DOI: 10.4025/jphyseduc.v27i1.2735

**Original Article**

# EFFECTS OF HIGH INTENSITY ACUTE RESISTANCE EXERCISE ON BLOOD GLUCOSE AND INSULIN SENSITIVITY IN RATS WITH INSULIN RESISTANCE

## EFEITOS DO EXERCÍCIO RESISTIDO AGUDO DE ALTA INTENSIDADE SOBRE A GLICEMIA E SENSIBILIDADE À INSULINA EM RATOS COM RESISTÊNCIA À INSULINA

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**RESUMO**

O objetivo do estudo foi avaliar o efeito do exercício resistido agudo sobre o metabolismo glicêmico em animais com resistência à insulina. Foram utilizados 30 ratos Wistar divididos em três grupos: Controle (CON), Dexametasona Sedentário (DS) e Dexametasona + Exercício (DE). O exercício resistido foi realizado no aparelho de agachamento composto por cinco séries, 10 repetições, com intensidade de 70% de 1RM. Concomitantemente, os grupos DS e DE receberam diariamente dexametasona intraperitoneal (4,0mg/kg). Foram aferidos o peso corporal, a glicemia e o teste de sensibilidade à insulina de todos os grupos. Única sessão de exercício resistido reduziu a glicemia e melhorou a sensibilidade à insulina, o grupo DT apresentou menor área sob a curva em relação ao grupo DS. O exercício resistido agudo de alta intensidade promoveu redução da glicemia e melhorou a sensibilidade da insulina em ratos com resistência a insulina induzidos com dexametasona.
**Palavras-chave**: Resistência à Insulina. Glicemia. Exercício físico. Exercício resistido.

**ABSTRACT**

The aim of the study was to evaluate the acute resistance exercise on glucose metabolism in animals with insulin resistance. 30 Wistar rats were divided into three groups: control (CON), Dexamethasone Sedentary (DS) and dexamethasone + exercise (DE). Resistance exercise was conducted in the squat machine consisting of five sets, 10 repetitions, with intensity of 70% of 1RM. Concurrently, the DS and DE groups received daily intraperitoneal dexamethasone (4.0mg / kg). The body weight, glycemia and insulin sensitivity test were measured in all groups. One single resistance exercise session reduced blood glucose levels and improved insulin sensitivity. The DT group showed a lower area under the curve when compared to the DS group. The high intensity acute resistance exercise promoted a reduction of blood glucose levels and improved insulin sensitivity in rats with insulin resistance dexamethasone- induced.
**Keywords**: Insulin Resistance. Glucose. Physical exercise. Resistance exercise.

## Introduction

Type 2 diabetes (T2DM) corresponds to more than 90% of all diabetes cases in the world, and is considered as a major threat to public health. In recent years. There has been an exaggerated growth of the epidemic prevalence of this disease around the world. Some factors have contributed to the development of T2DM, such as environmental, behavioral and lifestyle changes[1,2]. As a result, it is estimated 4 million people die every year due to DM2 and its complications, which represents 9% of global mortality, influencing directly in reducing life expectation and quality[3]. Given this situation, it is also noticeable the cost increase related to the treatment of the disease: approximately US$ 4 billion a year are spent in the treatment of diabetes by the Health System of Brazil (HSB), and outpatient spending exceeds two thousand US dollars/patient[1] .

Thus, the national and international health services should implement actions focusing on lifestyle changes in order to prevent DM2. This is necessary because, in most cases, patients with DM2 do not require exogenous insulin, and they would be able to control the disease with medicine, diet and/or exercises[1,4-6]. Among these recommendations, changes in their eating behavior prioritizing the consumption of healthy foods and the adoption of regular

practice of physical exercise are important non-pharmacological tools that help reduce the effects of DM2 on the body, by reducing the disease incidence, characterizing them as preventive measures, especially in high risk individuals. Furthermore, the exercise ends up being an important practice for the treatment of hyperglycemia, which is associated with insulin resistance[4,7-9]. Currently, several studies in humans beings and in animal models are investigating the mechanism by which physical exercises provide increased glucose uptake[4,10,11].

