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Analysis of Some Physiological and Histological Effects of Repaglinide on Liver and Lung Tissues in rats

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ABSTRACT

This sub-chronic toxicological study explored the potential adverse effects of repaglinide, an antidiabetic medication, on liver and lung function in rats following 30 days of repeated oral exposure. Male Wistar rats were assigned to three groups: a control group, a group receiving repaglinide at the therapeutic dose of 0.7 mg/kg, and a group receiving double the therapeutic dose of 1.4 1.4mg/kg. Blood glucose levels, liver enzymes, and various hematological parameters were measured, and histological examinations of liver and lung tissues were conducted. The study showed that both repaglinide-treated groups had higher levels of liver enzymes ($p < 0.05$) and changes in hematological parameters, such as higher erythrocytes, hemoglobin, hematocrit, and white blood cells, and lower levels of platelets, compared to the control group. In the lungs of the rats that were treated, histopathological analysis showed that inflammatory cells had moved in, the central vein was swollen, and the walls of the air sacs were getting thicker. These results suggest that repaglinide treatment, especially at higher doses, may lead to adverse effects on liver and lung function in rats, highlighting the need for careful monitoring during its therapeutic use.

تحليل بعض التأثيرات الفسيولوجية والنسيجية لعقار ريباجلينيد على أنسجة الكبد والرئة في الفئران

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الخلاصة
اظهرت هذه الدراسة التأثيرات السلبية المحتملة لعقار ريباجلينيد، وهو دواء مضاد للسكري، على وظائف الكبد والرئة في الجرذان. تم تقسيم ذكور جرذان ويستار إلى ثلاث مجموعات: مجموعة ضابطة، ومجموعة تلقت ريباجلينيد بالجرعة العلاجية (0.7 ملغم/كغم)، ومجموعة تلقت ضعف الجرعة العلاجية (1.4 ملغم/كغم). تم قياس مستويات سكر الدم، وإنزيمات الكبد، والمعايير الدموية المختلفة، إلى جانب إجراء فحوصات نسيجية لأنسجة الكبد والرئة. أظهرت النتائج ارتفاعًا ملحوظًا في إنزيمات الكبد ($p < 0.05$)، بالإضافة إلى تغيرات في المعايير الدموية، حيث لوحظ ارتفاع في عدد كريات الدم الحمراء، والهيموجلوبين، والهيماتوكريت، وكريات الدم البيضاء، وانخفاض في الصفائح الدموية لدى المجموعات المعالجة مقارنةً بالمجموعة الضابطة. كما أظهر التحليل النسيجي تسلل الخلايا الالتهابية، واحتقان الوريد المركزي في الكبد، وزيادة سماكة جدران الحويصلات الهوائية في الرئة لدى الجرذان المعالجة. تشير هذه النتائج إلى أن علاج ريباجلينيد، خاصةً بجرعات مرتفعة، قد يؤدي إلى تأثيرات سلبية على وظائف الكبد والرئة، مما يؤكد الحاجة إلى المراقبة الدقيقة عند استخدامه علاجيًا.

الكلمات المفتاحية: ريباجلينيد، نقص السكر في الدم، إنزيمات الكبد، نسيج الكبد، نسيج الرئة.

INTRODUCTION

Many studies have been concerned with diabetes, meaning the presence of hyperglycemia, while the study of hypoglycemia and its physiological and histological effects has been limited. Hypoglycemia may increase inflammatory cytokines and white blood cell counts following hypoglycemia. This shows that there is a link between hypoglycemia and the occurrence of infections. This makes the cause of death increase because there is a link between hypoglycemia and increased mortality, and episodes of hypoglycemia may not be recognised, as self-reporting of hypoglycemia is often inaccurate. The presence of oxidative stress and increased inflammation is the primary mechanism linking hypoglycemia to the resulting diseases, including heart disease (Joy et al., 2015). We use antidiabetic drugs to lower blood sugar levels. These are biguanides, which are drugs used to treat type 2 diabetes., meglitinides, sulfonylureas, and thiazolidinediones. To regulate blood sugar, these drugs are taken orally either alone or in combination with other classes (Chukwunonso Obi et al., 2016).

