ORIGINAL ARTICLE

CONTENTS

Tirzepatide therapy counters inflammatory and apoptotic responses induced by high-fat diet in rat liver

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ABSTRACT

Aim: To examine potential protective effect of Tirzepatide against obesity-induced metabolic dysfunction and hepatic inflammatory and apoptotic responses.
Materials and Methods: A total of 28 adult male Sprague-Dawley rats were employed and divided into four groups, normal control group involved seven rats fed a regular diet, while other rats received a high fat diet. Obese rats were separated into three groups after eight weeks of high fat diet: obesity, Tirzepatide (10 nmol/kg) s.c and vehicle groups, and treated for four weeks. Data regarding body weight, blood glucose, serum insulin, liver enzymes, and TNF-α, IL-1β and caspase-3 levels in the liver tissue were obtained.
Results: results revealed that Tirzepatide-treated obese rats exhibited significantly reduced body weight, blood glucose, serum insulin ALT, triglyceride, VLDL levels. Additionally, liver specimens from Tirzepatide group demonstrated lower levels of TNF-α, IL-1β and caspase-3 compared to obese untreated rats.
Conclusions: It concluded that Tirzepatide treatment mitigates the metabolic dysregulations induced by High Fat Diet, additionally; it ameliorates the inflammatory and apoptotic responses in hepatic tissue triggered by High Fat Diet.

KEY WORDS: Tirzepatide, obesity, inflammation, apoptosis, liver

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ABBREVIATIONS

HFD: High Fat Diet
T2DM: Type 2 Diabetes
GLP-1: Glucagon-Like Peptide-1

INTRODUCTION

Obesity is a widespread public health problem that affects people of all age groups [1]. The phenomenon has significant societal and economic influences, directly impacting individuals' well-being and overall standard of living. Accumulation of fat in the subcutaneous and visceral tissues results in obesity, this increment in body weight can negatively impact people health [2]. In addition to adipose tissue, the liver is also a common place for buildup of lipids and ectopic fat [3]. Avoiding and managing obesity involves controlling body weight and adiposity by conserving a negative energy balance, with diet and physical activities playing vital roles, however, as people's lifestyles have changed, with reduced physical activity and changes in eating habits, the investigation of alternate approaches to treating obesity, such as functional foods and bioactive substances, has become increasingly important [1]. The prevalence of obesity is steadily rising, suggesting that the existing treatments employed to manage this condition are inadequate and that further preclinical investigations are required. To examine the progression of obesity and its associated risk factors, scientists employ animal models of diet-induced obesity. Scientists prefer these models over genetic models because they replicate human obesity more accurately. Furthermore, controlled environments facilitate the comprehension of the findings in experiments conducted on animal models [4]. Obesity significantly increases the likelihood of developing many non-communicable diseases, such as sleep apnea, osteoarthritis, gout, dyslipidemia, gallbladder disease, T2DM, coronary heart disease, hypertension, and stroke, which primarily affect the lungs, joints, metabolism, and cardiovascular system [5]. Excessive energy consumption generates visceral fat in non-fat tissues and the enlargement and multiplication of fat cells, leading to liver and cardiovascular diseases. Also, adipokines and inflammatory cytokines made by adipose tissue may influence the environment, causing high blood sugar and insulin resistance and starting up signaling pathways related to inflammation. This increases the likelihood of developing and

