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# Association Between Exercise and Treatment with Liraglutide in Obese Rats by Cafeteria Diet

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**HIGHLIGHTS**

- Liraglutide reduced deposits of fat and triglycerides in obese rats.
- Glycemia and insulinemia of obese rats were reduced by liraglutide.
- Physical exercise potentiated the effects of liraglutide.

**Abstract:** The objective of this study was to evaluate the effect of liraglutide, an analog of glucagon-like peptide-1 (GLP-1) in association with physical exercise, on the metabolic and biochemical parameters of rats induced to obesity with a cafeteria diet. Male Wistar rats, aged 21 days, were randomly divided into: Controls (CON) receiving standard feed and water ad libitum; and obese (OBESE) receiving cafeteria diet ad libitum, added to the standard diet. Groups were then subdivided into: Liraglutide animals that received subcutaneous injections of liraglutide from 80 to 90 days of life; exercised (EXE) animals submitted to swimming sessions, three days a week (15 min); and liraglutide + EXE animals that received liraglutide in association with physical exercise. Treatment with liraglutide reduced deposits of mesenteric and periepididymal fat, HOMA-IR, triglycerides, glucose and insulin in obese group. It is important to note that the association of the two treatments reduced the body weight in animals, deposits of mesenteric and periepididymal fat, HOMA-IR, blood triglyceride levels, glucose and insulin in obese rats. As such, the association of liraglutide with exercise potentiated the effects of the drug and ameliorated obesity pathology more effectively. retirar

**Keywords:** obesity; liraglutide; GLP-1; metabolic syndrome; exercise.

## INTRODUCTION

There is scientific consensus that obesity increases the risk of cardiovascular diseases, among other comorbidities such as diabetes mellitus type 2. Obesity is characterized by excessive accumulation of fat tissue in the body, due to an imbalance between calorie intake and spending [1,2]. Obesity prevalence is worsening worldwide, and multiple factors induce healthy individuals to obesity, including; environment, dysregulated diet, hyperlipidic diet and physical inactivity [3]. Other pathological complications may be associated with these habits, such as cardiovascular diseases (including hypertension), infertility, lower back pain, diabetes and others [4].

During recent decades, various efforts have been made by the scientific community to solve this problem, which is increasing on an alarming scale [5]. Among the alternatives to limit obesity is physical exercise, where the practice of physical activity, 3 to 5 times a week, exerts favorable influence on the control and prevention of obesity and metabolic syndrome [6]. Aerobic physical exercise has the ability to mobilize lipid stores by raising lean mass and reducing fat mass [7], through the uptake of fatty acids by tissues and the increase in thermogenesis, leading to weight reduction and altered body composition [8,9]. Swimming training leads to loss of adiposity and wetting serum cholesterol in high-fat-fed animals [10]. Exercise is a potent and effective alternative for reducing adiposity, being low cost and non-pharmacological [11].

Numerous drugs are already use clinically to treat diabetes mellitus type 2 and prevent the development of obesity. In this regard, incretin has recently gained attention as a member of a class of drugs used to treat the diabetes [12,13]. Intestinal cells secrete incretin hormones, which increase glucose-induced insulin secretion in response to food ingestion. There are 2 known incretins, the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) [14]. GLP-1 is produced by post-translational proteolytic cleavage of the proglucagon gene product and mainly secreted from the enteroendocrine L cells in the intestine, in response to nutrient ingestion [15]. GLP-1 derivatives have reported actions in the pancreas and other non-pancreatic functions, including suppression of appetite and body weight regulation, reduction of lipid accumulation in the liver [16,17], suppression of glucagon production, stimulation of insulin secretion in β-pancreatic cells and slowing of gastric emptying [14]. GLP-1 accounts for almost half of the total insulin secretion after meals, inhibits beta cell apoptosis, inhibits hepatic glucose production, and stimulates glucose uptake in both adipose and muscle tissues [18].

Native GLP-1, however, is degraded rapidly. Since GLP-1 agonists have been shown to be resistant to degradation, the administration of GLP-1 agonists is now widely used as a therapeutic strategy for the treatment of DM2 and obesity [19]. Although the effect of physical

exercise for reduce obesity is well documented in the literature, no study has showed the results of its association with liraglutide. Thus, in the current study, we examined the ability of exercise to modulate the effects of treatment with the GLP-1 analogue, liraglutide, on body composition, inflammation and oxidative stress in rats induced to obesity by a cafeteria diet.

