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Effect of different doses of Saxenda and Rybelsus on some physiological parameters in obese male albino rats

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Abstract: Background: The present study attempts to analyze the impact of semaglutide on oxidative stress levels in the liver in an animal model of high-lipid induced obesity.This study used 30 albino male rats, obtained from the animal house of the College of Veterinary Medicine, Tikrit University, from January 1, 2025, to March 21, 2025. The study used 30 male white rats weighing between 170 and 200 grams and aged between 6 and 8 weeks. The experiment was divided into six groups: Group 1 (G1): Control group that received the standard diet throughout the experiment. Group 2 (G2): Fattened control group that received the special diet throughout the experiment. Group 3 (G3): obese rats with low doses of semaglutide. Group 4 (G4): obese rats with high doses of semaglutide. Group 5 (G5): obese rats with low doses of liraglutide. Group 6 (G6): obese rats with high doses of liraglutide. The study results showed significant differences between the various groups in blood glucose, cholesterol, triglycerides, and lipoprotein (LDL, HDL, VLDL) levels at a significance level of ($P < 0.05$). The current study revealed substantial disparities among the experimental groups in metabolic, hepatic, renal, and oxidative stress parameters ($P < 0.05$). The obese group exhibited significant increases in blood glucose, total cholesterol, triglycerides, LDL-C, VLDL-C, AST, ALT, urea, and MDA levels, alongside notable decreases in HDL-C, GSH, and GPx activity relative to the control group. semaglutide and liraglutide, effectively lowered blood sugar, liver enzymes (AST, ALT), urea levels, and oxidative stress marker (MDA). They also improved lipid profile disturbances (TC, TG, LDL-C, VLDL-C). They also improved antioxidant defence markers, especially GPx activity and HDL-C levels. Liraglutide was better at lowering glucose and triglycerides and raising GSH levels, while semaglutide was better at raising GPx activity and lowering MDA levels.

Keywords: albino rats, antioxidant, oxidative stress.

INTRODUCTION

Obesity is a chronic condition with an increasing prevalence that presently impacts over one-third of the global population [1]. Obesity is characterised by excessive fat buildup, typically defined as a body mass index (BMI) of 30 kg/m² or greater. Obesity may result from an imbalance between energy consumption and energy expenditure [2]. Weight management via lifestyle adjustment entails decreased calorie consumption and enhanced physical activity [3]. Pharmacotherapy, in conjunction with lifestyle adjustments, is essential for effective weight reduction [4]. Various anti-obesity pharmacotherapies are employed in weight management to avert obesity-related problems, such as cardiovascular risk factors and hyperglycemia [5]. Liraglutide and semaglutide are two structurally related glu- cagon-like peptide-1 analogues indicated for the treatment of type 2 diabetes, both with established cardioprotective prop erties in these patients. Liraglutide is also indicated for the treatment of obesity. Liraglutide has been observed to reduce elevated serum aminotransferases and hepatic steatosis in individuals with type 2 diabetes [6]. Semaglutide is an incretin mimetic that

binds to the glucagon-like peptide-1 receptor, promoting insulin production and inhibiting glucagon secretion [7]. Semaglutide, a glucagon-like peptide-1 (GLP-1) agonist, facilitates weight loss via central processes by prolonging gastric emptying, enhancing satiety, diminishing desire, and lowering energy intake[8]. Numerous studies offered critical insights into the application of semaglutide for obesity management, including its potential advantages, adverse effects, and underlying mechanisms of action [9].

Oxidative stress may contribute to obesity by promoting the accumulation of white adipose tissue and affecting food consumption [11]. Studies conducted on cells and animals have demonstrated that oxidative stress enhances the growth of pre-adipocytes, the formation of adipocytes, and the enlargement of mature adipocytes [12]. Additionally, reactive oxygen species (ROS) appear to influence body weight regulation by exerting various effects on hypothalamic neurons responsible for controlling feelings of fullness and hunger [12]. Therefore, this work attempts to analyze the impact of semaglutide on oxidative stress levels in the liver in an animal model of high-lipid induced obesity.

Methodology

Studies Animals

This study used 30 albino male rats, weighing between 170 and 200 grams, obtained from the animal house of the College of Veterinary Medicine, Tikrit University. The rats were placed in plastic cages and reared for 80 days, from January 1, 2025, to March 21, 2025, at the animal house of the College of Veterinary Medicine, Tikrit University. The rats were kept under suitable environmental conditions, including ventilation, a temperature of 25°C, and 12 hours of light. The cages were lined with wood shavings, and the animals were left for two weeks before the start of the experiment to settle in and adapt to their environment**..**

Drug Doses & Method of Admenstration

Rybelsus tablets containing 14 mg of the active ingredient semaglutide, obtained from a pharmacy and manufactured by the Danish company Novo Nordisk, were used. Saxenda, administered as a 0.3 mg/L subcutaneous injection, was also tested. Saxenda was obtained from a pharmacy and manufactured by the Danish company Novo Nordisk.