exacerbating obesity-related diseases [6]. The human body accumulates excess energy in its adipose tissues which commonly occurs when the number of calories consumed exceeds the energy expended. Obese people have a high abundance of adipocytes ad excess energy intake can lead to continuous proliferation of adipocytes ultimately leading to the onset of obesity [7]. The correlation between obesity and inflammatory disorders can be attributed to several processes; for instance, adipose tissue in overweight individuals makes more pro-inflammatory adipocytokines, which create reactive oxygen species (ROS). Moreover, the elevated level of oxidative stress changes adipose tissue in important ways that cause a systemic, low-grade inflammatory response affecting the whole body [8], while a range of stressors can upset homeostasis and trigger inflammation as a natural physiological response to restore it, excessive or persistently high levels of inflammation can be detrimental to health. It is thought that overeating is the initial signal of inflammation and that the pathway originates in tissues involved in metabolism, such as adipose tissue, liver, and muscle, which triggers the inflammatory [9-10]. Previous reports have linked hepatic steatosis, insulin resistance, and the recruitment of macrophages into adipose tissue to the increase in adipose tissue associated with obesity. Adipocyte apoptosis is common in obese individuals and animals where activation of certain apoptosis mechanisms was seen in the adipose tissue of dietary models of obesity. Blocking these processes prevented hepatic steatosis, insulin resistance, and macrophage infiltration of adipose tissue, as well as adipocyte apoptosis [11]. Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist that is recommended to help persons with T2DM manage their blood sugar levels in addition to diet and exercise [12]. It activates GLP-1 receptors 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. It also suppresses food consumption and the desire to eat simultaneously [13]. Conversely, it increases the responsiveness of islet β cells to GIP, facilitating GIP function in stimulating initial insulin release and enhancing insulin sensitivity, resulting in a more efficient and consistent reduction in blood sugar levels [14]. Recent studies have demonstrated that the concurrent administration of GLP-1 and GIP can provide mutually enhancing effects, leading to improved regulation of blood sugar levels and a greater reduction in body weight. This can significantly protect against cardiovascular and cerebrovascular ailments [15]. In addition to their effects on diabetes mellitus and reduction of body, GLP-1 act to decrease oxidative stress where GLP-1 receptor agonists have anti-inflammatory and anti-apoptosis properties [16-17].

AIM

This study aims to examine the potential protective effect of Tirzepatide against obesity-induced metabolic dysfunction and hepatic inflammatory and apoptotic signals.

MATERIALS AND METHODS

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. Tumor necrosis factor-α (TNF-α) assay kit, interlukin-1β (IL-1β) assay kit, caspase-3 assay kit and insulin assay kit from SUNLONG BIOTECH CO. LTD, China.

STUDY DESIGN

Animals were housed in the animal facilities, Faculty of Pharmacy, University of Kufa in a temperature-controlled environment at 24±2°C with 12-hour light and dark cycles. The investigation lasted for 12 weeks. Twenty-eight mature male Sprague-Dawley rats weighing 250±5 grams were employed. Rats were randomly divided into four groups, each consisting of 7 rats: control, obesity, vehicle, and Tirzepatide groups. For 12 weeks, the rats in the control group received a regular pellet whereas the other groups were fed HFD (30% fat). In the last four weeks, high-fat fed animals were 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 group.

COLLECTION OF BLOOD AND TISSUE SAMPLES

Ketamine and xylazine 75 mg/kg were used to euthanize the animals, and then they were sacrificed after collecting the blood samples. A midline incision was performed to access the liver then the tissue was kept at -80°C. On the analysis day, the liver was homogenized in a fresh PBS and ELISA approach was performed.

MEASUREMENT OF BODY WEIGHT

Throughout the 12-week investigation, animal weights were measured and recorded once weekly using an animal balance.

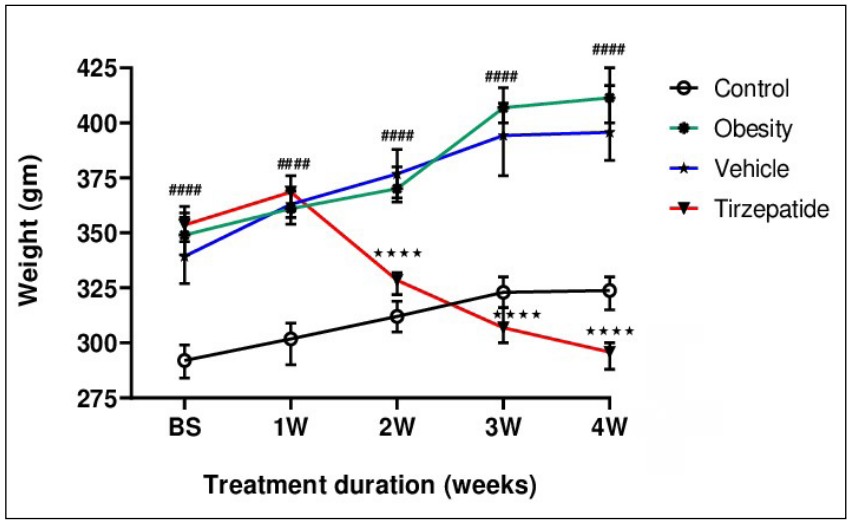

Fig. 1. Effect of tirzepatide on body weight in HFD-fed rats. ****p <0.0001. ####p <0.0001.

