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Changes in Cardiac Morphology and Visceral Fat After the Use of Testosterone Associated with Aerobic Exercise in Wistar Rats Induced Diabetes

Cambios en la Morfología Cardíaca y la Grasa Visceral Después del Uso de Testosterona Asociada al Ejercicio Aeróbico en Ratas Wistar con Diabetes Inducida

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SUMMARY: Exercise and anabolic steroids are expected to promote improvements in cardiovascular structure and reduction of visceral fat and, thus, help promote health in hyperglycemic patients. The aim of this study was to verify the influence of aerobic exercise associated with the use of steroids on cardiac structure and visceral fat in hyperglycemic Wistar rats. Methods: Thirty-two young male Wistar rats were divided into four groups: control group (n=8), control with treatment (n=8), diabetic (n=8) and diabetic with treatment (n=8). All animals were subjected to intense aerobic exercise and the animals undergoing treatment received intramuscular testosterone. Body weight, visceral fat and cardiac measurements (weight, length and width) were evaluated. The groups treated with testosterone showed a smaller than expected increase in body weight for food intake. Visceral, perirenal, retroperitoneal and epididymal fats were lower in the treated groups. Heart weight was relatively greater in the treated groups and greater width and length in the untreated groups. The proposed association of testosterone administration with aerobic exercise can provide significant benefits for the metabolism of hyperglycemic individuals.

KEY WORDS: Anabolic steroids; Physical activity; Hyperglycemia.

INTRODUCTION

Diabetes Mellitus is an endocrine-metabolic disease characterized by inefficient production or action of insulin and, in untreated individuals, progresses with increased serum glucose. Constantly elevated glycemic levels cause increased fat accumulation, major cardiovascular changes, and other organ decompensations that compromise patients' quality of life (American Diabetes Association, 2021). Although, the benefits of aerobic exercise in improving cardiac function and decreasing body fat are well known, the association of exercise with testosterone use and the impact of this combination on cardiac morphology and metabolism in hyperglycemic individuals needs further elucidation.

In cardiac muscle tissue, the distribution of androgen receptors is wide and similar to that of musculoskeletal tissue. At these sites, the action of the hormone causes biochemical and morphological changes, demonstrated mainly by hypertrophy of muscle cells. In patients with deficiency of

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this hormone, a reduction in weight and cardiac output, peak systolic pressure, ejection fraction, and oxygen consumption have been observed. These findings directly impact cardiac function and have been attributed to androgen deficiency, although this correlation still needs further understanding (Kirby *et al*., 2019; Rizk *et al*., 2023).

The heart of hyperglycemic patients also undergoes morphological changes, such as increased left ventricular mass and thickness, reduced systolic chamber and myocardial function, and increased arterial stiffness. The accumulation of visceral fat, which also participates as a predisposing factor for cardiovascular consequences, is higher in hyperglycemic patients. Such changes predispose to potentially serious cardiovascular outcomes such as coronary artery disease, which is the most common cause of death in these patients, and diabetic cardiomyopathy, one of the major complications of Diabetes Mellitus (Gastaldelli *et al*., 2002; Chuang *et al*., 2024). In addition, hyperglycemic patients usually present serum testosterone dosages below normal and this decrease besides potentiating insulin resistance is also associated with increased cardiovascular risk (Kumari *et al*., 2021).

In view of this, and considering the action of testosterone and physical exercise on these tissues, there is the possibility that the association between them may provide real benefits to these patients. The objective of this study, therefore, was to analyze the effects of the use of testosterone on cardiac tissue and on visceral fat in diabetic rats submitted to aerobic physical training.