## MATERIAL AND METHODS

### Ethics Statement

Rats of the Rattus norvegicus species of the Wistar lineage were used in this experimental study. The study was previously evaluated and approved by the Committee for Ethics in Animal Experimentation (CEUA #027/2014), of the State University of Ponta Grossa (UEPG), in accordance with animal welfare act guidelines. The procedures and methods performed with the animals were followed by the ARRIVE Guidelines and the procedures for the euthanasia of animals followed the norms of the American Veterinary Medical Association's Guidelines on Euthanasia.

### Animals

The animals were obtained from the central animal house of the State University of Ponta Grossa at 21 days of life. Animals were housed in standard caging at 21°C on a 12-hour light, 12 hour-dark cycle. The rats were randomly divided into 8 groups (10 to 12 animals for each group), as follows: CON - normal animals that received commercial chow and stayed sedentary during the entire experimental protocol; CON EXE - control animals that received commercial chow and were exercised from 21 days until 90 days of life; CON liraglutide - animals received commercial chow, remained sedentary during the entire experimental protocol and received injections of liraglutide, a GLP-1 analog; CON Liraglutide+EXE - animals received commercial chow, were exercised from 21 to 90 days of life and received injections of liraglutide; OBESE - animals that received a cafeteria diet and remained sedentary during the entire experimental protocol; OBESE EXE- animals that received a cafeteria diet and were exercised from 21 days to 90 days of life; OBESE Liraglutide - animals that were fed on a cafeteria diet, remained sedentary, and received GLP1-analog injections; and OBESE Liraglutide EXE - animals that received a cafeteria diet, were exercised from 21 to 90 days of life, and received liraglutide injections.

### Standard Diet

A standard diet was offered ad libitum every day to the control group. The diet consisted of chow and water, according to the AIN-93 recommendations; the Nuvilab CR-1 chow (NUVITAL, Brazil) used contained 55% carbohydrates, 22% proteins, 4.5% lipids, and a total of 2.95 Kcal/g (information provided by the manufacturer).

### Cafeteria Diet

The cafeteria diet (CAF) resembles the human diet because it provides foods with a nutritional variety, high palatability and high-calorie content, reflecting the main obesogenic characteristics of the human diet [20]. The cafeteria diet was offered *ad libitum* daily to the obese group; the diet's contents were grouped into three distinct combinations that were alternately offered (A, B and C, see Table 1), and were composed of fresh foods, flat soda, standard chow and water.

**Table 1.** Menu of supply of hypercaloric foods.

| FOOD | Amount (g) | Calories (kcal) | Carbohydrate (g) | Protein (g) | Fat (g) | Sodium (Mg) |
|---|---|---|---|---|---|---|
| | **MENU A** | | | | | |
| **STANDARD CHOW** | 1 | 2.95 | 0.55 | 0.22 | 0.04 | 0.00 |
| **SNACK FLAVOR CHEESE** | 1 | 3.92 | 0.72 | 0.08 | 0.09 | 12.30 |
| **CHOCOLATE WAFER** | 1 | 5.56 | 0.63 | 0.03 | 0.51 | 0.76 |
| **COKE SODA** | 1 | 0.42 | 0.11 | 0.00 | 0.00 | 0.05 |
| | **MENU B** | | | | | |
| **STANDARD CHOW** | 1 | 2.95 | 0.55 | 0.22 | 0.04 | 0.00 |
| **MARSHMALLOW** | 1 | 3.35 | 0.82 | 0.04 | 0.00 | 0.25 |
| **HAM** | 1 | 1.85 | 0.07 | 0.13 | 0.16 | 11.70 |
| **COKE SODA** | 1 | 0.42 | 0.11 | 0.00 | 0.00 | 0.05 |
| | **MENU C** | | | | | |
| **STANDARD CHOW** | 1 | 2.95 | 0.55 | 0.22 | 0.04 | 0.00 |
| **SNACK FLAVOR BACON** | 1 | 5.08 | 0.52 | 0.08 | 0.29 | 6.40 |
| **CRACKER** | 1 | 4.30 | 0.73 | 0.07 | 0.12 | 4.33 |
| **COKE SODA** | 1 | 0.42 | 0.11 | 0.00 | 0.00 | 0.05 |

Food combinations were offered on alternate days to provide daily variation. All foods were arranged on the grid of the residence cage. The food consumption of the animals was calculated on alternate days, at the same time of day, by subtracting the weight of the remaining food on the grid from the initial food weight. The animals were weighed 3 times a week, starting at 21 days until the date of sacrifice at 91 days of life.

