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Role of Gemfibrozil in Hyperlipidemia: A Focus on Liver Function, Tissue Integrity and Lipid Regulatory markers in Rats

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ABSTRACT:

Background:

Gemfibrozil is a strong and trusted medicine used to lower cholesterol and triglyceride levels in the body. High levels of these can lead to serious heart and brain problems. This study looks at the possible protective effects of Gemfibrozil in treating liver problems in rats with high cholesterol. The research investigates different physical indicators and analyzes liver tissue using a microscope to assess the drug's efficacy.

Subject & Methods:

In this study, 30 male rats were utilized. Six rats were assigned to each of the five groups formed by dividing the animals. The study includes five groups of rats. The first one is the control group. The second group has rats that were made to have high fat levels and they were given a high-fat diet without any treatment. The third group includes rats with high fat levels in their blood that were given Gemfibrozil at a dose of 600 mg/kg/day. The fourth group consists of rats with high fats in their blood that were given Gemfibrozil at a dose of 1200 mg/kg/day. Finally, the fifth group has rats with high fat levels that were given Gemfibrozil in a dose of 1500 mg/kg/day.

Results:

The analysis revealed notable differences ($P < 0.05$) in the average values of lipid profile components (TC, TG, HDL and LDL), liver enzymes (AST,ALT and ALP), and FGF21 between group 2 (high fat diet) and the other experimental groups when compared with control group1. These variations were found to be statistically significant. Following the administration of the medication gemfibrozil, which helps to restore normal liver function, these tissue alterations totally improve as it clearly seen in the results of liver function test, FGF21 and adiponectin levels.

In Conclusion:

The liver of rats experiencing high blood fat levels is shielded by gemfibrozil through its ability to reduce cholesterol and triglycerides. This contributes to avoiding liver injury and minimizing inflammation.

INTRODUCTION

The condition known as hyperlipidemia is marked by high blood fat levels. This can happen because of problems with how the body processes fats, often due to bad eating habits, being overweight, or genetic issues like family high cholesterol or diabetes (Natesan & Kim, 2021). Those with significant amounts of fat in their blood are more prone to experiencing heart disease. Because of this, having high levels of fats in the blood is an important risk factor for predicting atherosclerosis and coronary artery disease (Alloubani *et al.,* 2021). Changes in lipid parameters associated with atherosclerosis include elevated triglycerides

(TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C). Because elevated blood cholesterol levels play a role in the development of atherosclerosis (Grundy *et al.,* 2019). Gemfibrozil is a fibrate medication that has FDA approval and is frequently administered to treat dyslipidemia. The primary mechanism of fibrates is thought to be as PPAR-α receptor agonists; nevertheless, it has recently been discovered that Gemfibrozil possesses anti-inflammatory and antioxidant qualities in a variety of contexts (Nikravesh *et al.,* 2018). The nuclear receptor (peroxisome proliferator-activated receptor α (PPARα)) facilitates the body's reaction to fibrates and oversees genes essential for fat metabolism and lipoprotein regulation (Montaigne *et al.,* 2021). Fibrates raise the amount of HDL cholesterol while causing a slight drop in plasma (TG) concentration (Hammond & Finlay, 2017). Along with plasma very low density lipoprotein (VLDL) and TG, gemfibrozil also reduces (LDL) cholesterol, but less dramatically. Over the course of long-term therapy, gemfibrozil's impact on LDL increases (Gabani *et al.,* 2023). Fibroblast growth factor (FGF) 21 is mostly generated in the liver and belongs to the endocrine FGF subfamily. From a physiological perspective, FGF21 is essential for controlling the metabolic reactions to fasting and famine because it promotes fatty acid oxidation and ketogenesis and causes growth hormone resistance (Lin *et al.,* 2015). Recombinant FGF21 has been shown to pharmacologically treat obesity and related metabolic disorders in nonhuman primates and rodents. These conditions include fatty liver disease, insulin resistance, hyperglycemia, dyslipidemia, and adiposity reduction (Geng *et al.,* 2020). One of the primary adipokines that are produced solely by adipose tissues is adiponectin, which has anti-inflammatory and insulin-sensitizing qualities as well as controls the metabolism of fat and glucose (Li *et al.,* 2020). Obesity, type 2 diabetes, problems of lipoprotein metabolism, and cardiovascular illnesses are all associated with low plasma adiponectin levels (Xia *et al.,* 2018). It is additionally recognized that adiponectin levels fluctuate with age, and it has been clinically demonstrated that long-lived individuals and some of their offspring have elevated adiponectin levels(Li *et al.,* 2021). This study sought to assess the possible therapeutic benefit of gemfibrozil on the livers of rats that had hyperlipidemia at doses comparable to or greater than those used by humans, as well as any potential interactions with certain biochemical markers.