MATERIAL AND METHOD

Experimental design. In this experiment, 32 healthy male Wistar rats, 3 months old, provided by the Central Animal Facility of the Federal University of Acre, were used. The animals were kept in collective cages with an average of 4 rats per cage, the room temperature was kept between 22 ºC and 25 ºC and there was a light-dark cycle in which the change was made every 12 h. The feeding was done with hyper caloric food and access to water was ad libitum (Nuvilab™, Curitiba, PR, Brazil). All care and procedures were carried out in accordance with national and international laws and carefully followed the resolutions of the Brazilian College of Animal Experimentation (COBEA), and in accordance with the ARRIVE guidelines, carried out in accordance with the Animals Law (Scientific Procedures) of the United Kingdom, 1986 and associated guidelines, the EU Directive 2010/63/EU for experiments on animals and the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications No. 8023, revised 1978). The study was duly approved by the Animal Use Ethics Committee (CEUA) of the Federal University of Acre (UFAC) under registration number 23107.018612/2016.31.

All animals were submitted to the same physical training protocol. The animals were divided into groups with 8 animals per group, the division occurred according to the following nomenclature: Normal (N), diabetic (D), treated with anabolic steroids (T); totaling 4 groups: normal group (N) (control group), normal treated group (NT), diabetic group (D), and diabetic treated group (DT). The day and time of the testosterone injections were strictly controlled and the application was performed twice a week by deep intramuscular injection into the quadriceps muscle. The application leg was rotated weekly.

Treatment, adaptations and training program. During six weeks of treatment, the NT and DT groups received intramuscular injection with 15 mg/kg^{-1} of the testosterone ester mixture Durateston™, Sigma Pharma, Brazil. The application was done in 1 ml disposable syringes (BD brand. São Paulo, Brazil). The applications occurred twice a week, on Tuesdays at 4:30 pm for the NT group, and on Fridays, also at 4:30 pm for the DT group. The dose of testosterone was used according to previous studies by Silva *et al*. (2017) and Santos *et al*. (2018). Equal doses of insulin were administered in groups D and DT, in addition, in the control animals of group N, an injectable vehicle composed of peanut oil with 10 % (v/v) benzyl alcohol was administered.

Prior to the training period, the animals went through a period of adaptation consisting of swimming exercises in a 48 cm deep pool, water temperature between 30 and 36 ºC, with lead spheres corresponding to 5 % of body weight tied to the tail, for two weeks, three days a week, with an initial duration of 10 min and a maximum of 40 min at the end of two weeks. During the training period, animals were trained five times a week for six weeks, between 2 and 5 PM, with lead spheres corresponding to 5 % of body weight tied to the tail, as proposed by Schmidt *et al*. (2011) and Silva *et al*. (2017).

Maximum test and sacrifice of the animals. At the end of the eight weeks (two weeks of adaptation and six weeks of training), the animals were submitted to intense training until complete exhaustion, with the time to exhaustion characterized when the animal could not keep its nostrils out of the water for more than 10 s. The animals were then quickly removed from the water and placed on a bench. Body and tail were carefully dried with sterile paper towels. After the last maximal test session, we anesthetized with 50 mg/kg (i.m.) xylazine and 50 mg/kg (i.p.) ketamine (VETEC, Rio de Janeiro, RJ, Brazil). Blood was collected by cardiac puncture causing death by exsanguination.

Before and after the exhaustion test, samples of 25 ml of blood were transferred from the tail of each animal, using heparinized capillary glass, directly into vials containing 50 µl of 1 % sodium fluoride for inhibition of glycolytic activity. These samples were used for determination of glucose and lactate. The lactate and glucose concentration were determined in duplicate, by the electro-enzymatic method in a Sport L-lactate analyzer YSI 1500 (USI Inc, Yellow Springs, Ohio).

Induction to Diabetes Mellitus. To obtain experimental Diabetes Mellitus, after fasting for 24 h, the animals received Sigma Aloxan monohydrate® (45 mg/kg body weight), dissolved in 0.01M citrate buffer, pH 4.5, injected intraperitoneally. The animals were anesthetized with Xylazine (50 mg/kg i.m.) and Ketamine (50 mg/kgi.p.) (Vetec Química, Rio de Janeiro, Brazil) and the antibiotic used was Pentabiotic at a dose of 240000 IU of penicillin per kg and 100 mg Streptomycin and Dihydrostreptomycin per kg (Forte Dodge®; volume, 0.1 mL/100 g of animal weight). After the procedure, the animals had free access to food and received glucose solution (30 %) for 24 h.