Design of experiment

The study used 30 male white rats weighing between 170 and 200 grams and aged between 6 and 8 weeks. The experiment was divided into two phases**:**

Phase 1 (Fattening Phase): This phase began from week 0 to week 6, during which the animals were fed a special diet containing fats, with the exception of the control groups, which were fed the standard diet**.**

Phase Two (Treatment)

This phase began after week 6. During this phase, the rats were treated with the aforementioned drugs. The rats in the second group continued to be fed the special diet, while the control group and the remaining groups were fed the standard diet. The groups were divided into six animals each, as follows**:**

- Group 1 (G1): Control group that received the standard diet throughout the experiment
- Group 2 (G2): Fattened control group that received the special diet throughout the experiment
- Group 3 (G3): Fattened rats + 5 mg/kg of semaglutide [13]
- Group 4 (G4): Fattened rats + 10 mg/kg of semaglutide [13]
- Group 5 (G5): Fattened rats + 0.**2** mg/kg doses of liraglutide [14]
- Group 6 (G6): Fattened rats + 0.4 mg/kg doses of liraglutide[14]

Blood Sample Collection

After the end of the experiment period (80) days, the animals were anesthetized using chloroform. Blood samples were then drawn from each animal by piercing the heart. The blood was placed in gel tubes. The samples were centrifuged at a speed of 3000 rpm for 15 minutes. The serum was separated from the other components using micropipettes. The serum was stored in the freezer at a temperature of -12°C until the required tests were performed, which are the determination of the concentration of sugar, cholesterol, triglycerides, urea, and creatinine, the determination of the activity of the enzyme AST and ALT, the determination of the concentration of both glutathione and glutathione peroxidase, and the concentration of malondialdehyde.

Assessment level of biochemical parameters

The concentration of all biochemical parameters with MDA, GSH, and GPX was estimated by using the Enzymatic Colorimetric Method.

Result

The study results showed significant differences between the various groups in blood glucose, cholesterol, triglycerides, and lipoprotein (LDL, HDL, VLDL) levels at a significance level of ($P < 0.05$)**.** Regarding blood glucose levels, the obese group recorded the highest mean (149.69) compared to the control group (111.44). The mean blood glucose level in the obese group treated with the low dose of semaglutide was 110.59, decreasing to 98.20 at the high

dose. Liraglutide, on the other hand, recorded a mean of 98.87 at the low dose, decreasing to 91.51 at the high dose, the lowest value recorded. Regarding total cholesterol levels, the obese group recorded the highest mean (88.01) compared to the control group (65.34). Treatment with semaglutide and Liraglutide showed a decrease from (76.90 , 73.86) respectively at the low dose to (68.36, 64.48) at the high dose**.** As for TG, the obese group recorded the highest mean (119.63) compared to the control group (87.72). Semaglutide and semaglutide decreased significantly with from 91.21 to 85.65 at the high dose. Liraglutide showed an even more pronounced effect, with values decreasing from 72.45 at the low dose to 37.88 at the high dose**.** LDL-C increased in the obese group to 16.97 compared to the control group (9.59). Treatment with semaglutide led to a decrease from 15.27 to 11.64, and with liraglutide, it decreased from 13.26 to 11.13 at the high dose**.** HDL-C l did not show a significant difference between the obese group (37.77) and the control group (38.53). However, drug treatments resulted in a significant increase in its level; the high dose of semaglutide reached 41.14, while the low dose of liraglutide achieved the highest value at 47.01, compared to 41.31 at the high dose**.** VLDL, the obese group recorded the highest mean value at 17.21 compared to the control group (7.06). The values decreased with semaglutide from 8.17 to 6.42 at the high dose. Liraglutide also showed a decrease from 14.66 to 7.27 at the high dose**.**

Table (1):levels of blood glucose and lipid profile in all study groups.