MATERIALS & METHODS

1. Experimental design:

1.1. Induction of hyperlipidemia in male rats:

Group I (n= 6): serving as the control group, which is fed a regular meal and given distilled water for two months.
Group II (n= 24): given a high-fat diet containing animal fat over a period of two months in order to cause hyperlipidemia.

1.2. Gemfibrozil treatment groups:

In order to examine the effects of therapy over a two-month period, the animals from the first phase were subsequently subdivided into three subgroups:

G1 (n= 6): administered 2 ml of regular saline daily for two months, acting as a control negative.

G2 (n= 6): acted as a positive control and were fed an animal-fat diet for two months without receiving any therapy.

G3 (n= 6): administered orally for two months using 600 mg of Gemfibrozil daily, dissolved in two milliliters of N.S.

G4 (n= 6): administered orally daily for two months at a dose of 1200 mg of Gemfibrozil dissolved in 2 milliliters of N.S.

G5 (n= 6): administered orally daily for two months at a dose of 1500 mg of Gemfibrozil dissolved in 2 milliliters of N.S.

2. Study animals:

The study animals were sourced from the University of Al-Naharin, animal facility. Thirty male albino rats weighing between 200 to 250 grams were kept in a dedicated room with a temperature of 25°C and 12 hours of natural light. The animals were given commercial pellets and unlimited access to tap water.

3. Drug Dose Preparation:

The trade name of Gemfibrozil (Lopid, *Pfizer*) was purchased from a private pharmacy in Baghdad city for study purposes. The formula animal weight (in kg) human dose was used to determine the dosage for the animal trials based on the body weight (Jacob *et al.,* 2022).

4. Blood and tissue sample collection:

In order to measure biochemical markers, blood samples were extracted by cardiac puncture under ether anesthesia at the conclusion of the therapy period. Cervical amputation was the next method used to kill the animals. Blood then transferred to gel tubes to aid in clotting. Following three minutes of centrifugation at 3500 rpm, the clotted blood was extracted to extract serum for the biochemical and physiological analysis.

5. Physiological and Biochemical measurements:

5.1. Serum level lipid profile:

A spectrophotometer was used for assessing the serum level lipid profile (TC, TG, HDL, and LDL), and the Randox company (Randox labs Ltd; UK) provided the reagents.

5.2. Serum liver enzymes:

Diagnostic RANDOX kits (Randox labs Ltd; UK) were used to measure the activity of the enzymes aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP). A spectrophotometer was used to evaluate the calorimetric activity of these two enzymes at 546 nm.

5.3. Measurements of Fibroblast growth factor 21 and Adiponectin in the serum:

The levels of FGF21 and Adiponectin in the serum were measured using the enzyme linked immunosorbent assay (ELISA) with kits manufactured by Bioassay Technology Laboratory.

6. Statistical Analysis:

The findings were shown as means ± standard error (mean ± SE). The GraphPad Prism software, version 9 for Windows, was used to analyze the data. With Duncan's post-test, one-way analysis of variance was used to compare the means of the various groups to the control group; $p<0.05$ was deemed significant.