Diabetes was confirmed two weeks after the administration of alloxan through the measurement of glycemic levels by the Accu-Chek[â] device (Accu-Chek Advantage[â] 2007. Manufacturer Roche Farmacêuticaâ, São Paulo-SP, Brazil). The animals in the control group (N) underwent similar manipulation, but instead of alloxan, citrate buffer solution was injected. Induced diabetes conditions were considered and used in the study those that presented fasting glucose levels higher or equal to 126 mg/100 ml of serum.

Collecting and weighing the organs. After euthanasia, laparotomy was performed with a median incision and excision of the organ. The organs were washed in 5 % saline solution and weighed on a precision analytical balance (Marte® Model AS500). Seminal glands, testicles and heart were measured with a Digital Caliper 150mm – 6 in.-DIGIMESS®-100-174BL. The measurements of the heart were carried out as follows: Checking the length from the apex to the base, and the width, by its largest circumference, using the atrioventricular septum as a reference. Seminal glands and testicles were evaluated at their greatest length in relation to their smallest width.

Statistical Analysis. A normal distribution across the obtained results was assessed by the Shapiro-Wilk test. All results were expressed as mean and standard deviations. To check statistical differences, both directions ANOVA and Tukey post-hoc tests were applied via GraphPadPrism™ software version 5.0 (GraphPad Software, Inc., San Diego, CA, USA). The differences were considered significant at the level $p<0.05$ (or <5 %).

RESULTS

Table I shows the parameters of food intake and body measurements. The NT and DT treated groups had significantly higher food intake than the untreated groups, with the NT group having the highest food intake and the highest body weight, and the D group having the lowest food intake and the lowest body weight ($p<0.05$).

With regard to total visceral fat, perirenal fat, mesenteric fat, retroperitoneal fat, and epididymal fat, the treated groups had the lowest weights ($p<0.05$). The results show that even with the higher food intake, the treated groups evolved with significantly lower visceral fat accumulation than the untreated groups. The NT and DT treated groups also showed a difference in total visceral fat, but in a more discrete way ($p<0.05$). Among the treated groups, perirenal fat and mesenteric fat values were higher in the DT group, and compared to all groups, the NT group had the lowest value ($p<0.05$). With regard to retroperitoneal fat and epididymal fat the lowest value was observed in the DT group and the highest values were observed in group D ($p<0.05$).

In Table II, all measurements evaluated in the seminal glands as weight, length and width had differences between the treated and untreated groups, and the highest values were observed in the treated groups ($p<0.05$). The highest value was found in the NT group and the lowest value was observed in group D in all measurements ($p<0.05$). In the evaluation of tests measurements - weight, length and width - there was also a difference between treated and untreated groups, but the highest values were observed in the untreated group ($p<0.05$), the highest value was found in N and the lowest value was observed in DT in all measurements ($p<0.05$).

Regarding the heart evaluation, in Figure 1A, it was observed the absolute heart weight, with higher value in the DT group (1.28±0.17g) for a $p<0.05$. The groups N (1.21±0.18g), NT (1.11±0.09g) and group D (1.26±0.24g) obtained lower difference for a $p>0.05$. The lowest absolute heart weight was observed in the NT group.

In Figure 1B, the length of the heart from the base to the apex was analyzed. The group D (18.95±0.73mm), obtained a difference, with $P<0.05$. It is worth noting that their increase in absolute heart weight is directly linked with absolute length. The normal group N (18.02±1.77mm), also obtained remarkable value, with $p<0.05$.

In Figure 1C, when comparing the width of the heart, group N (14.3±1.14mm) and group D (14.18±2.6mm) had $p<0.05$. The NT and DT groups obtained $p>0.05$, with no difference in the last two groups. The width of the heart was greater in groups N and D compared to groups NT (12.96±1.19mm) and DT (13.54±0.88mm) for $p<0.05$.