Parameters	**BG mg/dl**	**V L D L mg/dl**	**LDL mg/dl**	**HDL mg/dl**	**T R I mg/dl**	**Cholesterol mg/dl**
G1	111.44 ± 7.78 b	7.060±0.975 de	9.594±0.629 e	38.53±2.290 c	87.716 ± 1.893 c	65.340± 2.89 e
G2	149.69 ± 4.94 a	17.212±0.680 a	16.974±1.222 a	37.77 ±4.660 c	119.630 ± 4.691 a	88.010 ± 3.92 a
G3	110.59 ± 5.57 b	8.174±1.159 c	15.272±0.666 b	38.65±4.330 c	91.210 ± 2.980 b	76.902 ± 1.30 b
G4	98.20± 2.26 c	6.424±0.847 e	11.640±0.593 d	41.14±1.281 b	85.648 ± 0.544 c	68.360 ±3.89 d
G5	98.87 ± 0.94 c	14.660±0.709 b	13.264±0.544 c	47.01±1.353 a	72.450 ± 3.152 d	73.862 ± 1.99 c
G6	91.51 ± 1.45 d	7.272±1.051 cd	11.134±0.513 d	41.31 ±2.580 b	37.880 ± 2.811 e	64.482 ± 1.37 e

The results showed significant differences between the different groups in liver function tests (AST, ALT, and Br)**.** Regarding AST enzyme activity, the highest level was recorded in the obese group (110.08) compared to the control group. Treatment with semaglutide led to a significant decrease in enzyme activity compared to the obese, with values reaching 100.58 at the low dose and 99.32 at the high dose. Liraglutide did not show a significant difference at the low dose (111.52) compared to the obese group, while the value decreased to 102.92 at the high dose.

Regarding the ALT enzyme, its activity increased significantly in the obese group compared to the standard control group, rising from 46.84 to 66.94. Conversely, semaglutide treatment led to a significant decrease in ALT activity, registering 54.36 at the low dose and decreasing to 50.3 at the high dose. Liraglutide also showed a significant decrease in ALT activity, with values of 57.16 at the low dose and 50.18 at the high dose, approaching the normal control level**.**

As for Urea levels, they increased significantly in the obese group compared to the control group on the standard fat-free diet, rising from 32.5 to 49.46. This indicates a clear disturbance in this biomarker as a result of the high-fat diet. Treatment with semaglutide resulted in a significant decrease in Br levels to 41.51 at the low dose and 33.51 at the high dose. Liraglutide also showed a significant decrease, registering 37.75 at the low dose and decreasing to 32.53 at the high dose**.**

Table (2) :levels of live and kidney function test in all study groups.

Parameters	Urea µmol/l	Creatinin µmol/l	ALT IU/L	AST IU/L
G1	32.50 d± 2.88 d	0.3600 ± 0.0548 a	46.84 ± 3.64 e	66.94±5.90 c
G2	49.46 ± 2.99 a	0.4000 ± 0.02 a	66.94 ± 5.90 a	110.08± 7.79 a
G3	41.51 ± 1.68 b	0.3600 ± 0.0548 a	54.36 ± 3.16 c	100.58 ± 9.51 b
G4	33.51 ± 2.38 d	0.3400 ± 0.0548 a	50.30 ± 2.73 d	99.32 ± 1.77 b
G5	37.75 ± 2.62 c	0.3400 ± 0.0548 a	57.16 ± 2.09 b	111.52 ± 9.54 a
G6	32.53 ± 3.54 d	0.3600 ± 0.0548 a	50.18 ± 2.74 d	102.92 ± 8.52 a

Regarding malondialdehyde (MDA) levels, a significant increase was observed in the obese group compared to the control group on the standard diet, reaching a high of 9.907. This indicates a clear increase in oxidative stress resulting from the high-fat diet, and elevated MDA is a direct indicator of increased lipid peroxidation and cell membrane damage. In contrast, administering semaglutide led to a significant decrease in MDA levels, with values dropping to 8.645 at the low dose and reaching a low of 6.147 at the high dose. This suggests a dose-dependent protective effect in reducing oxidative stress. Liraglutide treatment also showed a decrease in MDA levels compared to the obese group, with values of 7.724 at the low dose and 7.109 at the high dose. However, this decrease was less pronounced compared to semaglutide , particularly at the high doses**.** As shown in Table (3).

