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Tirzepatide protects against hepatic oxidative stress in high-fat induced obesity in male rats

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ORIGINAL STUDY

Tirzepatide Protects Against Hepatic Oxidative Stress in High-fat Induced Obesity in Male Rats

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Abstract

Background: **Obesity is a prevalent health issue that affects people of all ages at a high rate. Tirzepatide (TZP) is a hypoglycemic medication that acts as a dual antagonist for both the GIP-1 and GIP receptors. Previous reports have shown that TZP treatment demonstrated substantial weight reduction as well as lipid-modulating effects in obese and overweight individuals.**

Objective: **The aim from this study is to examine the potential protective effect of TZP on oxidative stress status and HFD induced obesity in male rats.**

Methods: **This research employed a total of 28 adult male Sprague−Dawley rats. Normal control group involved seven rats fed a regular diet, while the other rats received a high-fat diet (HFD). Obese rats separated into three groups after eight weeks of HFD: obesity, tirzepatide (10 nmol/kg) s.c, and vehicle groups, and treated for four weeks. Data regarding body weight, blood glucose, and lipid profile, as well as the levels of SOD and MDS in the liver tissue were obtained.**

Results: **The results have demonstrated that TZP-treated obese rats exhibited significantly reduced body weight, blood glucose levels, TG and VLDL. Additionally, liver specimens from TZP group showed increased content of SOD enzyme compared to obese untreated rats.**

Conclusion: **Treating obese rats with TZP improved body weight, blood glucose lipid profile and elevating the level of the antioxidant defense.**

Keywords: Tirzepatide, Obesity, Oxidative stress, Liver

1. Introduction

Obesity is a prevalent disease process. Due to the combination of hereditary and environmental causes, obesity has persisted for centuries and is currently a pandemic with grave health implications [1]. There are over a billion overweight persons according to World Health Organization statistics in the world. We can classify 300 million individuals as obese. In Europe, the prevalence of overweight individuals among boys, girls, and teenagers is 20%, whereas the prevalence of obesity is 5% [2].

Psychological, lifestyle, and family history variables influence the predisposition to obesity. Unhealthy eating and exercise habits, as well as a genetic predisposition to gain weight in the family, can both contribute to an elevated risk of obesity. A significant risk factor for the severity of childhood obesity is having a family history of obesity and cardiometabolic diseases [3,4].

Additionally, Fat significantly increases a number of noncommunicable diseases, including respiratory disorders like sleep apnea, gout, gallbladder disease, dyslipidemia, osteoarthritis, type 2 diabetes, hypertension, stroke, coronary heart disease and others. The primary adjustable risk factor for type 2 diabetes (T2DM) is obesity [5].

Adoption of the western lifestyle, characterized by the consumption of energy-dense, tempting but unhealthy foods, a decrease in dietary fiber intake, an elevation in sweets and animal fats, and minimal

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physical activity, often results in a rise in the incidence of obesity [6,7]. Increased consumption of fruit juice, sugar-sweetened beverages and dietary fat from saturated, animal fat was linked to higher weight gain. Also, lower physical activity, sedentary activities at home or work and interaction between lifestyle factors and genetic predisposition result in a high risk of obesity [8].

Oxidative stress happens when the body produce an excess of ROS relative to the magnitude of antioxidants present. The accumulation of fat exacerbates oxidative stress, a primary factor contributing to obesity and other metabolic problems. Triglyceride levels that are too high in cultured adipocyte cells cause NADPH oxidase to work harder. This causes oxidative stress and less production of adipocytokines, which are hormones that help the body burn fat [8].

Tirzepatide (MOUNJARO)™ is a glucagon-like peptide-1 (GLP-1) receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist that is recommended to help persons with T2DM manage their blood sugar levels in addition to exercise and diet [9]. The gut produces the incretin hormones GLP-1 and GIP, which regulate postprandial glucose and fat metabolism. In order to ascertain whether GIP could augment the known glucose-lowering action of GLP-1RAs in diabetes, TZP was created [10]. The combined physiological activity of GLP-1 and GIP is what causes this weight reduction effect where GLP-1 decreases body weight through peripheral (slowing stomach emptying) and central (reducing food intake, increasing satiety) effects. GIP complements these effects; its receptors are present in subcutaneous white adipose tissue and the brain, where they partially overlap with GLP-1 receptor expression patterns as shown in Figure 1 [11].