Table III shows swimming time, glucose and lactate concentrations in rats from different groups. Animals treated with testosterone (NT and DT) showed longer swimming times and lower glucose and lactate concentrations after reaching the maximum time than their respective untreated controls (N and D) for a ($p < 0.05$).

Table I. Mean and standard deviation of adipose tissue and food consumption in rats subjected to swimming exercises and use of anabolic steroids.

	Without treatment		With treatment	
Variables	Normal N	Diabetic D	Normal NT	Diabetic DT
Food consumption (g/day)	9,43±1,17[a]	8,53±0,59[ab]	16,83±1,37[abc]	12,88±0,98[abc]
Body Weight (g)	316,16±4,08[a]	305,25±4,02[ab]	332,25±4,77[ac]	323,87±1,95[abc]
Total visceral fat (g)	5,57±0,42[a]	8,14±0,86[ab]	3,03±0,77[abc]	4,70±0,67[abc]
Perirenal fat (g)	0,60±0,08[a]	0,78±0,05[ab]	0,51±0,03[a]	0,52±0,05[ab]
Mesenteric fat (g)	3,68±0,2[a]	4,19±0,37[ab]	2,69±0,26[a]	3,11±0,10[ab]
Retroperitoneal fat (g)	5,84±0,44[a]	6,20±0,13[b]	4,21±0,52[ab]	4,14±0,07[ab]
Epididymal fat (g)	3,33±0,15[a]	3,84±0,17[b]	3,33±0,15[abc]	2,91±011[abc]

Symbols represent significant differences ($p<0.05$) between: normal control group N and the other groups (a), diabetic group D and the other groups (b), control and testosterone treated group NT and the other groups (c). The results were compared with 2-way ANOVA and Tukey's post-hoc.

Table II. Mean and standard deviation of body parameters in rats subjected to swimming exercises and use of anabolic steroids.

	Without treatment		With treatment	
Variables	Norm	Diabetic D	Normal NT	Diabetic DT
Seminal glands (g)	0.99±0.14[a]	0.89±0.12[b]	2.04±0.27[ab]	1.70±0.32[abc]
Seminal glands length (mm)	13,86±2,24[a]	12,30±1,60[ab]	29,48±3,90[abc]	23,86±4,91[abc]
Seminal glands width (mm)	9,84±0,18[a]	9,45±0,86[ab]	12,94±0,84[ab]	11,2,0±2,71[ab]
Testicles (g)	1,34±0,1[a]	1,11±0,18[ab]	0,54±0,19[ab]	0,46±0,13[ab]
Testicles length (mm)	20,08±1,69[a]	18.04±2.36[b]	13,74±2,68[abc]	11,55±2,40[abc]
Testicles length (mm)	14.92±0.32[a]	12.30±0.59[b]	8.98±0.07[abc]	6.26±0.16[abc]

Symbols represent significant differences ($p<0.05$) between: normal control group N and the other groups (a), diabetic group D and the other groups (b), control and testosterone treated group NT and the other groups (c). The results were compared with 2-way ANOVA and Tukey's post-hoc.