Regarding reduced glutathione (GSH), the results showed a significant decrease in the obese group compared to the control group, dropping from 95.68 to 82.21. This reflects the reduced antioxidant capacity resulting from the high-fat diet. Treatment with semaglutide, at either the low (80.98) or high (80.53) dose, did not show a significant improvement in GSH levels compared to the obese group; the values remained similar and statistically significant. In contrast, liraglutide showed a clear improvement, with GSH levels rising to 82.2 at the low dose and increasing significantly at the high dose to 91.08, approaching the normal control level**.**

Regarding glutathione peroxidase (GPx) activity, it was significantly reduced in the fattened diet group compared to the control group, decreasing from 0.8358 to 0.5036, indicating a clear inhibition of the antioxidant defense system. In contrast, semaglutide treatment led to a marked improvement in GPx activity, rising to 0.7596 at the low dose and reaching a maximum value of 0.8476 at the high dose, approaching the normal control level. This demonstrates a strong, dose-dependent effect in enhancing antioxidant systems. Liraglutide treatment also showed a significant increase in GPx activity, reaching values of 0.6336 at the low dose and 0.779 at the high dose. However, this improvement was less pronounced compared to semaglutide, particularly at the high dose**.**

Table (3): levels of antioxidant and oxidative stress in all study groups.

Parameters	Glutathion (IU/L)	Glutathione Peroxidase (mg/L)	Malondialdehyde (nmol/L)
G1	95.68 ±2.620 a	0.8358 ± 0.0364 a	7.500±2.055 bc
G2	82.21± 4.680 b	0.5036 ± 0.1360 d	9.907 ±1.346 a
G3	80.98 ±1.737 b	0.7596± 0.0747 b	8.645 ±1.584 b
G4	80.53 ±4.743 b	0.8476± 0.0144 a	6.147±0.764 d
G5	82.20 ±4.290 b	0.6336 ±0.0814 c	7.724 ± 1.471 bc
G6	91.08 ±1.213 a	0.7790± 0.0443 b	7.109 ± 1.138 cd

DISCUSSION

The current results showed elevated blood glucose levels in the obese group compared to the control group. These findings are consistent with [15], who also reported elevated blood glucose levels in the obese group compared to the control group. Their findings demonstrated that obese rats suffer from hyperglycemia and insulin resistance, as a high-fat diet leads to obesity, hyperinsulinemia, and impaired glucose homeostasis. This may be attributed to inadequate replacement of beta cells in the pancreatic islets[16]. These results do not align with [17], who reported no significant differences in glucose levels in the obese rat group. Furthermore, the study indicated that high-dose semaglutide and liraglutide were more effective in reducing blood glucose levels than low-dose treatments.

High doses also have a greater effect on gastric emptying, reducing the rate of glucose absorption, in addition to increasing the effect on appetite and weight loss. The study results are consistent with [18], who showed a decrease in fasting and random blood glucose levels after semaglutide treatment, which they attributed to the reduction in glucose absorption associated with high-fat intake. The results are also consistent with studies that have shown a reduction in blood glucose in a group of obese individuals without type 2 diabetes [19]. Liraglutide has been shown to significantly reduce glucose and glucagon levels in obese individuals without diabetes [20]. The study results were consistent with [21], who demonstrated that obese mice had elevated levels of total cholesterol and triglycerides, and that these indicators improved significantly after treatment with liraglutide and semaglutide. A series of studies in hamsters and mice showed that the GLP-1 receptor is essential for regulating intestinal lipid and lipoprotein metabolism by controlling the synthesis and secretion of lipoproteins in the intestine [22]. A study by [23] also indicated the effect of liraglutide on ApoB-48 metabolism, showing that liraglutide treatment led to a significant reduction in blood lipids through a mechanism that decreases ApoB-48 production and increases its breakdown. [21] observed that after injection of both liraglutide and semaglutide, mice fed a high-fat diet lost 17.8% of their body weight when liraglutide was administered and 20.1% when semaglutide was administered. Normal-weight mice also experienced weight loss (<10%) after administration of both liraglutide and semaglutide, suggesting that these two drugs possess appetite-suppressing effects.

The results show elevated triglyceride levels in the obese mouse group compared to the control group, consistent with the study by [24], who also observed elevated triglycerides in the obese group. Obesity leads to a significant increase in blood lipid and glucose levels, causing metabolic disturbances [25]. The results demonstrated that obesity resulting from a high-fat diet in laboratory animals led to elevated triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), as well as increased fasting blood glucose levels [26]. The group treated with semaglutide and liraglutide showed a dose-dependent decrease in triglyceride levels, consistent with the findings of [21], who observed a decrease in triglyceride levels with a 2.4 mg dose of semaglutide.

The results showed no statistically significant differences in high-density lipoprotein (HDL) cholesterol levels between obese mice and those treated with low-dose semaglutide compared to the control group. This is attributed to the reduced metabolic activity of HDL in obesity, which may affect plasma HDL production. These results are consistent with a previous study that indicated a decrease in HDL in the obese group. The study's findings are also consistent with [27], who demonstrated a decrease in HDL cholesterol in the high-fat diet group, along with a significant increase in body weight compared to the negative control group, confirming the success of inducing obesity. While the results showed a significant increase in HDL levels in the group treated with high-dose semaglutide , as well as in the groups treated with both low and high doses of liraglutide, these findings are consistent with those of [28], who observed an increase in HDL in the liraglutide-treated group. They also align with those of [29], who indicated that high-dose semaglutide improved the blood lipid profile.