In addition to their effects on diabetes mellitus and reduction of body, GLP-1 and GIP act to decrease the oxidative stress where GLP-1 receptor agonists have antioxidative properties [12,13]. Therefore, this research aimed to investigate potential protective effect of TZP on the state of oxidative stress in male, obese rats given a HFD.

Abbreviations

ANOVA	Analysis of variance
ARN	Arcuate nucleus of the hypothalamus
cAMP	Cyclic adenosine monophosphate
CETP	Cholesterylester transfer protein
CNS	Central nervous system
CREB	cAMP response element-binding protein
D.W	Distilled water
DIO	Diet-induced obesity
ELISA	Enzyme-linked immunosorbent assay
FBG	Fasting blood glucose
FFA	Free fatty acids
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GLP-1RA	Glucagon-like peptide-1 receptor agonist
gm	Gram
H_2O_2	Hydrogen peroxide
HDL	High-density lipoprotein
HFD	High-fat diet
LDL	Low-density lipoprotein
LPL	Lipoprotein lipase
MDA	Malondialdehyde
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcholic statohepatitis
NOX	NADPH oxidase
PBS	Phosphate buffered saline
PKA	Protein kinase A
POMC	Pro-opiomelanocortin
ROS	Reactive oxygen species
SOD	Superoxide dismutase
T2DM	Type 2 diabetes mellites
TG	Triglyceride
TZP	Tirzepatide
VLDL	Very low-density lipoprotein

2. Materials and methods

2.1. Materials

Tirzepatide (CAS no.:2023788-19-2) from Hangzhou Go Top Peptide Biotech Co., Ltd., China. The glucometer and test strip from on call plus, USA. Chemical analyzer type Cobas from Roche, Germany. Malondialdehyde assay kit and superoxide dismutase assay kit from SUNLONG BIOTECH CO. LTD, China.

2.2. Study design

The University of Kufa's faculty of pharmacy house served as the study's location. The trial investigation lasted for 12 weeks. This experiment utilized twenty-eight mature male Sprague–Dawley rats weighing between 249 and 255 g. Rats were ra divided into four groups, each consisting of seven rats: normal group, obesity group, obesity + vehicle group, and obesity + tirzepatide group. The animals were kept in a temperature-controlled environment at 24 ± 2 °C with 12-h light and dark cycles. For 12 weeks, the rats in the normal group received a regular pellet. For rats fed HFD (30% fat), in the last four weeks, animals were either treated with tirzepatide at a daily dose of 10 nmol/kg s.c or its vehicle D.W or left untreated as an obesity control. The obesity + vehicle and obesity + tirzepatide groups fed the rats a HFD for 12 weeks.