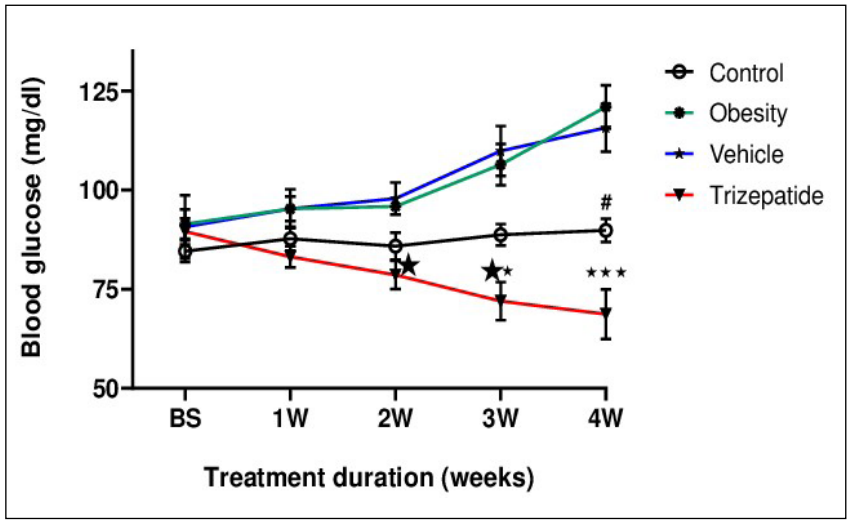

Fig. 2. Effect of tirzepatide on fasting blood glucose in HFD-fed rats. ***p<0.001. #p<0.05.

MEASUREMENT OF FASTING BLOOD GLUCOSE (FBG)

After the completion of eight weeks of HFD, fasting blood glucose was estimated once weekly using a glucometer once weekly throughout the 4-week treatment period.

MEASUREMENT OF INSULIN, LIPID PROFILE AND LIVER FUNCTION TESTS

Blood samples were drawn from rats under anaesthesia via heart puncture using a 5 cm syringe using a gel tube. Blood samples were centrifuged at 3000 rpm for 15 minutes. Chemical analyzer was employed to obtain the lipid profile parameters and liver function tests. Insulin concentration was measured by ELISA sandwich technique.

MEASUREMENT OF INFLAMMATORY AND APOPTOSIS BIOMARKERS

Liver tissue samples were homogenized on ice and then used to measure TNF-α, IL-1β and caspase-3 by the ELISA sandwich technique using commercially available kits.

STATISTICAL ANALYSIS

GraphPad Prism (version 9.0.0) was used for data analysis and presentation. Data were showed as mean plus or minus the standard error of the mean (SEM). Depending on data, either one-way or two-way Analysis of Variance (ANOVA) was used followed by Tukey's multiple comparison tests. Statistical significance was set at $P<0.05$.

ETHICAL APPROVAL

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

RESULTS

EFFECT OF TIRZEPATIDE ON BODY WEIGHT

After eight weeks of HFD and before commencing the treatment (baseline), there was no significant difference between the obesity, vehicle and Tirzepatide groups, whereas the normal control group differed significantly

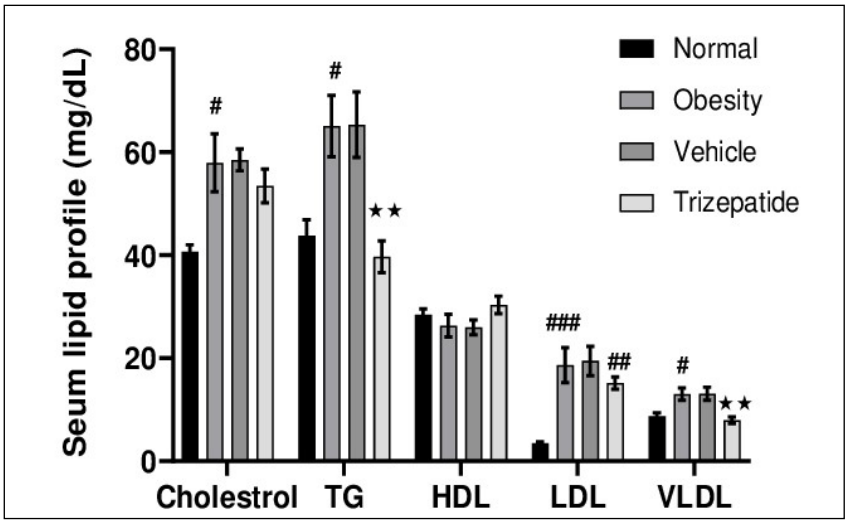

Fig. 3. Tirzepatide improves lipid profile parameters in HFD-fed rats. **p<0.01. ###p<0.001.