### Exercise

Control and diet rats were exercise trained with free swimming in a glass tank, filled with water at 32± 3°C. Rats swam over a period of 9 weeks, for 15 min a day, 3 days a week. Six rats from each group were placed simultaneously in the pool at 16:00 h. A lead weight, corresponding to 5% of the animal's body weight, was attached to the tip of the tail to ensure that theanimal was in constant swimming activity. After each exercise session, rats were dried with paper towels and returned to their respective boxes until the next swimming session [21,22].

### GLP-1 Analog Administration

80-day-old rats in the GLP-1 group received subcutaneous injections of the GLP-1 analogue, liraglutide, at a dose of 0.0077 mg/day for 10 consecutive days. This dose was based on use in humans (current recommendation ranges from 0.6 to 3 mg/ dose). In order to test a short period of liraglutide administration, the drug was given daily for 10 days. Liraglutide was diluted in saline solution and always administered at 17:00 h.

### Obesity and Euthanasia

To evaluate obesity onset, 91-day-old rats were anaesthetized by an i.p. injection of sodium pentobarbital (5mg/g body weight) and euthanized by decapitation. Periepididymal fat pads, retroperitoneal fat pads and mesenteric fat pads were removed, washed, and weighed to estimate obesity [23].

### Biometric Parameters

Naso-anal length (cm) was measured and tissues and organs were removed immediately after euthanasia. The naso-anal lengths and body weights were used to calculate the Lee Index (body weight [g]1/3/ naso-anal length [cm] x 1000), which is an indicator of obesity in rodents [24].

**Serum Analysis**

Blood was collected from animals and centrifuged at 3,000 rpm for 10 minutes, before measuring the following: a) glucose, b) triglycerides, c) total cholesterol, d) total proteins (all by enzymatic colorimetric methods) [25], and e) Plasma insulin, determined by radioimmunoassay [26].

**Homa Index espaço**

The HOMA-IR is determined by the formula: HOMA IR = serum insulin (mmol/L) x (blood glucose (mmol/L)/22.5 [27].

**Statistical Analysis**

Initially, results were submitted to the Kolmogorov-Smirnove normality test. Considering parametric data, two-way analysis of variance (ANOVA) followed by post-hoc Tukey test was carried out for multiple comparisons among groups. All results are presented as means ± standard errors of mean (SEM); $p<0.05$ was considered as statistically significant. Graph pad Prism version 7.00 for windows was employed for analyses (Graph Pad Software, San Diego, CA, USA).

**RESULTS**

Our results show that the cafeteria diet provoked an increase in body weight, as observed in Figure 1A, and that body weight was influenced by treatment [$F(3.83)=11.19$ $p<0.0001$] and obesity [$F(1.83)= 73.79$ $p<0.0001$]. The obese animals demonstrated an increase of 13 % in body weight, when compared with control animals. Treatment with liraglutide did not significantly decrease the body weight of animals; however, exercise and the association and liraglutide and exercise decreased the body weight of the animals.

Two way ANOVA showed an interaction effect of obesity and treatment on the Lee Index [$F(3.69)=5.74$ $p=0.0014$]. The Lee Index was also increased by liraglutide treatment [$F(3.6)=22.64$ $p<0.0001$] and obesity [$F(1.69)=72.47$ $p<0.001$]. The OBESE liraglutide group demonstrated a 2% reduction in Lee Index, compared to the OBESE rats, showing a possible effect of liraglutide intervention in obese animals; however, the normal groups did not present significant differences between them (Figure 1b).