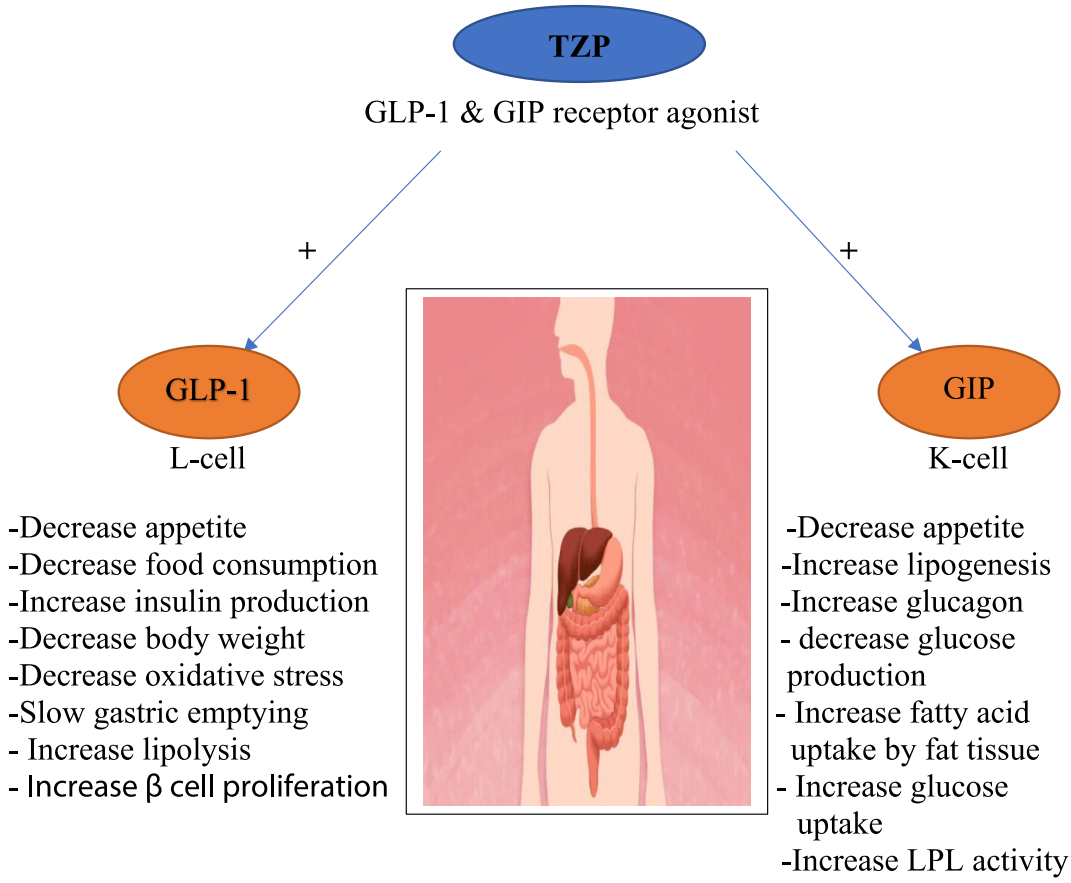

Fig. 1. Mechanism of action of tirzepatise.

2.3. Collection of blood and tissue samples

Ketamine and xylazine (75 mg/kg) were utilized to euthanize the animals then they were sacrificed after collecting of blood samples. A Midline incision was performed to access the liver. One portion of the liver tissue was subjected to freezing at a temperature of −80 °C to be homogenized in a fresh buffer solution of PBS. The homogenization was performed using a glass homogenizer to test the oxidative stress biomarker using the ELISA approach.

2.4. Measurement of body weight

Throughout the 12-week investigation, measuring and recording the body weight was performed once a week using an animal balance.

2.5. Measurement of fasting blood glucose (FBG)

After the completion of eight weeks of HFD and starting animal treatment with either tirzepatide or vehicle for a 4-week investigation period, fasting blood glucose was estimated using a glucometer once weekly.

2.6. Measurement of lipid profile

Blood samples were drawn from rats under anaesthesia via heart puncture using a 5 cm syringe using a gel tube. Blood sample was centrifuged at 3000 rpm for 15 min. Chemical analyzer was employed to obtain the lipid profile parameters from the obtained serum.

2.7. Measurement of oxidative stress biomarker

Using commercially available kits, liver tissue samples were homogenized on ice and subsequently subjected to the ELISA sandwich technique for measuring MDA and SOD.

2.8. Statistical analysis

For statistical analysis, Graphpad Prism version 10 was used in this investigation. The mean value of the data was shown, either plus or minus the standard error of the mean (SEM). To assess and compare several groups, one-way and two-way Analysis of Variance (ANOVA) were utilized. The statistical significance between the groups was then

assessed using Tukey's multiple comparison technique. Statistical significance was defined as $P < 0.05$ at the significance level.

3. Results

3.1. Effect of tirzepatide on body weight

Before starting animal treatment with TZP or its vehicle, there is no notable disparity between obesity, Obesity + vehicle and Obesity + Tirzepatide groups. On the other hand, the normal control group differed significantly from the all the other groups ($p < 0.0001$) as shown in Table 1.

Upon the conclusion of the research, mean value of body weight in obesity group raised significantly compared to normal group ($p < 0.0001$). The mean body weight value in the obesity + tirzepatide group decreased significantly compared to obesity + vehicle group ($p < 0.0001$) as shown in Table 1.

3.2. Effect of tirzepatide on fasting blood glucose in HFD-fed rats

After eight weeks of HFD, there was insignificant difference in FBG between all the treatment groups. However, after twelve weeks of HFD, a significant increment ($p < 0.05$) in FBS occurred between rats on regular diet and untreated rats fed HFD as shown in Table 2.

In contrast, the average FBG in the obesity-tirzepatide group decreased considerably compared to obesity-vehicle group ($p < 0.01$).

3.3. Impact of tirzepatide on lipid profiles in HFD-fed rats

There were significant increases in TG and VLDL levels in obese group compared to control group ($p < 0.05$). In obesity + tirzepatide group, mean value of TG and VLDL levels decreased significantly ($p < 0.01$) compared to obesity + vehicle group.