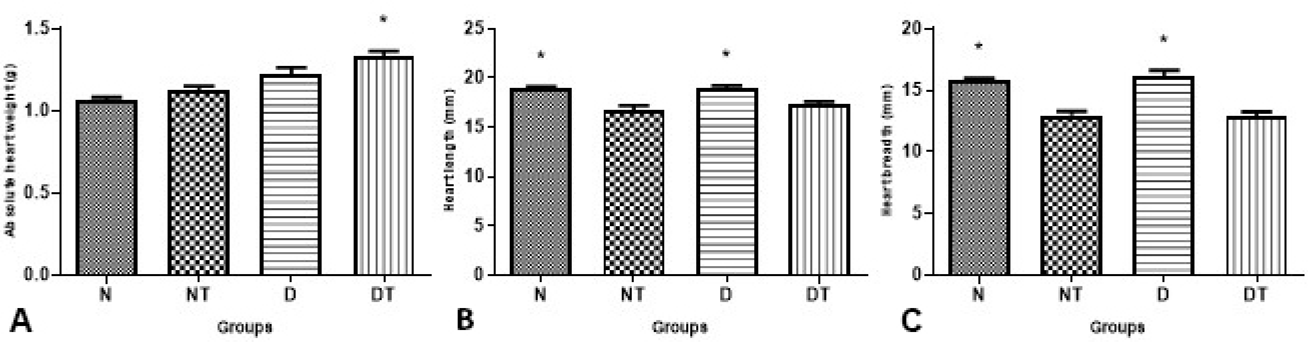

Fig. 1. Effect of swimming exercises and anabolic steroids on cardiac morphology. (A), Absolute cardiac weight; (B), Heart length and (C), Heart width C. Symbols (*) represent significant differences between groups ($P<0.05$). Results were compared through two-way ANOVA and Tukey's post-hoc test.

Table III. Swimming time and plasma concentrations of lactate and glucose before and after the high intensity test in rats subjected to swimming exercises and use of anabolic steroids.

	Normal				Diabetic			
	Without treatment		With treatment		Without treatment		With treatment	
	Before	After	Before	After	Before	After	Before	After
Swimming time	203,75±6,69^{a}		300,5±37,09^{a}		119,25±18,49^{a}		163,75±29,64^{a}	
Lactate mmol/L	2,53±0,25^{a}	11,51±0,40^{ab}	2,58±0,19^{bc}	10,21±0,55^{abd}	3,52±0,2^{ab}	12,71±0,60^{ab}	2,83 ±0,22^{bd}	11,05 ±0,95^{ac}
Glucose mg/dL	95,125±5,7^{ac}	51,25±3,10^{abc}	93,37±6,02^{bc}	57,62±1,84^{c}	143,62±3,24^{abc}	81,75±9,33^{abc}	115±8,58^{abc}	58,12±8,2^{ab}

Averages followed by same letter are diferente. Results were compared through two-way ANOVA and Tukey's post-hoc test.

DISCUSSION

Few studies have demonstrated the benefits of physical activity associated with the use of testosterone on cardiac morphological changes in patients with hyperglycemia. In this study, it was possible to observe both a reduction in visceral fat and an increase in lean body mass in rats treated with testosterone and exposed to exercise.

Based on an initial analysis, this study showed that the rats treated with testosterone evolved with an increase in food intake. The analysis of the effect of testosterone on food intake was also proposed by Nunez *et al*. (1980), who, in their study, identified that besides the peripheral action, there is a hypothalamic action of testosterone in controlling hunger and satiety. It was observed that, under a regime of high doses of androgen administered, the initial pattern evidenced was an increase in food intake. Although they had higher food intake, the treated rats were observed to have less visceral fat, and despite this reduction in fat, they had higher absolute weight than the untreated rats. This suggests a possible increase in lean mass.

Despite the increased food intake, it was possible to observe that the rats that received testosterone cursed with lower visceral fat values. This observation can be explained by the metabolic changes caused by testosterone administration and can be correlated with the result found by Abdelhamed *et al*. (2015), who observed that testosterone replacement can decrease the size of visceral fat cells. In addition to this change in adipocyte size, fat deposition in the abdominal region is higher in patients with hypogonadism as had been observed in the study by Kapoor *et al*. (2007). These authors also concluded that this increase in fat deposition further decreases serum testosterone concentrations, causing a metabolic cycle that courses with a progressive testosterone deficiency and increasing visceral fat deposits.

When analyzing the reproductive system, looking at the testes, the pattern of smaller measurements in the treated groups was maintained. The reduction in testicular volume after the use of testosterone was also demonstrated by Palacios *et al*. (1981), who conducted an experimental study with testosterone administration in men and showed that the reduction in testicular size is dose-dependent and reversible, and is directly related to the functional activation of the organ. In contrast, this study showed that the measurements of the seminal glands were much larger in the treated groups.