It has been demonstrated that aerobic exercise feature increases the glucose uptake due to the increase of insulin sensitivity in the muscle tissue receptor. These beneficial changes were detected both in increased protein expression of insulin receptor (IR) and its substrates (IRS-1, IRS-2) as well as the enzymatic activity of protein kinase B (also known as Akt), a key protein involved in the translocation of vesicles to the plasma membrane that culminate in glucose uptake[7,11,12]. These results show that aerobic exercise can promote important therapeutic effects on glycemic control and on reducing insulin resistance and T2DM.

However, few studies presented information on the acute effects of high-intensity resistance exercise (RE) on glucose concentrations and on the improvement of insulin sensitivity in skeletal muscle[13]. Therefore, there are many questions about practice ER still waiting to be clarified, especially on the influence of training variables (duration, intensity and frequency), in order to develop strategies that allow individuals with insulin resistance and T2DM carry out RE in a safe way, and mainly in a way that contributes to the glycemic control.

## Methods

*Population and Sample*

We used 30 Wistar rats, three months old, weighing between 300 and 350g from the central vivarium of the Federal University of Sergipe. They were taken to the vivarium of the Research Center in Intracellular Signaling (NUPESIN/DMO/UFS). The animals were kept in plastic cages (five animals per cage) with food and water "*ad libitum*", and photoperiod of 12 hours, at a temperature of 23±2°C throughout the experiment. The experimental protocol of this study was approved by the Ethics Committee on Animal Research of the Federal University of Sergipe under number 07/2013, following the Declaration of Helsinki and the Ethical Principles on Animal Experimentation by the Brazilian College of Animal Experimentation (Cobea).

*Categorization of study groups*

The rats were divided into 3 groups: Control (CON), consisting of 10 healthy and sedentary animals that did not perform resistance exercise; Dexamethasone Sedentary (DS), with 10 animals treated with dexamethasone for seven consecutive days (4mg/kg body weight - intraperitoneally); and Dexamethasone + Exercise (DE), with 10 animals treated with dexamethasone for seven consecutive days (4 mg/kg body weight, intraperitoneally), which underwent a single resistance exercise session (as mentioned in protocol below).

*Resistance exercise protocol*

On the eighth day after the insulin resistance induction protocol, the DE animals performed a single RE session in the squat machine, following Tamaki's model[14] with minor modifications[15]. The animals went through three days of adaptation, 5 min/day without a load, to minimize the stress caused by the animals' exposure to exercise[16]. The exercise by electrical stimulation consisted of 5 sets of 10 reps, with 60s of rest intervals, and 70%-

intensity of the load, which was established by the one-repetition-maximum test (1RM), ad performed 48 hours after 1RM[17]. Animals from CON and DS groups underwent the same protocol training procedures, but without performing the movement of paw extension and flexion, since they remained suspended in the rest position.

The electrical stimulation parameters were performed as described by Baraúna et al (2005). The animals were stimulated to perform the series by applying electrical stimulation (20 V, 0.3" long and 3" interval) using self-adhesive electrodes (ValuTrode, CF3200 Model, Axelgaard, Fallbrook, CA, USA), placed in their tails and connected to a stimulator (BIOSET, Physiotonus four, Model 3050, Rio Claro, São Paulo). These were the parameters we used, given that they do not induce changes in the concentration of plasma catecholamines or changes in morpho-architecture of the adrenal medulla[18].

*Insulin Resistance Experimental Protocol*

Dexamethasone is a synthetic glucocorticoid. The chronic use of this substance can cause several side-effects, such as changes in carbohydrate, lipid, and protein metabolism, as well as induce glucose intolerance[19,20]. Thus, the treatment with glucocorticoids may result in insulin resistance followed by hyperinsulinemia and hyperglycemia[21].

In this study, animals from DS and DE were treated with dexamethasone (Dex 4 mg/kg/day ip) (Decadron®, Prodome, Brazil) for 7 consecutive days and always at the same time. This dosage, according to some researchers, causes insulin resistance in 7 days[13].