The mean value of cholesterol and LDL levels in the obesity group increased significantly compared to control group ($p < 0.05$ and $p < 0.001$ respectively). The mean value of cholesterol and LDL level in the obesity + tirzepatide group decreased compared to the obesity + vehicle group, however, it did not reach to statistical significance. There is no notable disparity was observed in serum HDL measurement between all the studied groups as shown in Table 3.

Table 1. Comparison between animal body weight before and after treatment.

Body weight (gm)	Groups			
	Normal	Obesity	Obesity + vehicle	Obesity + Tirzepatide
Before treatment	292 ± 1.75	349 ± 1.95####	339.29 ± 4.23####	353.57 ± 1.6####
After treatment	323.86 ± 2.18	411.43 ± 2.93####	395.71 ± 4.39####	295.86 ± 1.47****

Data are presented as mean ± SEM of seven rats in each group. ****p < 0.0001 compared with obesity-vehicle group. ####p < 0.0001 versus Normal control.

Table 2. Effect of tirzepatide on fasting blood glucose before and after the treatment.

Fasting blood glucose	Groups			
	Normal	Obesity	Obesity + vehicle	Obesity + Tirzepatide
Before treatment	84.57 ± 2.68	91.42 ± 3.7	90.71 ± 7.94	89.57 ± 3.29
After treatment	89.86 ± 2.95	121 ± 5.46 #	115.71 ± 6.02	70 ± 5.87 ***

Data are presented as mean ± SEM of seven rats in each group. ***p < 0.001 compared with obesity-vehicle group. #p < 0.05 versus Normal control.

Table 3. Impact of tirzepatide on lipid profiles in HFD-fed rats.

Biochemical parameter	Groups			
	Normal	Obesity	Obesity + vehicle	Obesity + Tirzepatide
Cholesterol	40.61 ± 1.42	57.94 ± 5.63 #	58.51 ± 2.11	53.44 ± 3.26
Triglyceride	43.79 ± 3.04	65.07 ± 5.99 #	65.34 ± 6.34	39.7 ± 3.07 **
HDL	28.43 ± 1.11	26.3 ± 2.22	25.98 ± 1.41	30.33 ± 1.69
LDL	3.42 ± 0.37	18.62 ± 3.4 ###	19.46 ± 2.84	15.17 ± 1.17
VLDL	8.756 ± 0.61	13.01 ± 1.19 #	13.07 ± 1.27	7.94 ± 0.61 **

Data are presented as mean ± SEM of seven rats in each group. **p < 0.01 compared with obesity-vehicle group. #p < 0.05, ###p < 0.001 versus Normal control.

3.4. Effect of tirzepatide on hepatic MDA level in rats fed HFD

It was found that the MDA concentration in obesity group raised significantly compared to normal group ($p < 0.05$). On the other hand, the hepatic MDA content in obese animals treated with tirzepatide tended to decrease however it did not reach to statistical significance (Fig. 2).

Rats fed HFD were treated with tirzepatide 10 nmol/kg daily for four weeks. In vehicle group, obese rats were administered tirzepatide vehicle. Data are presented as mean ± SEM of seven rats in each group. #p ≤ 0.05 versus normal control.

3.5. Tirzepatide treatment elevates SOD content in the liver tissue in rats fed HFD

Feeding the rats HFD for 12 weeks resulted in a significant drop in SOD concentration in liver tissue of the obesity group to the normal healthy group ($p < 0.01$) as shown below in Fig. 3.

The SOD concentration in obesity + tirzepatide group raised significantly compared to the obesity + vehicle group. The difference in mean ± SEM between vehicle-treated group and tizepatide group indicates there is a significant difference ($p < 0.05$) as shown below in Fig. 3.

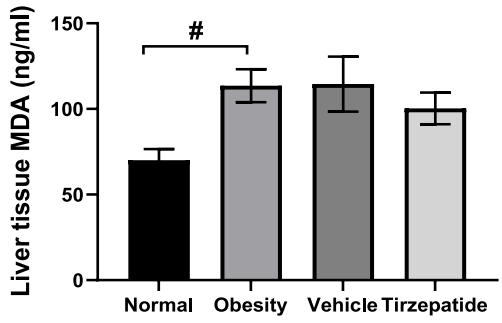

Fig. 2. Effect of tirzepatide on hepatic MDA level in rats fed HFD.