RESULTS & DISCUSSION

1. Estimation of animal's body weight:

The findings displayed in table (1) demonstrated that the animals gained body weight over the research period and that the second group's mean (positive control) increased significantly ($P<0.05$). Once *Gemfibrizol* dosages were administered daily for two months, the findings similarly showed a drastic drop ($P <0.05$) in the mean body weight.

Table (1): mean of animal's body weight during study periods.

Animal groups	First period (gm) Mean ±SE	Second period (gm) Mean ±SE
G1 (negative control)	250.3 ± 2.46a	265.87 ± 1.06a
G2 (positive control)	239.4 ± 0.98b	314.40 ± 2.20b
G3 (gemfibrozil 600mg/day)	250.2 ± 2.89c	270.94 ± 1.05c
G4 (gemfibrozil 1200mg/day)	249.7 ± 2.79a	260.72 ± 1.09a
G5 (gemfibrozil 1500mg/day)	245.8 ± 1.25a	250.30 ± 0.49a

SE: standard error; **a, b, c:** different letters indicate the presence of a significantly differences ($P < 0.05$).

2. Biochemical study of animal groups:

2.1. Estimation of Lipid Profiles for studied groups:

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Table (2) revealed that the mean TC, TG, and LDL levels in the positive control group were significantly higher (P=<0.05) than those in the control negative and other treatment groups. substantial decline (P= <0.05) with time in those receiving *Gemfibrizol* dosages. Moreover, a noteworthy decline was seen in the positive control group when compared to group I and other treatment groups.

Table (2): mean of lipid profiles among studied groups.

Animal groups	Lipid profiles parameters			
	TC mean ±SE	**TG** mean ±SE	**HDL** mean ±SE	**LDL** mean ±SE
G1	± 7.05a 155.3	46.14 ± 0.73a	± 0.79a 45.2	± 4.01a 99.5
G2	± 2.4b 197.07	± 3.8b 75.5	± 2.6b 36.5	± 5.6c 144.5
G3	± 1.4c 169.18	± 1.2c 59.6	± 2.3c 39.02	± 9.9b 121.8
G4	± 7.17a 160.9	± 1.6a 50.4	± 1.4ba 43.3	± 2.8b 109.06
G5	± 5.02a 157.3	± 4.3a 48.09	± 4.19ca 45.4	± 3.8a 103.9

SE: standard error**; TC:** total cholesterol**; TG:** triglycerides**; HDL:** high density lipoprotein**; LDL:** low density lipoprotein**; a, b, c:** different letters indicate the presence of a significantly differences (P<0.05).

2.2. Liver Enzymes level:

Table 3 shows that the mean liver enzyme (AST, ALT and ALP) activities in the G2 were higher (P <0.05) than in the G1. In addition, the enzymes activities in G3 were significantly higher than those of G4 and G5, which tend to have lower liver enzyme means following *Gemfibrizol* treatment.

Table (3): means of liver enzymes among studied animal groups.

Animal groups	Liver enzyme levels		
	AST mean ±SE	**ALT** mean ±SE	**ALP** mean ±SE
G1 (-ve control)	123.6± 9.7a	± 1.4a 38.05	95.9± 1.8a
G2 (+ve control)	192.2± 2.6 a	± 3.1c 77.9	293.7± 4.03b
G3 (gemfibrozil 600mg/day)	± 8.07b 166.6	± 2.3b 60.5	160.3± 2.01c
G4 (gemfibrozil 1200mg/day)	133.4± 3.4 a	± 2.14a 40.5	125.7± 3.01a
G5 (gemfibrozil 1500mg/day)	120.06± 5.4a	± 2.8a 39.10	113.2± 1.01a

SE: standard error; **a, b, c:**different letters indicate the presence of a significantly differences (P<0.05).