This study demonstrates that administering liraglutide and semaglutide to obese rats produced significant dose-dependent effects on several hepatic and metabolic parameters, specifically a significant increase in the liver enzyme AST. The decrease in AST levels in rats treated with both semaglutide and liraglutide at low and high doses suggests that GLP-1 receptor activation can produce hepatoprotective effects even at high doses [30]. In one study, high doses of liraglutide also resulted in hepatoprotective effects [31].

Studies in mouse models of non-alcoholic fatty liver disease (NAFLD/NASH) have shown that treatment with semaglutide or liraglutide significantly reduces hepatic steatosis, accompanied by significant improvements in ALT and AST levels [32]. Recent studies have demonstrated that liraglutide possesses antioxidant and anti-inflammatory properties in hepatocytes. Liraglutide reduces oxidative stress and inflammatory cytokine levels, including TNF-α and TGF-β1[33]. It has also been shown to inhibit NF-κB transcription factor activation in endothelial cells, leading to decreased IL-1β and TNF-α production [34].

The current study indicates elevated MDA levels in obese rats compared to the control group. This is attributed to the increased free radicals (ROS)

resulting from obesity, which may lead to lipid peroxidation and the production of toxic MDA. Increased lipogenesis, inflammation, and oxidative stress contribute to excessive MDA production due to lipid peroxidation. MDA levels are correlated with mitochondrial activity, cell membrane damage, and the extent of oxidative damage. In contrast, MDA levels decreased in the groups treated with high doses of semaglutide and Liraglutide. These findings are consistent with [35], who observed elevated MDA levels in obese laboratory animals, while levels decreased with semaglutide.

ROS play a crucial role in regulating cellular processes such as proliferation, differentiation, and cell death; however, their overproduction leads to oxidative stress, mitochondrial dysfunction, and apoptosis. Antioxidant systems work to reduce ROS levels and mitigate their harmful effects[36].

The study results were consistent with [37], who demonstrated a decrease in MDA levels after liraglutide administration, suggesting its anti-inflammatory properties. The findings also indicated a decrease in glutathione levels in the obese group. This decrease may be attributed to the rapid consumption and depletion of glutathione stores during the fight against free radicals generated during obesity development, or to its inactivation by S-glutathionylation under oxidative stress conditions. S-glutathionylation is a regulatory mechanism that relies on the formation of disulfide bonds between protein thiols and oxidized glutathione[38]. The study results were also consistent with those of [39].

The animal body has demonstrated effective mechanisms for protecting against free radical-induced cellular damage, consisting of a group of antioxidant enzymes and proteins such as GPx and GSH. When the balance between ROS production and antioxidant defenses is disrupted, oxidative stress arises, leading, through a cascade of events, to cellular dysfunction and various pathological conditions [40]. The results showed elevated glutathione levels in the high-dose liraglutide group, consistent with [37], while no significant differences were observed between low-dose liraglutide and low- and high-dose semaglutide when compared to the obese group. The marked decrease in glutathione peroxidase activity in obesity may be attributed to the rapid depletion of the enzyme's stores due to the continuous counteracting of free radical production as obesity progresses. Furthermore, the activity of key free radical neutralizing enzymes may be insufficient in obese individuals [39]. GPx is a crucial antioxidant enzyme that plays a pivotal role in the decomposition of hydrogen peroxides and lipid peroxides; therefore, its reduced activity indicates an increased susceptibility to oxidative tissue damage, a common feature in obesity resulting from high-fat diets [41].

CONCLUSION

The study results indicated that high-fat diet clearly raised liver enzyme activity (AST and ALT) and lowered kidney function (urea). It also raised glucose, cholesterol, triglyceride, and lipoprotein (LDL, HDL, VLDL) levels. Oxidative stress also rose, as shown by higher MDA levels and lower antioxidant capacity (GSH and GPx). Most of these indicators got a lot better with semaglutide and liraglutide treatments. Semaglutide was better at lowering glucose, lipids, and MDA and raising GPx, while liraglutide was better at raising GSH levels and lowering ALT. The effects were also dose-dependent, with higher doses causing the biggest changes in biochemical markers and antioxidant function, bringing them closer to the normal levels of the control group.

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