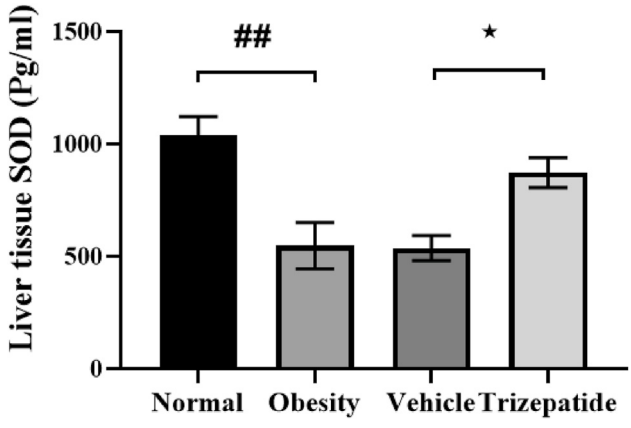

Fig. 3. Tirzepatide treatment elevates SOD content in the liver tissue in rats fed HFD.

Tirzepatide was used to treat rats given a high-fat diet in dose 10 nmol/kg daily for four weeks. In vehicle group, obese rats were administered tirzepatide vehicle. Data are presented as mean ± SEM of seven rats in each group. *p ≤ 0.05 versus obesity-vehicle group. ##p ≤ 0.01 versus normal control.

4. Discussion

Obesity is an urgent public health issue that requires immediate attention. To fully understand the reasons for obesity, it is crucial to grasp elements such as consuming too many calories, leading a sedentary lifestyle, making poor food choices, genetic predisposition, and other related factors; in addition to understanding the role of genetics in obesity [14].

This study utilized a male rat as an animal model to induce obesity. Rats are commonly used in obesity research. Researchers recommend rats for obesity studies because of their genetic similarity to humans, shorter lifespan for quick observations, ease of experimental manipulation, and ability to simulate human conditions like obesity through interventions like dietary modifications [15].

A considerable rise in body weight among animal groups that were fed a HFD, compared to the normal group. Obesity resulting from a high-fat diet can manifest in various ways such as hyperphagia, a condition characterized by an excessive increase in food intake that results in weight gain, which can cause obesity while consuming HFD [16].

The glucose levels reflect the balance between muscular glucose absorption and hepatic glucose production. The liver significantly contributes to the onset of obesity-induced hyperglycemia and influences various metabolic pathways. Insulin promotes glycogen synthesis and suppresses hepatic glucose release. In cases of obesity, glucose production in the liver increases through glycogenolysis and gluconeogenesis, but muscle glucose absorption decreases, resulting in elevated blood glucose levels. When an individual has a condition that reduces insulin effectiveness, blood sugar levels increase while anabolic and anti-inflammatory actions decrease [17] Insulin and blood glucose levels, which target glycogenolysis and gluconeogenesis in the liver, regulate hepatic glucose production. Moreover, studies show that insulin and blood glucose levels affect the CNS, which controls the liver's production of glucose [18].

Moreover, the obesity and obesity + vehicle groups significantly elevated lipid profile parameters such as TG, cholesterol, LDL, and VLDL compared to the control rats. Consuming too much energy and not expending enough energy leads to obesity. The adipose tissue nowadays is acknowledged as a significant endocrine organ, releasing numerous peptides into the bloodstream that influence metabolism. Accumulation of adipose tissue leads to an increased release of free fatty acid (FFA) into the bloodstream. Insulin inhibits the release of FFA from adipose tissue in both lean and obese people. However, with obesity, this process becomes resistant to insulin [19].

Individuals with obesity release fewer fatty acids per unit of fat mass compared to those who are lean. However, obesity leads to an increase in fat mass, resulting in an increased supply of FFA to the bloodstream. Obese individuals are unable to reduce the release of FFA from their adipose tissue, even though they have high levels of insulin in their blood after eating a regular meal. The increased presence of fatty acids will reduce muscle glucose use and promote liver glucose production. Increased levels of FFA also lead to the accumulation of lipids in pancreatic β-cells [20,21].

