Self-monitored glucose levels ↓Basal values in the insulin curve
Cambri and Santos (2006)	6 sedentary men and 2 women (52.86 ± 3.40 years).	10 resistance exercises alternated per segment and performed in a circuit format. Frequency: 3 non-consecutive times a week. Intensity: Progressive over the weeks Volume: 1-2 (1x 15-20 reps), 3-4 (2x 15-20 reps), 5-9 (2x 12-15 reps), 10-12 (3x 12-15 reps). Duration: 12 weeks.	↑Lean mass, body mass, and BMI ↓Waist-hip ratio, %fat, and the sum of skinfolds. ↓Capillary blood glucose = glycated hemoglobin
Castaneda et al (2002)	40 men and 22 women (66 ± 8 years).	5 pneumatic resistance exercises. Frequency: 3 times a week. Intensity: 1-8 (60 – 80% MR*), 9 decreases ~10%, 10-14 (70 – 80% MR), 15 decreases ~10%. Volume: 3x 8 reps max. Duration: 16 weeks.	↓ Glycated hemoglobin ↑ Muscle glycogen ↓ Medication dose ↑ Lean mass ↓ Systolic blood pressure and body fat
Kwon et al (2010)	28 obese women (56.4 ± 7.1 years).	Elastic resistance training with 6 exercises for upper limbs, 4 exercises for lower limbs, and 1 for the trunk. Frequency: 3 times a week. Intensity: Low and progressive over the weeks. Volume: 3x 10-15 reps. Duration: 12 weeks.	↑ Muscle mass ↓ Fat mass and abdominal fat ↑ Muscle strength = insulin resistance
Ishii et al (1998)	17 sedentary men (approximately 50 years old).	9 resistance exercises for the main muscle groups with <1 min interval between sets. Frequency: 5 times a week. Intensity: 40-50% of MR. Volume: 2 series for each exercise, 10 reps for upper limbs and 20 reps for lower limbs. Duration: 4 - 6 weeks.	↑ Glucose uptake = Body composition ↑ Quadriceps strength = VO2Max
Dunstan et al (2002)	29 men and women aged between 60 and 80 years.	9 resistance exercises, 6 exercises for upper limbs, 2 for lower limbs, and 1 for trunk with intervals of 90 to 120s between sets. Frequency: 3 non-consecutive days per week. Intensity: 1-2 (50 – 60% MR), after that 75 to 85% MR. Volume: 3 x 8 – 10 reps. Duration: 6 months.	↓ Glycated hemoglobin ↓ Body weight and fat mass. ↑ Lean mass = fasting glucose, insulin, serum lipids, and lipoproteins, or resting blood pressure.

7. Final considerations

The practice of RT becomes one of the main means of treatment and prevention of DMT2, considering that the responses caused by stimuli are essential due to the inefficiency that insulin has on blood glucose concentrations, especially in moments of a sedentary lifestyle. In the condition of insulin resistance, the muscle contraction caused by RT activates specific reactions in the metabolism that make glucose uptake increase and occur efficiently, promoting physiological benefits to the patient with T2DM. In this way, the practice of RT should be encouraged, as well as minimized sedentary behaviors. From the point of view of intensity, more intense activities seem to produce better adaptive responses. However, the training volume must also be advocated. Finally, further research on the subject is still needed; despite the RT showing a good response in improving the T2DM condition, its adaptations seem to be attenuated after rest periods. Therefore, studies that investigate chronic interventions can better elucidate the subject.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Not applicable.

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