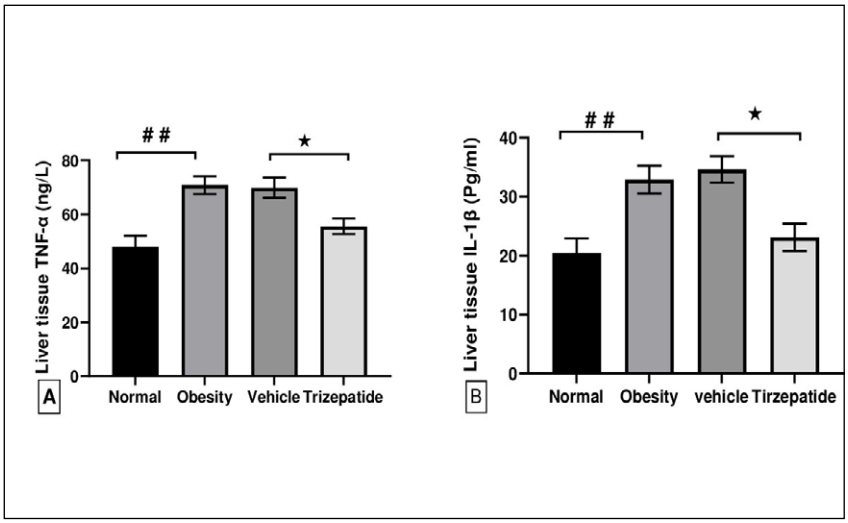

Fig. 4. A)Effect of tirzepatide on hepatic TNF-α, B) IL-1β levels in HFD-fed rats. *p<0.05. ##p<0.01.

from all the other groups p<0.0001 as shown in (Fig. 1). At the end of treatment period, the mean body weight for tirzepatide treated group decreased significantly compared to the vehicle group p<0.0001 as shown in (Fig. 1).

Rats fed HFD were treated with tirzepatide 10 nmol/kg daily for four weeks. In vehicle group, obese rats were administered tirzepatide vehicle. BS: baseline. Data are presented as mean ± SEM of seven rats in each group, p <0.0001 compared with vehicle group, p< 0.0001 versus normal group.

EFFECT OF TIRZEPATIDE ON FASTING BLOOD GLUCOSE IN HFD-FED RATS

After eight weeks of HFD, there was an 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 (Fig. 2). In contrast, the average FBG in the tirzepatide group decreased considerably compared to the vehicle group (p<0.001) (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<0.001 compared with vehicle group, p<0.05 versus normal group.

IMPACT OF TIRZEPATIDE ON SERUM INSULIN AND LIVER FUNCTION IN HFD-FED RATS

The level of serum insulin in the obesity group increased significantly compared to the normal control p<0.05, however, tirzepatide treatment reduced serum insulin level in obese animals to an insignificant level compared to normal rats as shown in (Table 1). Regarding liver functions, data showed that ALT and AST enzymes in the obesity group increased significantly compared to the normal group p<0.05, whereas obese animals treated with tirzepatide demonstrated lower level of ALT compared to vehicle group (p<0.05) as shown in (Table 1).

Table 1. Effect of tirzepatide on insulin level and liver functions in HFD-fed rats

Biochemical parameter	Groups			
	Normal	Obesity	Obesity+vehicle	Obesity+Tirzepatide
Serum insulin	0.869±0.163	1.413±0.092#	1.446±0.117	0.996±0.041*
ALT	30.57±6.963	52.01±4.819#	54.39±3.296	35.24±4.492*
AST	111.1±10.44	203.3±21.69#	212.8±26.17	161.2±18.94

Data are presented as mean ± SEM of seven rats in each group, *p<0.05 compared with vehicle group, #p<0.05 versus normal group.

Fig. 5. Effect of tirzepatide on hepatic caspase-3 level in HFD-fed rats. *p<0.05. ##p<0.05.