In cases of obesity, the adipose tissue becomes overwhelmed with TG, resulting in a decreased ability of adipocytes to store lipids. Adipocytes are unable to fulfill their usual function of shielding other tissues from the continuous intake of dietary fatty acids. Obesity hinders the breakdown of triglyceride-rich lipoproteins due to decreased mRNA levels of lipoprotein lipase (LPL) in adipose tissue. When the liver makes too much very VLDL, it can stop the breakdown of chylomicrons, which can lead to hypertriglyceridemia. With the help of cholesterylester transfer protein (CETP), VLDL particles exchange enzymes with other lipoprotein particles, like HDL and LDL. Different lipases subject these high-TG lipoprotein particles to smaller HDL particles, which then undergo kidney metabolism and elimination, resulting in a reduction in HDL levels [22,23].

Hypertriglyceridemia causes a decrease in LDL cholesterol-ester content, while CETP causes an increase in LDL TG content. Hepatic lipase hydrolyzes the elevated triglyceride content present in LDL, resulting in tiny, compact LDL particles. Small, dense LDL particles have a relatively long circulation life of 5 days, which increases their ability to cause atherosclerosis. The VLDL particles also undergo lipolysis, which leads to the development of VLDL remnants and subsequently tiny, dense LDL particles [24,25].

The administration of HFD caused dyslipidemic alterations, as evidenced by elevated serum levels of triacylglycerol, total cholesterol, VLDL-cholesterol and LDL-cholesterol, and reduced HDL cholesterol levels compared to the normal group. The elevated triacylglycerol levels in the liver may be the cause of the dyslipidemic alterations in obesity. Recent findings link obesity to an elevated risk of several negative consequences due to changes in cholesterol levels and alterations in the quality of lipoprotein fractions [26,27].

Furthermore, researchers have identified changes in lipids as variables that contribute to oxidative stress in obesity [28]. Animal models of obesity have shown an increase in ROS formation and a decrease in antioxidant defense systems. It is believed that lipid peroxidation contributes to the emergence of obesity-related health problems [29].

The study's data demonstrated that obesity led to an increase in lipid peroxidation in liver tissues, as indicated by elevated level of MDA and reduced level of SOD. Due to ongoing and accumulating cell damage from excessive body weight, obesity can lead to higher levels of lipid peroxidation. Damage to cells causes cytokines, especially TNF-α, to be released. This causes tissues to produce ROS which then leads to lipid peroxidation [30].

The high levels of TG in obese rats may disrupt the equilibrium between oxidants and antioxidants, indicating that an increase in the availability of unbound fatty acids can enhance the process of lipid peroxidation. The increased lipid peroxidation causes enzymes to deactivate by forming crosslinks with MDA. This, in turn, this leads to a higher concentration of hydroxyl radicals, superoxide, and H2O2, all of which can accelerate lipid peroxidation [29]. HFD induced obesity generates ROS and oxidative stress [31,32].

Endogenous antioxidant enzymes, such as SOD, is crucial for removing ROS and safeguarding cells from the harmful impacts of oxidative stress. NADPH oxidase produces the superoxide anion, which SOD enzymatically converts into oxygen and H_2O_2 [31,33].

As shown in Fig. 3, HFD reduced the activities of SOD in the plasma of rats. Excessive ROS production and reduced synthesis of SOD proteins may cause feedback inhibition or oxidative inactivation of enzyme proteins, leading to a decrease in SOD activity [31].

A novel kind of hypoglycemic drug called tirzepatide (TZP) functions as a dual antagonist for the GIP-1 and GIP receptors. The TZP therapy showed significant weight loss and lipid-regulating effects in obese and overweight patients. Due to its dual

agonist activity on GIP and GLP-1 receptors, it is categorized as an unbalanced dual agonist. TZP is as attractive to the GIP receptor (GIPR) as endogenous GIP, but it is approximately five times less attractive to the GLP-1 receptor (GLP-1R) than endogenous GLP-1. Activating the GIP receptor (GIPR agonist) may lead to weight reduction in individuals with metabolic problems. Research indicates that GLP-1/GIP dual receptor agonists are more effective than GLP-1RA alone in promoting weight loss [34].

TZP's dual activation of GLP-1/GIP receptors and the combined action of the two enterostatins, which effectively suppress hunger, may be responsible for the weight reduction effect. For example, consistently high levels of GIP improved sensitivity of insulin and alleviated diet-induced obesity (DIO) in transgenic rats by reducing calorie intake. Moreover, GLP-1 and GIP receptors had a synergistic effect at the CNS level [35].