In the evaluation of cardiac morphology, the highest values were observed in the diabetic groups, with a higher value in the diabetic treated group in relation to weight. The length and width of the heart were greater in the untreated groups. Although the diabetic treated group had higher absolute heart weight, it showed significantly less heart length and width than the control group, suggesting possible concentric hypertrophy. Pirompol *et al*. (2016), also observed cardiac hypertrophy in rats that were exposed to supra physiological doses of testosterone. In their study, it was possible to infer a dose- and time-dependent relationship between androgen administration and structural effects on the heart, with both concentric and eccentric hypertrophy being evidenced, depending on these factors.

This study was able to show that performing aquatic aerobic exercises associated with the administration of anabolic steroids can improve the time to perform maximal exercises and present lower levels of lactate concentration, better conditions in terms of glucose concentration, presenting lower values in diabetic rats treated. This was also demonstrated in exercise performed with elderly rats in a situation of hyperglycemia treated with anabolic steroids (Silva *et al*., 2017). Physical exercises associated with treatment with anabolic steroids may be linked to an increase in erythropoiesis, which would improve oxygen transport, having a positive effect on energy production, improving efficiency in performing physical exercise, increasing swimming time (Voltarelli *et al*., 2002; Silva *et al*., 2017).

An important limitation of this study was the lack of a cardiac evaluation from a functional point of view. This study had as its priority the elucidation of structural changes, but it provides important data to promote the future clarification of possible functional changes.

CONCLUSION

The proposed association of testosterone administration with swimming exercise in rats may provide significant benefits for the metabolism of hyperglycemic individuals by modifying cardiac morphology and the structure and condition of visceral fat and physical performance. But we must be careful and pay attention to the levels of endogenous testosterone to be used.

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PERRONI KUDIESS, J.; FREITAS DA SILVA, C.; DE OLIVEIRA SOUZA, F. R.; DE CARVALHO BARROS, R. A.; DE ABREU, L. C.; MAGALHÃES-NETO, A. M.; OLIVEIRA GONÇALVES, L. C.; BALBINO LIZARDO, F.; MONTES FIDALE, T.; SILVA, L. M.; MAGALHÃES DE ABREU, R. M. & MARTINS SILVA, R. P. Cambios en la morfología cardíaca y la grasa visceral después del uso de testosterona asociada al ejercicio aeróbico en ratas Wistar con diabetes inducida. *Int. J. Morphol., 42(5)*:1216-1221, 2024.

RESUMEN: Se supone que el ejercicio y los esteroides anabólicos promuevan la mejora de la estructura cardiovascular y la reducción de la grasa visceral y, por tanto, ayuden a promover la salud en pacientes hiperglucémicos. El objetivo de este trabajo fue verificar la influencia del ejercicio aeróbico asociado al uso de esteroides sobre la estructura cardíaca y la grasa visceral en ratas Wistar hiperglucémicas. Treinta y dos ratas Wistar machos jóvenes se dividieron en cuatro grupos: grupo control (n=8), control con tratamiento (n=8), diabético (n=8) y diabético con tratamiento (n=8). Todos los animales se sometieron a ejercicio aeróbico intenso y los animales en tratamiento recibieron testosterona intramuscular. Se evaluaron el peso corporal, la grasa visceral y las medidas del corazón (peso, largo y ancho). Los grupos tratados con testosterona mostraron un aumento menor de lo esperado en el peso corporal según la ingesta dietética. Las grasas visceral, perirrenal, retroperitoneal y epididimaria fueron menores en los grupos tratados. El peso del corazón fue relativamente mayor en los grupos tratados y el mayor ancho y largo en los grupos no tratados. La asociación propuesta de la administración de testosterona con el ejercicio aeróbico puede proporcionar beneficios significativos para el metabolismo de los individuos hiperglucémicos.

PALABRAS CLAVE: Esteroides anabólicos; Actividad física; Hiperglucemia.

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