Type 2 diabetes can now be treated with repaglinide, a novel postprandial glucose-regulating medication (Marbury et al., 2000). Repaglinide lowers glucose levels in patients with type 2 diabetes during the fasting phase. As it works to control blood sugar levels, repaglinide treatment acts on pancreatic beta cells by stimulating them to secrete insulin after closing potassium ATP channels (Ding et al., 2019). Compared with sulfonylurea treatment, repaglinide is believed to reduce the incidence of hypoglycemia because its action secretes insulin only in hyperglycemia. In the case of sulfonylureas, it has been shown that it works to increase insulin secretion even if there is a noticeable decrease in blood glucose (Omori et al., 201-). Many studies have also shown that repaglinide lowers the risk of complications related to diabetes. For example, it lowers oxidative stress, which protects both large and small blood vessels from damage and is a major cause of vascular dysfunction (Tankova et al., 2003). One of the medications that has a relatively short half-life—roughly an hour—is repaglinide. It has a weak absorption from the upper gut and a bioavailability of about 50%. Following an oral or intravenous injection, oxidative transformation completely degrades it, leading to its conversion into glucuronic acid (Vijayan et

al. 2011). Researchers have shown that giving repaglinide to people with diabetic nephropathy raises the activity of antioxidants like superoxide dismutase and lowers the levels of lipid hydroperoxide (LPO) in their kidneys (Li et al., 2016). Repaglinide treatment is also one of the treatments with antioxidant effects resulting from high blood sugar. What may make it more helpful in treating type 2 diabetes is that it is essential in directly forming antioxidant properties and has excellent benefits at the therapeutic level (Gumieniczek 2005). Although repaglinide's therapeutic range is considered relatively safe based on its reported LD_{50} in rats (~1050 mg/kg), understanding its potential for sub-lethal organ toxicity at clinically relevant doses is crucial, especially in chronic use scenarios.

The phenomenon of high blood sugar, as well as hypoglycemia, is an undesirable condition for the body. Therefore, studying the characteristics of drug interactions is essential in the treatment of diabetes because it is one of the metabolic disorders that requires treatment for long periods and is a critical condition for maintaining the expected level of sugar in the blood (Harb et al., 2021), making it important to investigate the potential sub-chronic toxicological effects of antidiabetic agents like repaglinide.

MATERIALS AND METHODS

The materials and methods section should contain sufficient detail so that all procedures can be repeated. It may be divided into headed subsections if several methods are described.

Animals.

Fifteen male albino rats were used in this investigation. They weighed between 185 and 200 grams and ranged in age from two and a half to three months. The College of Veterinary Medicine, Tikrit University, Iraq kept the animals (albino rats) in good laboratory conditions. The ideal temperature was between 22 and 24ºC, the cage was kept clean, there was adequate ventilation, the lighting was about as excellent as it would be outside, and the animals were fed regular food for the experiment.

Determination of Repaglinide Dose in Rats.

The dosage was determined based on clinical procedures in humans, where repaglinide is commonly used to treat diabetes. Nair and Jacob (2016) described the use of body surface area normalization and a correction factor to calculate appropriate therapeutic dosages for rats. The results led to the establishment of a standard dose of 0.7 mg/kg body weight and the evaluation of an increased dose of 1.4 mg/kg body weight.

Sub-chronic Toxicological Study Design.

In alignment with sub-chronic toxicology protocols, the study was designed to evaluate the effects of repeated daily oral exposure to repaglinide over a 30-day period. Following a two-week acclimatization period, the 15 albino rats were randomly divided into three groups (n = 5 per group), ensuring weight parity across groups. The administration protocol was as follows:

- **Group 1 (G1: Control)**: Received distilled water orally for 30 consecutive days.
- **Group 2 (G2: Therapeutic Dose)**: Received repaglinide at a therapeutic dose of 0.7 mg/kg body weight orally for 30 days.
- **Group 3 (G3: Double Dose)**: Received a high dose of repaglinide (1.4 mg/kg body weight) orally for 30 days.

This experimental design simulates repeated human exposure to repaglinide at therapeutic and supra-therapeutic levels, allowing evaluation of potential sub-chronic toxicological effects on liver and lung function.

Sample collection.

At the end of the 30-day experimental period, the animals were anesthetized prior to blood and tissue collection. Anesthesia was administered intraperitoneally using ketamine at a dose of 75 mg/kg and xylazine at a dose of 10 mg/kg. A sterile syringe (1 mL; Terumo®, Japan) was used for injection. Deep anesthesia was confirmed by the loss of pedal withdrawal reflex. Blood samples were obtained via cardiac puncture using the cardiac stab method. The collected blood was divided into two portions: the first portion was placed in EDTA-containing tubes for hematological analysis, while the second portion was allowed to clot, then centrifuged at 3000 rpm for 10 minutes to obtain serum for biochemical assays.