When GLP-1 and GIP were given together to people with anorexia nervosa, their pro-opiomelanocortin (POMC) genes were turned up. This led to a decrease in appetite and food consumption. Furthermore, there could exist a distinct group of neurons in the arcuate nucleus of the hypothalamus (ARN) that is exclusively stimulated when GLP-1 and GIP are supplied together but not when either one is administered alone. These neurons are not dependent on the POMC gene and have both GLP-1 and GIP receptors. They send a chemical signal to nearby POMC gene-regulated neurons that are deprived of oxygen [36]. It activates GLP-1 receptor to stimulate glucose-dependent insulin secretion, suppress glucagon release, and slowdown gastric emptying. As a result, it produces hypoglycemic effects that are comparable to those of selective GLP-1 agonists [37,38].

In our study, we found that the levels of TG and VLDL dropped significantly in the groups of obese patients who were given TZP. These effects were more pronounced compared to obesity and obesity + vehicle groups. TZP also has substantial lipid-modulating effects. This can happen either directly by activating GIPR on adipocytes or indirectly through insulin's lipogenic effect, or both [39].

Furthermore, GIP can improve insulin sensitivity and optimize the function of islet β-cells in mice. It also has the potential to decrease steatosis and facilitate lipid metabolism in the body, leading to a decrease in the presence of free fatty substances in the bloodstream. Nevertheless, there is a limited amount of research focusing on the alterations in lipid profile, and additional investigations are required [40]. Obesity is a leading contributor to the onset of metabolic syndrome. Oxidative stress is one important pathogenic process in the development of obesity-related metabolic syndrome. It is defined as an imbalance between the body's capacity to detoxify reactive oxygen species and their generation. Accumulated fat tissue particularly exacerbates this oxidative stress. In both humans and mice, there is a strong association between fat buildup and oxidative stress throughout the body. Obese mice's adipose tissue specifically elevated the production of ROS. NADPH oxidase expression increased along with this increase, while antioxidative enzyme expression decreased [41]. Nonalcholic statohepatitis (NASH) is the pathological progression of non-alcoholic fatty liver disease (NAFLD) that arises from an abnormal and substantial fat buildup in the liver. It closely links to a heavy burden of metabolic comorbidities, including obesity [42]. Oxidative stress is considered to play a role in the development of primary nonalcoholic steatohepatitis (NASH) [43]. GLP-1 mimetics have demonstrated beneficial effects on lipid metabolism, glucose transport, and oxidative stress [42]. Many cells contain the GLP-1 receptor, which binds to G-protein. Activation of this receptor in pancreatic islets leads to a rise in intracellular calcium ion levels. Furthermore, it improves the functionality of adenylate cyclase, resulting in an increase in cAMP synthesis and phospholipase C activation. Moreover, it activates many pathways, including cAMP response element-binding protein (CREB) and protein kinase A (PKA) [44].

Many cells contain the GLP-1 receptor, which binds to G-protein. Activation of this receptor in pancreatic islets leads to a rise in intracellular calcium ion levels. In addition, it makes adenylate cyclase work better, which leads to more cAMP synthesis and phospholipase C activation. Furthermore, it stimulates several pathways, such as protein kinase A (PKA) and cAMP response element-binding protein (CREB) [45,46]. An evaluation of the impact of GLP-1 on antioxidant capacity is required. It is important to recognize that the body adjusts to greater levels of reactive oxygen species (ROS) by either decreasing ROS production and use or increasing the amounts of antioxidants [47]. TZP has the ability to prevent glucose levels from fluctuating and counteract the oxidative stress caused by hyperglycemia [48]. Hence, GLP-1R possesses the capacity to emerge as a pharmaceutical target for NASH(49). Tirzepatide, which works on both GLP-1R and GIPR, was better at controlling blood sugar than a GLP-1R agonist alone. Tirzepatide expressed a significant decrease in body weight during a phase 2 clinical trial, suggesting its clinical significance in the treatment of NASH [42,49].

5. Conclusion

The obesity animal model exhibited elevated body weight, blood glucose and worsened the lipid profile. Moreover, it augmented oxidative stress levels in hepatic tissue. Treating obese animals with TZP efficiently lowered body weight, blood glucose, and improved serum lipids. Finally, TZP treatment enhanced the level of the antioxidant enzyme SOD in the liver.

Ethical approval

The study received ethical approval from Kufa University, central ethics committee (under no. 6684) on 10 March 2024.

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