3. Physiological parameters:

3.1. Serum level of Fibroblast Growth Factor 21 (FGF21):

When comparing the second and third groups to the first, Table (4) revealed a substantial increase (P <0.001) in the amount of fibroblast growth factor 21. It was also observed that the concentration of FGF21 in G4 and G5 were significantly decreased than in other groups. (Table 4 ; Figure 1).

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Table (4): serum level FGF21 among studied groups.

Animal groups	Fibroblast Growth Factor 21 (FGF21) (pg/ml)	
	Mean	S.E
G1 (negative control)	16.45a	1.37
G2 (positive control)	142.53b	8.8
G3 (gemfibrozil 600mg/day)	35.3c	0.3
G4 (gemfibrozil 1200mg/day)	18.44a	1.5
G5 (gemfibrozil 1500mg/day)	14.64a	1.06
SE: standard error; **a, b, c:** different letters indicate the presence of a significantly differences (P < 0.05).		

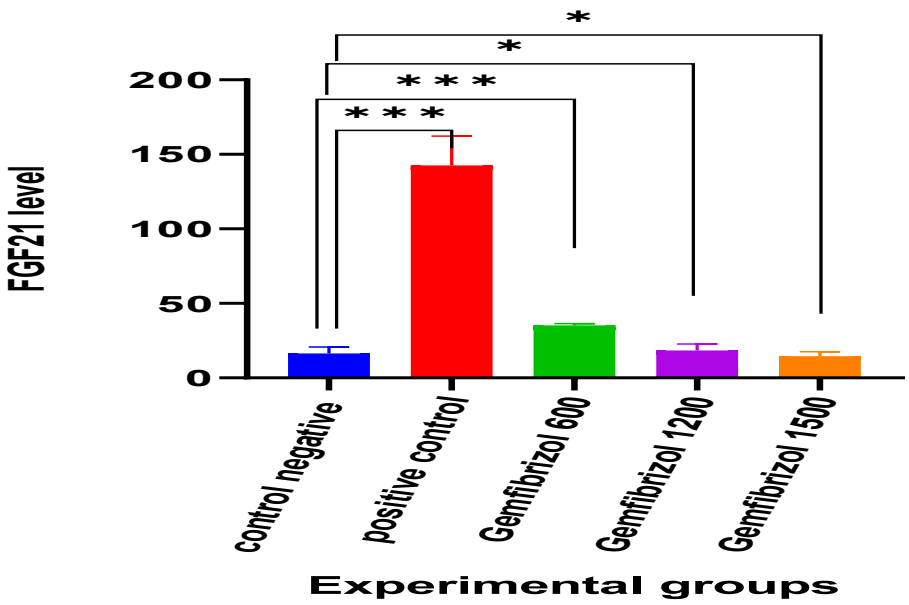

Figure (1): serum level of FGF21. The data presented as mean ± SE; N: 5, p. value <0.001 for five experimental groups.

3.2. Serum level of Adiponectin:

The mean adiponectin levels in the second and third groups were considerably higher (P <0.001) than in the negative control group, whereas the fourth and fifth groups exhibited non-significant increases compared to the first group, as shown in table (5) and figure (2).

Table (5): serum adiponectin level among studied groups.

Animal groups	Adiponectin (ng/ml)	
	Mean	S.E
G1 (negative control)	27.96a	0.44

G2 (positive control)	13.10b	1.3
G3 (gemfibrozil 600mg/day)	15.56c	0.58
G4 (gemfibrozil 1200mg/day)	25.52a	0.18
G5 (gemfibrozil 1500mg/day)	26.6a	0.65
SE: standard error; **a, b, c:** different letters indicate the presence of a significantly differences (P < 0.05).		