Histological preparation.

After obtaining liver and lung tissues, they were cleaned with water, and then the tissue samples were fixed for 24 hours using 10% formalin. Increasing concentrations of alcohol (70%, 80%, 95%, 100%, and 100%) were used to dehydrate the samples. The samples were then purified with xylene and then mixed with paraffin. Sections of paraffin-embedded tissue were cut with a microtome, and the sections were colored with eosin and hematoxylin for histological purposes. This study examines the samples under an optical microscope with 400X magnification after staining them (Feldman and Wolfe 2014).

Statistical Analysis

The data were analysed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA). All results are expressed as mean ± standard deviation (SD). Differences between the control and treatment groups were assessed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A p-value less than 0.05 was considered statistically significant. All graphs and figures were generated using GraphPad Prism version 9.0 for visual representation of the experimental data and comparative analysis.

RESULT AND DISCUSSION

The present investigation examined the impact of repaglinide, an antidiabetic medication, on hepatic and pulmonary function in rats. Figures 1 and 2 illustrate the physiological and metabolic alterations found. Giving repaglinide in both therapeutic and double doses caused a statistically significant ($P < 0.05$) drop in blood sugar levels compared to the control group. This proved that the drug was effective at lowering blood sugar. However, this low-blood sugar effect was linked to a significant ($P < 0.05$) rise in the liver enzymes AST and ALT, which suggests that the drug may be harmful to the liver.