TIRZEPATIDE IMPROVES LIPID PROFILE PARAMETERS IN HFD-FED RATS

Feeding animals' high-fat diet resulted in significantly higher levels of lipid parameters: total cholesterol p<0.05, LDL p<0.001, triglyceride p<0.05 and VLDL p<0.05 compared to rats fed regular diet as shown in (Fig. 3). On the other hand, tirzepatide therapy lowered the TG and VLDL to an insignificant level compared to normal rats as shown in Fig. 3. LDL level remained significantly higher than normal p<0.01 even after tirzepatide administration, whereas no significant difference was observed in serum HDL measurement between all the studied groups throughout the experiment.

Rats fed HFD were treated with tirzepatide 10 nmol/kg daily for four weeks. In vehicle group, obese rats were administered tirzepatide vehicle. TG: triglyceride. Data are presented as mean ± SEM of seven rats in each group, p<0.01 compared with vehicle group, #p<0.05, p<0.001 versus Normal control.

TIRZEPATIDE ATTENUATED THE HEPATIC INFLAMMATORY RESPONSE IN HFD-FED RATS

In obese untreated animals, TNF-α and IL-1β levels were increased significantly compared to the normal group p<0.01, while after treatment with tirzepatide, the hepatic TNF-α and IL-1β content decreased significantly p<0.05 compared to vehicle-treated group as shown in (Fig. 4: A-B).

Rats fed HFD were treated with tirzepatide 10 nmole/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 compared with vehicle group, p<0.01 versus normal group.

TIRZEPATIDE ADMINISTRATION COMBATED APOPTOSIS IN HEPATIC TISSUE OF FED HFD RATS

As illustrated in (Fig. 5), high fat intake caused a marked increment in the hepatic apoptosis level compared to normal rats. Caspase-3 estimation in liver homogenate revealed a significant elevation in obesity and vehicle-treated groups compared to normal control p<0.05. In contrast, administration of tirzepatide significantly decreased hepatic caspase-3 level p<0.05 compared to vehicle treated rats.

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 compared with vehicle group, p<0.05 versus normal group.

DISCUSSION

Obesity is prevalent in both affluent and emerging countries, impacting the health of around 500 million