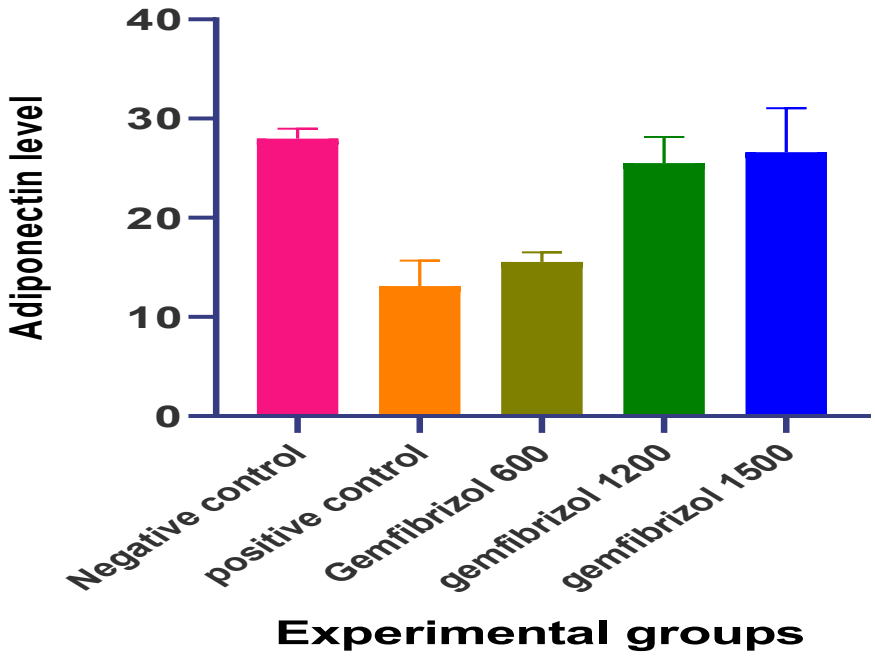

Figure (2): serum level of Adiponectin. The data presented as mean ± SE; N: 5, p. value <0.001, for five experimental groups.

DISCUSSION

The elevation in inflammation, lipidemia, hypertensive, insulin resistance and other vascular and metabolic disorders that were related to coronary threat all connected autonomously to obesity (Cercato & Fonseca, 2019). Obesity is a disorder characterized by a reduction in inflammation and an increase in body fat accumulation (Lin & Li, 2021). Furthermore, the current results showed that the mean weight of the animals receiving 1500 mg/day was much lower than that of the animals receiving other medication doses, and that the animals' mean weight growth drastically dropped as the dosages of therapy increased. The current study's findings, which are consistent with those of Cortés et al. (2014) and Marques et al. (2016), which demonstrate a gradual increase in body weight in rats fed a high-fat diet over the course of the study, revealed a significant increase in the weight of the rats treated with high-fat food compared to the control group. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDLC), and high-density lipoprotein-cholesterol (HDL-C) levels are all elevated in lipid metabolism disease (hyperlipidemia). Hyperlipidemia is the primary cause of coronary heart disease and other cardiovascular disorders (Munshi et al., 2014). When compared to the control group, there was a significant increase in TC, TG, LDL-C, and VLDL-C, while HDL-C decreased as previously reported, suggesting that rats fed high-fat foods over an extended period of time may develop these abnormalities (Nour et al., 2021). The current study's findings showed that groups treated with gemfibrozil had statistically significant lower levels of LDL, triglycerides, and total cholesterol, while HDL levels significantly increased. This