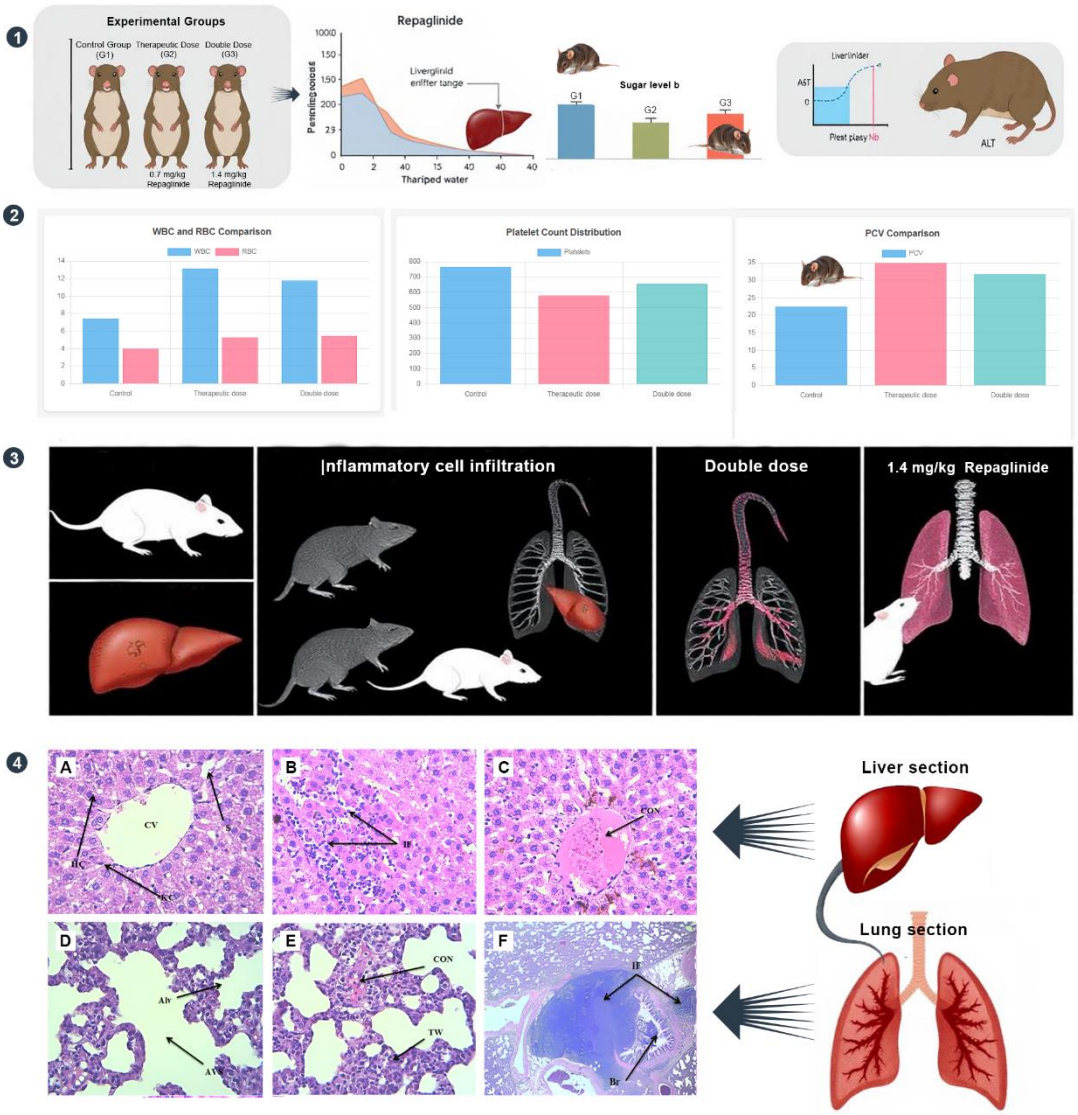

Figure 1. The effect of Repaglinide on the liver and lung tissues of male albino rats: a study of its physiological and histological effects, 1: Group experiments and biochemistry. 2: Hamo analysis. WBC, RBC, PLT, and PCV counts are compared between groups in this section. Variations suggest repaglinide-induced physiological changes. 3 and 4: Effects on Liver and Lung Histology

In Figure 1 the laboratory rats were divided into three groups: Control (G1), Therapeutic Dose (G2 – 0.7 mg/kg repaglinide), and Double Dose (G3 – 1.4 mg/kg). Additionally, biochemical study shows variations in liver enzyme levels (AST & ALT), glucose, and repaglinide concentration. Graphical depictions show liver and lung inflammatory cell infiltration. Repaglinide's histological effects are confirmed by vascular congestion, alveolar thickness, and tissue damage in the double-dose group. Microscopic Histological Analysis. Liver and lung H&E-stained slices show cellular structural alterations. Images A- C show inflammatory cell infiltration (IC), central venous congestion (CV), and hepatocyte injury. D–F illustrate the degradation of lung tissue, encompassing alveolar wall thickening (Aw), vascular congestion (CON), and bronchial

inflammation. This picture illustrates the biochemical, hematological, and histopathological effects of repaglinide on rats. All histological images in this figure were captured at 400x magnification.

The increase in liver enzymes like AST and ALT shows that hepatocellular damage and compromised hepatic integrity may have happened because of the oxidative stress that repaglinide causes. Oxidative stress happens when the production of reactive oxygen species (ROS) and the antioxidant defense system are not balanced. This causes damage to cells (Halliwell and Gutteridge, 2015). Even though repaglinide's main job is to lower blood sugar by stimulating insulin secretion, the fact that liver enzyme levels went up goes against earlier research that suggested it might have antioxidant properties (Gumieniczek, 2005; Salih Al-Khafaji and Al-Hayawi, 20224). This is supported by the histological findings in Figure 1, which show a lot of inflammatory cells, clogged central veins, and damaged liver cells, especially in the high-dose group (G3). This indicates that repaglinide has the potential to cause dose-dependent hepatotoxicity via mitochondrial dysfunction and enhanced oxidative stress mechanisms (Sies et al., 2017). Histopathology of lung tissue reveals thickening of the alveolar wall, vascular congestion, and bronchial inflammation, indicating the extraglycemic effects of repaglinide. The paradoxes among its antioxidant activity and the noted liver toxicity require additional exploration of the molecular mechanisms underlying repaglinide-induced liver stress and its chronic effect on liver function (Li et al., 2015).The hepatic enzymatic alterations and glycemic modulation induced by repaglinide administration are comprehensively presented in Figure 2.