people globally [18]. Various behavioral, environmental, and socioeconomic factors contribute to the accumulation of fat in adipose tissue, which also influences the prevalence of obesity. GLP-1 agonists have demonstrated multiple beneficial effects in obesity; therefore, our study investigated the impact of tirzepatide on obesity-induced metabolic dysregulation and hepatic inflammatory and apoptotic status. Obesity was induced in animals by feeding rats a high-fat diet. Rats are valuable animal models in this field of research due to their extensive usage in studies on obesity to understand the underlying mechanisms, genetic factors, and potential therapies for obesity [19]. High-fat diet can lead to obesity as a result of multiple factors, including heightened calorie consumption, hormonal disparities, genetic predisposition, and environmental impacts [20]. The association between high blood glucose and obesity is due to decreased muscle glucose absorption and increased glucose synthesis in the liver by gluconeogenesis and glycogenolysis. A condition that causes insulin resistance, elevated blood sugar, weakened anabolic and anti-inflammatory capabilities, muscular protein loss, increased susceptibility to infections, and a worsened inflammatory response [21]. Previous studies have shown that when high-fat diet is present insulin becomes less efficient [22]. Insulin resistance is a defining feature of both obesity and the metabolic syndrome [23-24]. AST and ALT are two important markers of hepatocellular injury, specifically related to liver function. High fat diet induces hepatic insulin resistance, leading to increased oxidative stress and lipid peroxidation. In animal model of nonalcoholic fatty liver disease, feeding animals' high fat diet resulted in significantly higher levels of liver enzymes, such as AST and ALT [25]. The elevated TNF-α and IL-1β content in rat liver might be attributed to high fat intake. Consuming a diet high in lipids is linked to elevated levels of leptin in the bloodstream. Adipocytes, which are primarily responsible for producing leptin, also create other mediators, particularly inflammatory ones like TNF-α and IL-1β [26]. Leptin additionally affects the immune system by promoting the generation and movement of white blood cells in the bone marrow. Additionally, it enhances the synthesis of pro-inflammatory cytokines and promotes the attachment and engulfment of macrophages, while also stimulating the growth of T lymphocytes. Recent research has indicated that obesity leads to a reduction in blood flow to adipose tissue, resulting in a condition called hypoxia. This lack of oxygen triggers an inflammatory response [27]. Adipose tissue functions as an endocrine organ, releasing chemicals such as TNF-α. These factors can disrupt food consumption and the body's nutrient balance. Obesity upsets the balance by causing insulin resistance and increases the proinflammatory factors, such as TNF-α. Insulin primarily decreases lipolysis in adipose tissue. This entails the hydrolysis of triglycerides into glycerol and free fatty acids to produce energy. This process reduces the concentration of fatty acids in the blood and promotes the production of fatty acids and triacylglycerols in the body's tissues. It also enhances the absorption of triglycerides from the bloodstream into adipose tissue, leading to an increase in fat storage in fat cells when there is an excess of fat in the body, and it triggers inflammatory processes [28]. HFD stimulates the NLRP3 inflammasome via the AMPK-autophagy-ROS signaling pathway, while ceramides, which are metabolites of fatty acids, can activate NLRP3-Caspase-1 and release IL-1β in macrophages [29-30]. Additionally, it is plausible that other lipid constituents in HFD can trigger the activation of inflammasomes and the generation of IL-1 [31]. In a dietary model of obesity, adipose tissue triggers two main pathways for apoptosis, the extrinsic one which is regulated by death receptors on the cell surface, and the intrinsic one which is activated via mitochondrial pathway. Stopping these pathways stops adipocytes from dying and protects against macrophages getting into adipose tissue, liver steatosis, and insulin resistance [32-33]. Tirzepatide is a novel hypoglycemic medication that functions as a dual antagonist of the GIP-1 and GIP receptors. Tirzepatide therapy has shown significant weight reduction in overweight and obese individuals [34]. The GLP-1/GIP dual receptor agonists demonstrated superior weight loss compared to GLP-1RA alone; however, prolonged use of GIPRA does not lead to a reduction in body weight [35]. Tirzepatide administration leads to appetite suppression and increased energy expenditure, increasing concentrations of GIP. The combined actions of GIP and GLP-1 receptors may occur at the central nervous system level. When GLP-1 and GIP were given together to people with anorexia nervosa, their POMC genes were turned up. This led to a decrease in appetite and food consumption [36-37]. Tirzepatide activates GLP-1 receptors, which stimulate insulin secretion in response to glucose, suppresses glucagon release, and reduces the speed at which the stomach empties. Consequently, it generates hypoglycemic effects that are similar to those of selective GLP-1 agonists. On the other hand, it improves the ability of islet β cells to respond to GIP, enabling GIP to contribute to the stimulation of early insulin release and the improvement of insulin sensitivity. This results in a more effective and uniform decrease in blood glucose levels [38-39]. Both in vivo and in vitro investigations have demonstrated that GLP-1 in pancreatic beta cells

promotes the production of insulin. GLP-1 not only increases insulin production but also lowers glucose levels by slowing down stomach emptying, improving the body's response to insulin, and reducing glucagon release. These actions can lead to a decrease in the generation of glucose by the liver [40]. Therefore, Tirzepatide treatment has shown significant improvements in biomarkers related to β-cell activity, insulin sensitivity, glycemic control, and body weight reduction. The benefits of simultaneous GLP-1R agonism in lowering glucose may quickly restore GIP sensitivity, making the benefits of lowering glucose even better. Tirzepatide doses resulted in a notable decrease in biomarkers linked to non-alcoholic steatohepatitis (NASH), a condition stemming from obesity. Multiple investigations evaluated the effects of tirzepatide on AST and ALT enzyme activity, as well as adiponectin levels. Tirzepatide therapy significantly decreased ALT levels. GLP-1 agonists have strong inhibitory effects on indicators of oxidative stress after delivery, whereas treatment with GLP-1 agonists markedly increased the antioxidative indicators. Oxidative stress triggers degenerative processes, such as inflammatory and apoptotic signals. Previous evidence has shown that GLP-1 counteracts the increment in apoptotic cells that occurs due to chronic hyperglycemia and inhibits caspase-3 activity in pancreatic β-cells. The administration of GLP-1 considerably reduced the release of TNF-α and IL-1β decreased the number of macrophages infiltrating the body and the number of inflammatory cytokines that macrophages secrete, such as TNF-β and IL-1β.

CONCLUSIONS

The findings of this study suggest that consumption of high-fat diet causes metabolic dysregulations manifested by higher body weight, blood glucose, insulin level and worsened serum lipids. However, tirzepatide administration mitigates these metabolic dysfunctions. Moreover, treating obese animals with tirzepatide ameliorates the inflammatory and apoptotic responses in hepatic tissue triggered by HFD.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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