*Body Mass Monitoring*

The body mass of animals in all groups was monitored daily, using a precision scale (Bioprecisa, Model Bs 3000A). The first weighing of DS and DE groups was performed minutes before giving the first dose of dexamethasone. The same procedures (daily weighing) was adopted with the CON group.

*Glycemia*

The 12-hour fasting glucose level was measured after seven days of insulin resistance induction, without the performance of resistance exercise. In another group of animals, we measured the initial glucose level (before RE) and immediately after the completion of a single resistance exercise session. Blood was obtained by caudal puncture in both situations using a glucometer to determine the plasma glucose (Accu-Chek Advantage II, Roche, Sao Paulo / SP, Brazil).

*Assessment of insulin sensitivity*

An insulin sensitivity test was performed on the eighth day after the induction of insulin resistance. Animals were submitted to a dietary restriction for 6 hours and then subjected to caudal puncture (CON, DS and DE groups). We considered the first blood sample as the zero time. We used reagent strips and a glucometer (Accu-Chek Advantage II, Roche, Sao Paulo/SP, Brazil) according to the manufacturer's specifications. After this, the animals received 0.75 UI/kg of regular human insulin (Humulin R - 100U/ml Celiofarm) intraperitoneally. Blood samples were collected via the tail end of the animals at 30, 60 and 120 minutes to determining glucose.

*Data Analysis*

Statistical evaluation was performed through Student’s "t" test to assess blood glucose levels before and after the execution of the exercise and the stimulation. We also used ANOVA (one way) for the fasting glucose and the area under the curve. As for the body

weight and insulin sensitivity test, we used the two-way test. We carried out Bonferroni post-test for both tests. The value of $p < 0.05$ was considered statistically significant. The statistical program GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA) was used for all of these procedures.

## Results

*Body mass*

The animal body weight at the beginning of our study was similar in all groups. However, the body weight on the second day of treatment was significantly reduced in the groups treated with dexamethasone compared to the control; this weight reduction persisted until the last day of treatment (Figure 1). We did not detect significant differences in weight between the DS and DE groups.

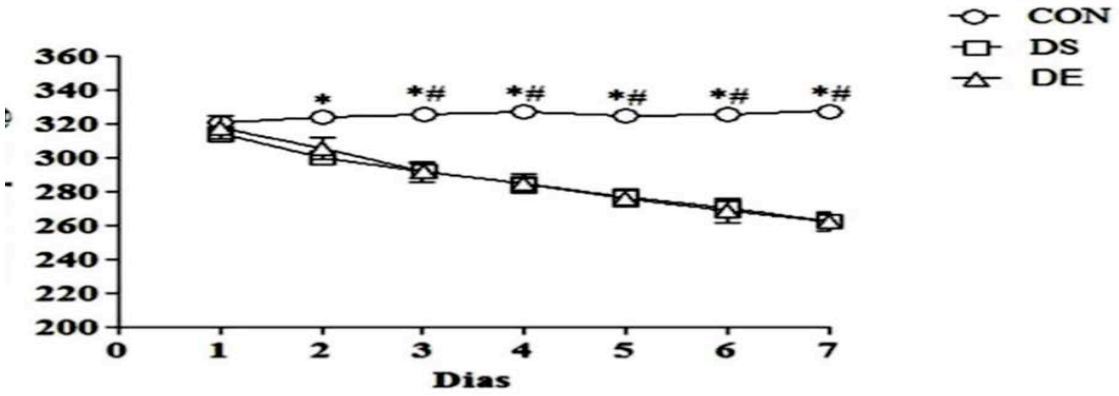


**Figure 1.** Effect of dexamethasone-induced resistance to insulin on body weight. Control group (CON), dexamethasone-treated sedentary group (DS); dexamethasone-treated + exercise group (DE).

* $p<0.05$ represents the comparison of means between the CON vs DS groups. #$p<0.05$ is the comparison of the mean values between the groups DE vs DS. Statistical differences between means were determined by two-way ANOVA test followed by Bonferroni post-test (inter-group).
Source: Authors

*Glycemia*

The 12-hour-fasting blood glucose after the seven days of treatment is shown in Figure 2. At the end of the study, groups CON (88 ± 2.33), DS (86.4 ± 3.86), and DE (93.2 ± 1.62) showed no significant difference after seven days of treatment in their fasting glucose.