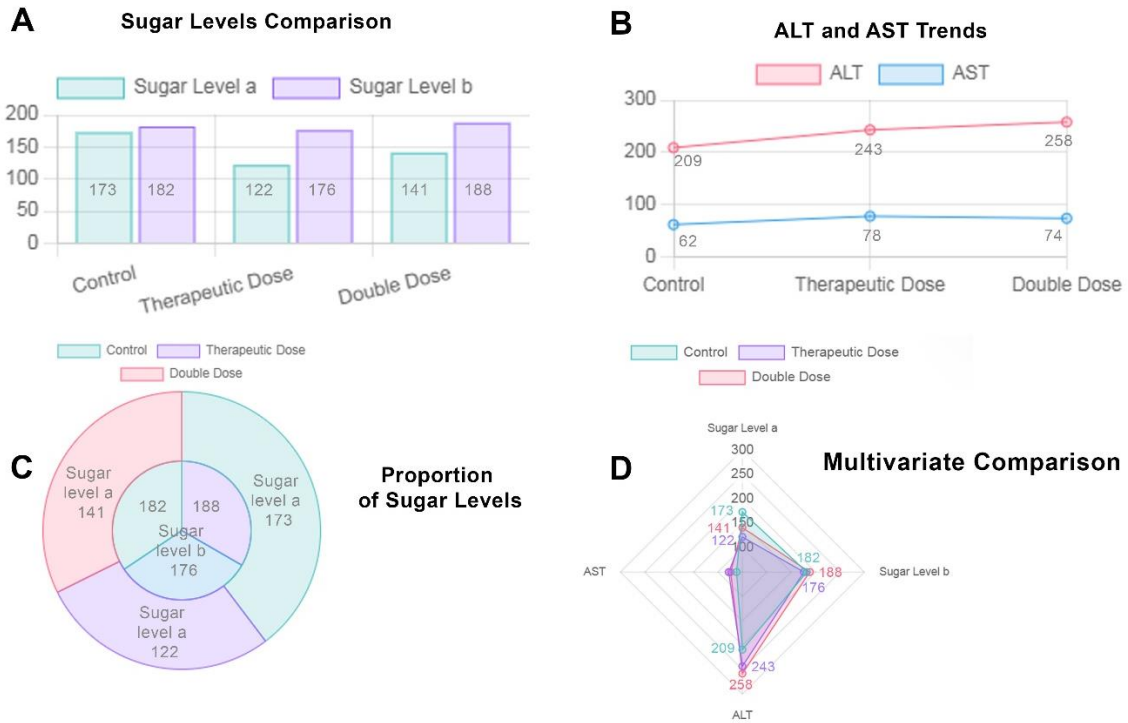

Figure 2. (A) Glucose concentration variations across experimental groups, (B) Illustrating temporal patterns in alanine aminotransferase and aspartate aminotransferase activities, (C) documenting carbohydrate metabolite concentrations, and (D) featuring a multidimensional radar visualization enabling comparative analysis of diverse biological parameters.

Figure 3 documents the extensive systemic impact of repaglinide administration on hematological indices and hepatic function markers in the experimental rodent model. The graphical representation tracks pre-intervention and post-intervention glycemic values alongside quantitative alterations in leukocyte populations, erythrocyte counts, hemoglobin concentration, thrombocyte distribution patterns, lymphocyte proportions, and hematocrit measurements. The study employs radar-type visualization methodology to integrate complete hematological profile data, encompassing white blood cell populations, red cell counts, packed cell volume measurements, hemoglobin concentrations, lymphocyte percentages, and platelet enumeration. This analytical approach facilitates a comprehensive interpretation of the physiological modifications resulting from repaglinide intervention and its consequent effects on hematopoietic parameters.

Figure 3 illustrates the effects of repaglinide on blood parameters and liver enzymes in rats, including WBC, RBC (A), hemoglobin (B), platelets (C), lymphocytes (D), and PCV (E). A combined analysis (F) summarizes these key factors

The experimental data demonstrate that repaglinide administration produces significant systemic effects, evidenced by substantial alterations in hematological markers documented in Figures 1 and 2, with statistical significance confirmed at $p<0.05$. In the groups receiving treatment and those on two doses there was a rise in the counts of white blood cells, red blood cells, packed cell volume, hemoglobin and lymphocytes, all of which were statistically significant with a p-value of less than 0.05. On the other side of things, the number of platelets dropped significantly when

matched up against the control group. The results indicate that repaglinide could lead to oxidative stress, which plays a major role in causing inflammation and the death of cells all over the body. When cells encounter too many reactive oxygen species (ROS) because of drug exposure, they can undergo harm. This damage can affect fats, proteins, and the very DNA, leading to cells not working right and dying on their own (Abood and Al Hayawi 2019; Zeng et al. 2023). When drugs cause harm to the liver, it can lead to the liver not working as it should. If this gets bad, it can cause sudden and severe liver failure (Niu et al. 2021). The presence of this toxicity is often tied to a decrease in antioxidants within cells; this situation leads to an increase in oxidative stress, damage to lipids, and problems with how mitochondria function, as pointed out by Villanueva-Paz et al. (2021) and Athersuch et al. (2018). When drugs cause harm to the liver, this harm is characterized by issues with the mitochondria. This results in a lack of energy and the start of inflammation, as highlighted by Shaker et al. (2020). In this study, the noticeable climb in liver enzymes points to the possibility that repaglinide, especially when taken in large amounts, might be playing a role in causing these damaging effects. The results we've come across highlight how crucial it is to adjust the dosage with precision and delve deeper into dose-dependent toxicity.