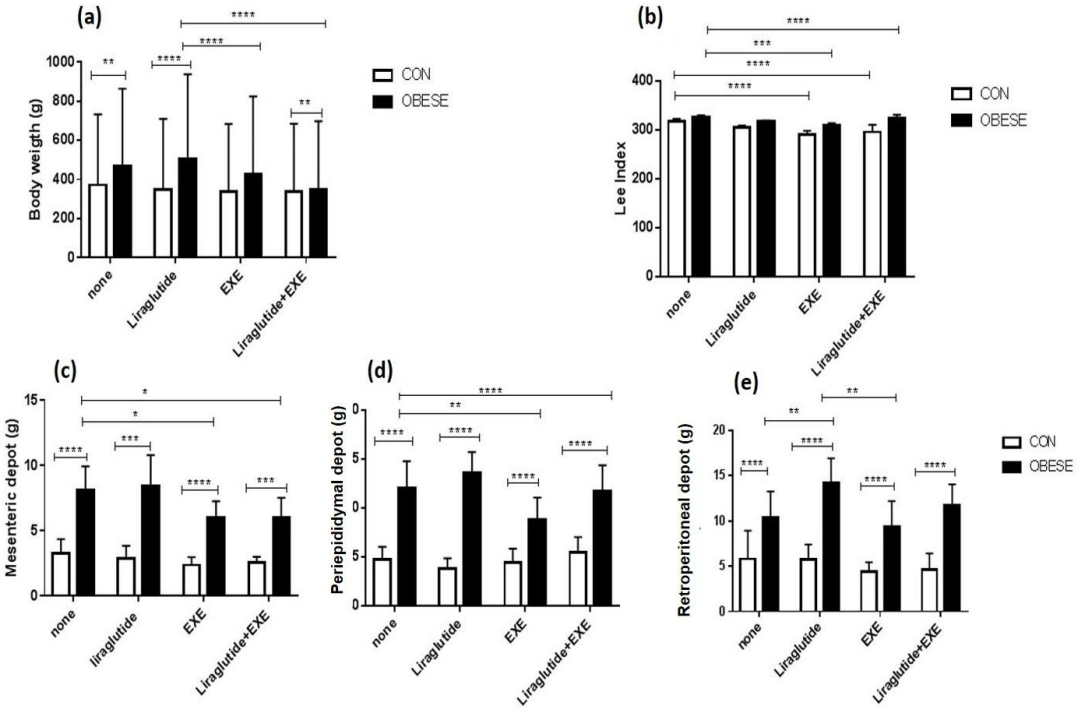


**Figure 1.** Effect of association of liraglutide treatment and exercise in biometrics parameters. (a) body weight; (b) Lee index; (c) mesenteric depot; (d) periepididymal depot and (e) retroperitoneal depot. The values are expressed as mean ± Standard Deviation of the Mean (n= 9-12 animals/group). The sign (*) indicates a significant difference between the groups (Two-way ANOVA with Post-hoc Tukey; *p≤0,05, **p≤0.01, ***p≤0,001 and ****p≤0,0001).

Figure 1c shows the interaction between mesenteric depot (two-way ANOVA) and obesity and treatment of liraglutide [F (3.74) = 2.876 P=0.0418]. The mesenteric adipose tissue was affected by liraglutide treatment there was decreased [F (3.74) = 8.075 P=0.0001] and by obesity [F (1.74) = 213.5 P<0.0001]. The animals of the OBESE group had high fat indexes, in relation to the CON group, suggesting that they achieved a profile of obesity; the OBESE group had a 57% higher percentage fat index in comparison with the CON group. Exercise and the association between exercise and liraglutide administration decreased the mesenteric adipose tissue.

The periepididymal depot of animals is shown in Figure 1d; an interaction can be observed between obesity and treatment [F (3.77) = 7.366 P=0.0002]. The periepididymal depot was affected by treatment [F (3.77) = 5.866 P=0.0012] and by obesity [F (1.77) = 260.3 P<0.0001]. Again, exercise and the association of exercise and liraglutide administration decreased this parameter. Liraglutide administration alone did not provoke alteration in the periepididymal depot.

The retroperitoneal adipose tissue showed an increase of 46% in the OBESE group, compared to the CON group. Two way ANOVA showed an interaction between treatment and obesity [F (3.89) = 3.61 P=0.0164], the retroperitoneal adipose tissue was influenced by treatment [F (3.89) = 7.01 P=0.0003] and by obesity [F (1.89) = 153.5 P<0.0001]. The treatment with liraglutide was able to induce a reduction in retroperitoneal adipose tissue, however only exercise was able to reduce this depot by 10%.