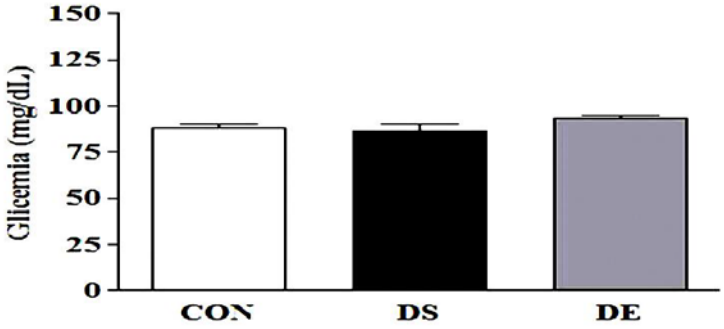


**Figure 2.** Effect of insulin resistance on the fasting-blood glucose level in the control group (CON), dexamethasone-treated sedentary group (DS); dexamethasone-treated + exercise group (DE).

* Statistical analysis was performed using an ANOVA test via followed by Bonferroni post-test (inter-group) ($p < 0.05$).
Source: The authors.

In addition, there was no change in blood glucose in the CON and DS group after stimulation (Figure 3A and 3B). However, there was a 23% reduction in blood glucose after a single resistance exercise session in animals in the DE group (Figure 3C). These results confirm that the acute effects observed in this study are directly related to resistance exercise.

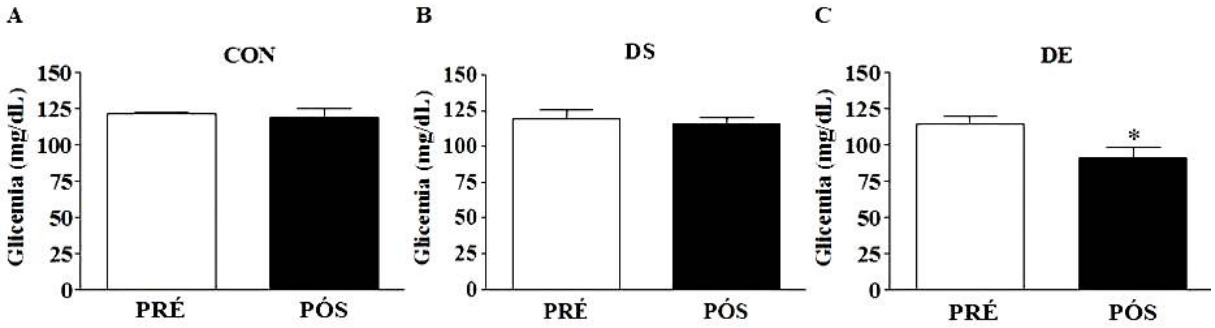


**Figure 3.** Effect of insulin resistance on blood glucose levels before (PRE) and after (POST) the single resistance exercise session at the end of the experiment. Control group (CON), dexamethasone-treated sedentary group (DS); dexamethasone-treated + exercise group (DE). Figure 3A is the CON group, Figure 3B is the DS group and 3C is the DE group.

* Statistical differences between means were determined by Student's t test unpaired (*p <0.05).
Source: The authors.

*Insulin sensitivity test*

The dexamethasone-treatment affected the sensitivity to insulin. We observed a lowering in the plasma glucose drop at 30, 60 and 120 time (* p <0.05) in the DS group when compared to the CON, characterizing a lessened sensitivity to insulin. However, the DE group (also treated with DEX) showed a glycemic response similar to the CON at 30, 60 and 120, showing an improvement of insulin sensitivity after a single resistance exercise session (# p <0.05 ; Figure 4).