finding agrees with previous research (Mohanalakshmi *et al.,* 2021). Furthermore, the results of liver enzyme analysis showed that there were a significant reduction in the level of AST & ALT alongside with restoring of normal liver tissue architecture in treated groups obviously from hyperlipidemic group. A study indicated to the defending role of gemfibrozil in contradiction of acetaminophen-induced acute hepatic toxicity (Nikravesh *et al.,* 2018). The liver plays a key role in the regulating the fat absorption, creation, and dissemination (Alves-Bezerra & Cohen, 2017). The existence of steatosis or steatohepatitis (steatosis, hepatocyte hypertrophy, and inflammation) associated with increase accumulation of hepatic triglycerides due to inequality of these processes (Heeren & Scheja, 2021). A positive correlation was demonstrated between high-fat diet and hepatic steatosis and elevation in hepatic saturated fatty acids which corresponds with acute liver necrosis that ultimately leads to rises in the existence of liver enzymes (AST, ALT &ALP) into blood stream (Zhang *et al.,*2014). Research by Szudzik *et al.,* (2024), revealed that rats consuming a high-fat diet for a duration of twelve weeks showed increased AST and ALT levels. This was associated with the accumulation of fat in their bodies. This might explain why extra fat builds up in the liver, causing fatty liver disease. This situation arises when there is an overload of fat produced in the liver while insufficient fat is expelled. As a result, certain fats accumulate, leading to higher levels of undesirable fats (LDL and VLDL) and a decrease in favorable fat (HDL) (Gowda *et al.,* 2023). Gemfibrozil aids in decreasing triglyceride and VLDL levels, which helps prevent the accumulation of fat in liver cells. This prevents damage to the liver caused by lipid-induced hepatotoxicity (Zhang *et al.,* 2019). The results of current study indicated to presence of significant elevation in the level of fibroblast growth factor 21among positive control when compared with negative control and treated groups. Although the liver is the primary site of FGF21 synthesis, adipose tissue is both a potential repository for FGF21 and a key target organ for FGF21 activity (Su *et al.,* 2019). Research has indicated that adipose stem cell-derived FGF21 has significant promise in the management of liver lesions. The scientists gave liver fibrosis-affected mice adipose stem cells that secrete FGF21 (Li *et al.,* 2024). In mice that were made obese by excessive fat, FGF21 controlled oxygen intake, muscular energy expenditure, and hepatic lipid metabolism in a dose-dependent manner. Increased circulating FGF21 alters the tendency of fat storage while also causing a considerable increase in oxygen intake and physical energy expended (Portincasa *et al.,* 2024). According to a clinical study conducted on obese individuals with type 2 diabetes mellitus, long-term treatment of a long-acting version of FGF21 results in a significant increase in adiponectin and a clear decrease in total and LDL cholesterol, but it has no impact on hyperglycemia (Lin *et al.,* 2015). According to Fisher *et al.,* (2010), mice fed a high-fat/high-sucrose diet for 22 weeks develop FGF21 sensitivity in their liver and white adipose tissues. Furthermore, studies have demonstrated that 12 weeks after being fed a high-fat diet, obese rats' hearts exhibited FGF21 resistance (Tanajak, 2017). Research indicates that adiponectin synthesis is suppressed by hyperlipidemia in obesity and diabetes, which leads to diabetic vascular damage (Baltieri *et al.,* 2018). Nonetheless, there is growing evidence that during the early stages of high-fat diet-induced diabetes, plasma adiponectin levels are up but biological activity is decreased, indicating that diminished adiponectin function may be a novel mechanism influencing cardiovascular etiology (Zhang *et al.,* 2022). Fibrate-induced FGF21, such as gemfibrozil, acts as a PPARα-dependent endocrine signal and raises adiponectin levels by activating PPARα, which is in line with the current study's findings (Goto *et al.,* 2017). According to studies conducted with animal models, Gemfibrozil effectively protects the liver by reducing tissue scarring and inflammation. When the liver is injured or under stress from disorders like excessive blood fat and infections, it aids the tiny blood flow in the liver, preventing issues with obtaining adequate oxygen (Kuebart *et al.,* 2023).

CONCLUSION

The research reveals that increased fat concentrations in the bloodstream can negatively affect liver tissue and lead to higher levels of liver enzymes, FGF21 and lowest level of adiponectin. Gemfibrozil is very effective in treating high cholesterol and helps prevent liver problems. Further research is necessary to understand the molecular mechanisms behind these processes and to develop effective treatments that require lower doses and less frequent administration.

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