Biochemical analyses (Figure 2) indicated that the cafeteria diet augmented the serum triglycerides levels of the animals in the OBESE groups by 46%, compared to the CON group. Two way ANOVA showed an interaction between treatment and obesity [F (3.68) = 4.414 P=0.0068]. This parameter was affected by treatment [F (3.68) = 17.83 P<0.0001] and obesity [F (1.68) = 28.45 P<0.0001]. The treatment with liraglutide was able to reduce the levels of triglycerides by 37.6 % in obese group. A similar reduction was observed in the EXE group and Liraglutide+EXE group (Figure 2b).

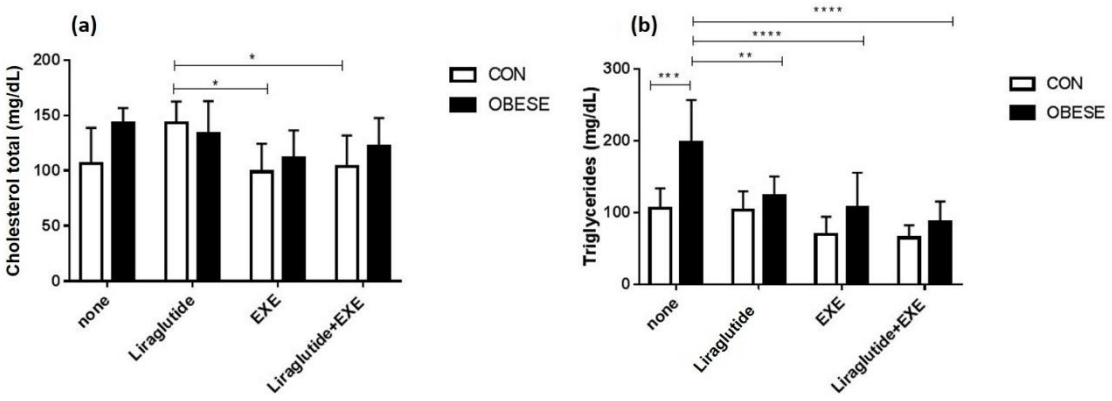


**Figure 2**. Effect of association of liraglutide treatment and exercise in lipids profile. (a) cholesterol total; (b) triglycerides. The values are expressed as mean ± Standard Deviation of the Mean (n= 9-12 animals/group). The sign (*) indicates a significant difference between the groups (Two-way ANOVA with Post-hoc Tukey; *p≤0,05, **p≤0.01, ***p≤0,001 and ****p≤0,0001).

Two way ANOVA did not find any interaction between treatment and obesity for blood cholesterol, but there was an influence of treatment [F (3.71) = 6.439 P=0.0006] and obesity [F (1.71) = 6.471 P=0.0131]. The Tukey post-hoc showed statistically significant differences for the EXE control group and Liraglutide + EXE control group, when compared to the CON liraglutide group. Treatment with liraglutide did not alter plasma serum cholesterol levels (Figure 2a).

When we evaluated the biochemical parameters, obese animals showed a 23% increase in plasma glucose concentration ($p < 0.05$), however, liraglutide treatment was able to abolish this increase, reducing this value to the same level as that of control animals. Two way ANOVA showed no interaction, but effects of treatment [F (3.77) = 15.26 P<0.0001] and of obesity were seen [F (1.77) = 5.882 P=0.0176]. The Tukey post-hoc showed that the treatment with liraglutide, exercise and the association of liraglutide and exercise reduced glycemia levels in OBESE group ($p<0.0001$) (Figure 3a).