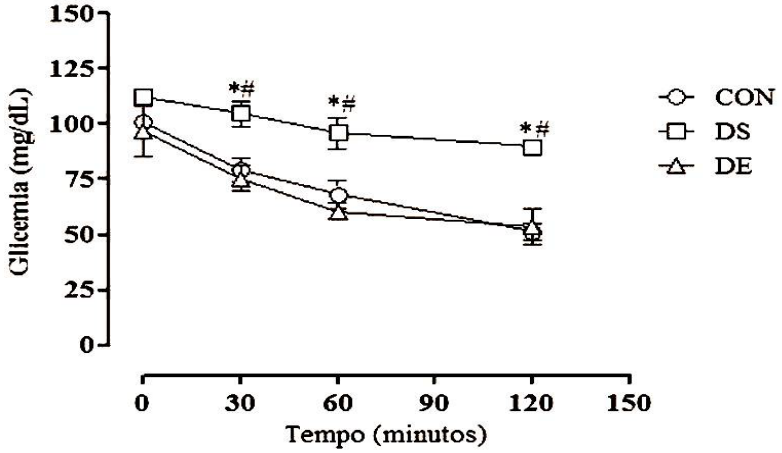


**Figure 4**. Graph of the plasma glucose drop during the insulin sensitivity test. Control group (CON), dexamethasone-treated sedentary group (DS); dexamethasone-treated + exercise group (DE).

* Values are expressed as means (± standard error). The ANOVA two-way was used, followed by Bonferroni post-test. *p<0.05 represents the comparison of means between CON vs DS groups. #p<0.05 is the comparison of the mean values between the groups DE vs DS.
Source: The authors.

Furthermore, the area under the blood glucose curve in the insulin sensitivity test (Figure 5) was 22% higher in the DS group compared to the CON (* p <0.05). In addition, when comparing the DS group results with those obtained by the DE (which held a single resistance exercise session) there was a 31% reduction (# p <0.05).

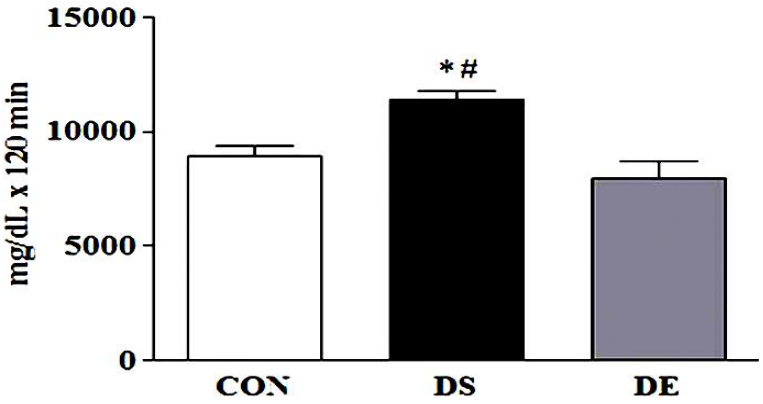


**Figure 5.** Area under the glycemya curve after the insulin sensitivity test. Control group (CON), dexamethasone-treated sedentary group (DS); dexamethasone-treated + exercise group (DE).

*p< 0,05 is the comparison of means between groups CON *vs* DS. #p < 0,05 is the comparison of means between groups DE *vs* DS. Statistical differences between means were determined by the one-way ANOVA followed by Bonferroni post-test.
Fonte: Os autores.

## Discussion

In this study, the dexamethasone-induced (DEX) insulin resistance protocol in rats resulted in weight reduction and decreased insulin sensitivity without causing changes in plasma glucose after food restriction for a period of 6 hours after stimulation. However, insulin-resistant animals, submitted to a single high intensity acute resistance exercise session (DE), showed a reduction in the plasma glucose concentration and improvement in insulin sensitivity when compared to the DS group. The main contribution of this study was to demonstrate that metabolic changes resulting from dexamethasone-induced insulin resistance can be alleviated and/or prevented after a single session of high-intensity resistance exercise.

Studies have demonstrated that the experimental model of dexamethasone-induced insulin resistance causes body weight reduction[13,19,21,22]. In this study, the DS animals had a marked loss of body weight when compared to the control (Figure 1), corroborating previous studies. This reduction in body weight in rats with dexamethasone-induced insulin resistance may be partially explained by reduced food-intake[23]. These effects are also due, in some extent, to the inhibition of protein synthesis associated with increased proteolysis, which contribute to the reduction of muscle mass as evidenced by other authors[13]. In addition to altering the metabolism of proteins and lipids, it has been observed that the dexamethasone-induced insulin resistance can also modify carbohydrate metabolism, contributing to increased plasma glucose concentration[24]. This hyperglycemia is most likely caused by the increased hepatic gluconeogenesis associated with peripheral insulin resistance[24].

In situations in which there is an imbalance in the metabolic homeostasis, such as obesity and/or T2DM – which generally exhibit insulin resistance as a consequence, contribute to the development of hyperinsulinemia and hiperglicemia[21,25-27]. These changes are associated to an impairment in the insulin signaling pathway in target tissues, such as decrease in insulin sensitivity and translocation of glucose transporters (GLUT4) to the membrane, resulting in reduced glucose uptake [25-27]. However, physical exercise acts as an

important non-pharmacological alternative to control blood glucose levels in these situations previously mentioned[12,28]. In this study, insulin-resistant animals treated with dexamethasone showed decreased blood glucose immediately after a single high intensity resistance exercise session and improvement in insulin sensitivity, which is important in reducing plasma glucose concentration and maintenance of glucose homeostasis, what was seen in the area under the insulin tolerance test curve.

One of the main mechanisms, responsible for the increased glucose uptake after physical exercises, is most likely the increase in the sensitivity by the insulin receptor (IR). Several studies have shown that running and swimming aerobic exercises[8,9,29-32] are capable of modulating the insulin receptor (IR) expression and/or activity, which promotes beneficial adjustments in insulin sensitivity. Furthermore, IR modulation assists in improving the expression and activation of important cellular proteins, contributing to the proper intracellular signal transduction in skeletal muscle, allowing glucose uptake by muscle cells [8,9,31,33-38].

Studies have demonstrated that aerobic exercises can elevate the expression and the degree of phosphorylation/activity of protein lower down the insulin receptor, called isoform insulin receptor substrate 1 and 2 (IRS-1, IRS-2)[8,9, 29,30,35,38,39], PI3K and Akt. These proteins are involved in the translocation of glucose transporters, contributing to glucose uptake in the skeletal muscle[8,9,12,29,34,35,39-41]. In addition, Krisan et all[37] in their study using resistance exercise with 75% 1RM (maximum repetition test) chronically, also showed changes of PI3K and Akt. This evidence suggests that the beneficial adjustments on the insulin pathway due to both the exercise of aerobic characteristic and the resistance exercise may possibly contribute to the reduction of plasma glucose concentration at baseline as well as in the control of blood glucose for people with insulin resistance and type 2 diabetes.

Thus, the beneficial effects of the resistance exercise protocol on insulin sensitivity used in our study is due, in part, to the possible increase in expression and in the activities of important intracellular molecules in the insulin signaling pathway such as IRS/PI3K/Akt mentioned before. It may also be due to the increase of glucose transporters (GLUT4) to the plasma membrane. Studies that investigated the effects of resistance exercise in rats and mice using the squat apparatus and isometry, respectively, showed an increase in GLUT4 expression in skeletal muscle fibers[13,37,42]. Similarly, resistance exercise performed by humans also showed an increase in the content of GLUT4, contributing to the reduction of hyperglycemia[42-44].

Our results indicate that a single high-intensity resistance exercise session can also be a form of treatment for insulin resistance and/or type 2 diabetes, for it increased insulin sensitivity, which may have contributed to the reduction of plasma glucose after the end of the session. Thus, the results suggest that RE can be of great clinical relevance both for prevention and for the control of diabetes. Moreover, data not yet published by our research group, showed that dexamethasone-treated rats submitted to resistance exercise for 30 days presented beneficial adjustments on insulin sensitivity.

## Conclusion

In this study, a single high intensity resistance exercise session was able to reduce blood glucose and improve insulin sensitivity. These evidences suggest that high intensity resistance exercise can be a promising non-pharmacological tool in the prevention and control of blood glucose in people with insulin resistance and type 2 diabetes.

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Received on Abr, 01, 2015.
Reviewed on Jun, 21, 2015.
Accepted on Jul, 20, 2015.

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