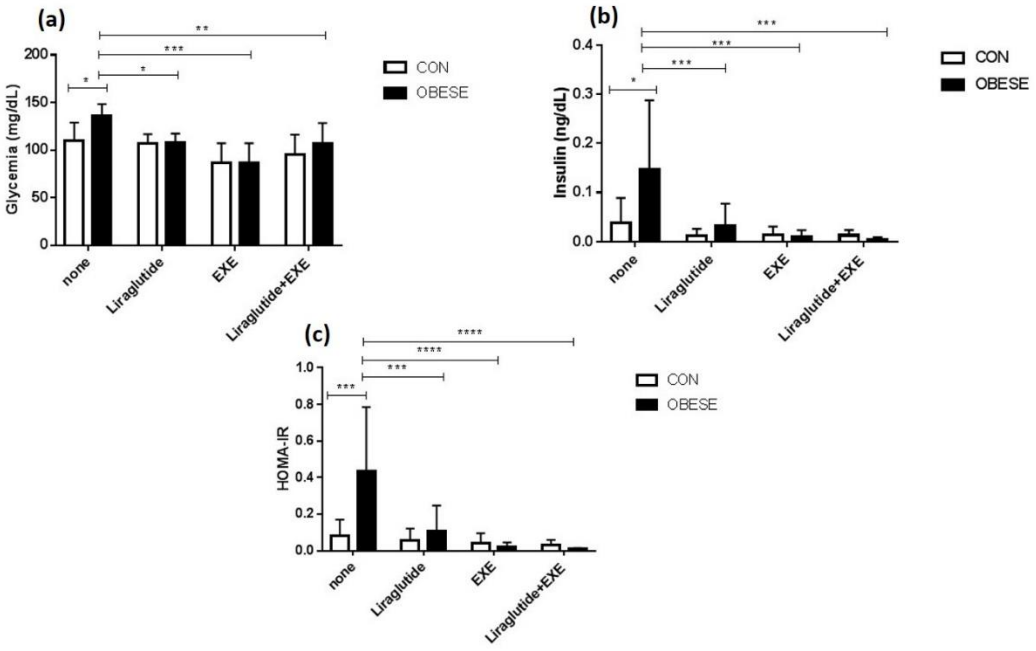


**Figure 3.** Effect of association of liraglutide treatment and exercise in metabolic profile. (a) glycemia; (b) insulin; (c) HOMA-IR. The values are expressed as mean ± Standard Deviation of the Mean (n= 9-12 animals/group). The sign (*) indicates a significant difference between the groups (Two-way ANOVA with Post-hoc Tukey; *p≤0,05, **p≤0.01, ***p≤0,001 and ****p≤0,0001).

Figure 3b shows blood insulin levels, where the obese group showed an increase of 286% in relation to the control group. Two way ANOVA showed an interaction between obesity and insulin levels [F (3.55) = 4.306 P=0.0085]. There was an effect of treatment [F (3.55) = 9.261 P<0.0001] and an effect of obesity [F (1.55) = 5.152 P=0.0272]. The Tukey post-hoc test showed that the treatment with liraglutide, exercise and the association of liraglutide and exercise decreases insulin levels when compared to the obese group alone (p<0.0001). Figure 3c confirms that obese animals were insulin resistant, as the HOMA index was approximately 5 times greater in obese rats, when compared to the CON group. Two way ANOVA showed an interaction between obesity and the HOMA index [F (3.53) = 6.67 P=0.0007] and an effect of treatment [F (3.53) = 10.02 P<0.0001] and obesity [F (1.53) = 6.644 P=0.0128]. The Tukey post-hoc test showed that treatment with liraglutide, exercise and the association between liraglutide and exercise caused a reduction in the HOMA index in the obese rats, this effect was increased in liraglutide -EXE group.

## DISCUSSION

The results showed that the cafeteria diet caused an increase in body weight in the animals, when compared to the animals that received standard chow. These data are in agreement with the literature, where animals submitted to the cafeteria diet show an increase in body weight as well as in fat deposits, as observed in Figure 1C, 1D and 1E of the present study. We observed that the animals that received a cafeteria diet displayed increased body weight, as well as augmented stores of mesenteric, periepididymal and retroperitoneal adipose tissue. A study developed in females fed on the cafeteria diet showed very similar results to ours [28].

Twelve weeks of cafeteria food diet has been shown to lead to increased body weight and adipose tissue deposits, both in exercised and sedentary animals, compared to the control group [29]. Treatment with liraglutide alone did not cause a reduction in body weight, nor in the Lee index or fat deposits. However, the regular practice of physical exercise and its association with liraglutide therapy was able to reduce body weight, Lee index and fat deposits. We observed that the intervention with liraglutide, in association with physical

exercise, showed better results when analyzing body weight compared to the intervention of physical exercise or liraglutide alone.

Use of physical exercise presented better effects on the epididymal and retroperitoneal fat deposits compared to the group that received liraglutide only. In contrast to our results, non-peptide GLP-1 analogs have been previously shown to reduce the weight of mesenteric fat in obese animals that received a high-fat diet; however, the treatment time was longer than that used in our study [30].

The Lee index is known to indicate obesity and the degree of obesity [24]. Our data show that animals that performed physical exercise presented a reduction in the Lee index when compared to obese animals that received treatment with liraglutide alone or the association of liraglutide and physical exercise, indicating that physical exercise presents better results in the reduction of this parameter. The Lee index can be used as a method of measuring obesity in animals, as it shows correlation with adipose tissue deposits [31], suggesting that physical exercise is an important factor in the reduction of obesity.

Total cholesterol levels did not show significant differences between obese and control groups. However, the cafeteria diet animals presented an increase in the circulating levels of triglycerides, when compared to the control animals, as can be observed in Figure 2C. The literature shows that animals exposed to a cafeteria diet show higher amounts of serum triglycerides than animals fed on a standard diet [32].

The treatment with liraglutide, as well as physical exercise, and the association between both was effective in reducing the circulating levels of triglycerides; furthermore, the effects of the treatments were potentiated when used together. Hermansem et al. [33] showed that diabetics patients who received liraglutide treatment for 3 weeks, had a reduction in triglyceride levels compared to patients receiving placebo, suggesting that the decrease in triglyceride levels is related to a decrease in ApoB48 secretion and a reduction in the intestinal absorption of triglycerides by an, as yet, unclear mechanism. The literature also shows that moderate exercise for 12 weeks is effective in reducing triglyceride levels in humans [34]; in our study, we found that swimming for 12 weeks was able to produce such an effect. However, the association between liraglutide and physical exercise did not lead to potentiation of the effect.

Administration of a cafeteria diet for 10 weeks caused an increased in fasting blood glucose, as can be seen Figure 3A. These data are in agreement with the literature that shows that animals that receive a high-carbohydrate diet present hyperglycemia [35]. Treatment with liraglutide induced a decrease in glucose levels in obese rats. The release of GLP-1 by intestinal cells is related to an improvement in peripheral insulin sensitivity, causing blood glucose levels to decrease [19], and liraglutide has been previously shown to reduce glucose levels in animals on a high-fat diet [36].

Physical exercise also lowered blood glucose; it is known that the regular practice of physical exercise improves insulin sensitivity by mechanisms not yet fully understood. Patients with diabetes that performed physical exercise showed a significant improvement in insulin sensitivity [37]; again, the association between liraglutide treatment and physical exercise improved circulating glucose levels but did not potentiate the effect of each intervention alone.

The obese animals presented hyperinsulinemia, data that are in agreement with the work of He [30] who showed that mice on a high-calorie diet showed 7 times increase in fasting insulin levels, when compared to control animals. Our animals presented hyperglycemia, accompanied by hyperinsulinemia, leading us to suggest that rats presented insulin resistance. The intervention with liraglutide was effective in reducing the levels of basal insulin in obese mice, returning values to levels that were similar to those of the control animals. Similar results were observed in a study with pre-diabetic pigs receiving treatment with liraglutide, where after 90 days of treatment there was a 36% reduction in insulin levels, compared to animals treated with placebo, plus a significant reduction in HOMA-IR [38].

Insulin sensitivity can still be estimated using the HOMA-IR index. The HOMA-IR index is used as an instrument for the diagnosis of insulin resistance by many authors, mainly in

epidemiology and has been validated against the gold standard [39]. In the present study, the obese group show a high HOMA-IR in comparison to the control animals, suggesting that insulin resistance occurred in the obese animals. Similarly, to our findings, animals that were fed on a high-fat diet showed higher values for the HOMA-IR index [40]. Treatment with liraglutide reduced the HOMA-IR index, confirming liraglutide as a regulator of glucose and insulin. In addition, regular exercise provoked a decrease in HOMA-IR, suggesting that exercise effectively improves insulin resistance. Galgani [41] hypothesized that exercise activates the skeletal muscle, causing changes in lipid turnover and improving insulin resistance. Exercise is also known to increase adiponectin, an important cytokine that improves insulin resistance [42,43].

## CONCLUSION

In summary, the current study shows that obese animals that received early swimming physical exercise intervention or that received liraglutide for 10 days presented reductions in mesenteric and periepididymal fat deposits, as well as reductions in blood cholesterol, triglycerides and insulin. Swimming also reduced the retroperitoneal fat deposit, in contrast to liraglutide that reduced the HOMA-IR. The association of physical exercise with liraglutide, which has not been previously studied, potentiated the effects of these interventions alone, reducing factors related to obesity and decreasing the body weight of the animals, the Lee index, fat deposits and blood levels of cholesterol, triglycerides and insulin. It is important to emphasize that this association presented alterations in these parameters of greater statistical significance than the interventions when administered alone.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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