Toxicological benchmarks such as the median lethal dose (LD_{50}) are essential in assessing the safety profile of pharmaceutical agents. Previous experimental studies have estimated the oral LD_{50} of repaglinide in rats to be approximately 1050 mg/kg, indicating a relatively wide therapeutic index (Marbury et al., 2000; Vijayan et al., 2011). In the current study, the administered doses (0.7 mg/kg and 1.4 mg/kg) were significantly lower than the reported LD_{50}, falling well within the therapeutic safety margins. However, the emergence of dose-dependent physiological and histological alterations despite sub-lethal exposure underscores the importance of distinguishing between acute lethality and subacute organ toxicity. While the LD_{50} provides a reference for gross toxicity, the findings of hepatocellular damage, pulmonary inflammation, and hematological shifts at these lower doses suggest that chronic or repeated exposure to repaglinide may lead to cumulative toxicological effects not predicted by LD_{50} alone. Therefore, reliance on LD_{50} values alone may be insufficient to evaluate drug safety, and more nuanced biomarkers of organ-specific toxicity are warranted in long-term repaglinide administration studies.

Figures 4 and 5 depict histological changes in hepatic and pulmonary tissues. In the liver (Figure 4), repaglinide exposure caused inflammatory cell accumulation in blood sinusoids (B), distension of the central vein (C and E), and inflammation surrounding the hepatic artery and bile duct (D). These histological observations align with the biochemical data, reinforcing evidence of repaglinide-induced liver injury.

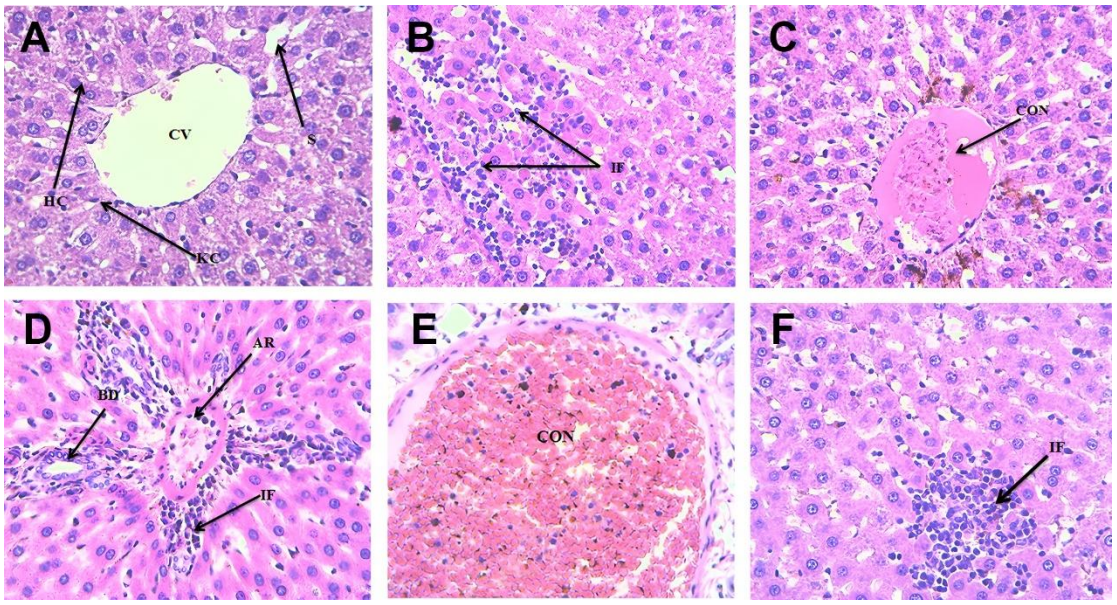

Figure 4. Rat liver histopathological changes (400X magnification); A: Central vein; B: Treatment group liver section; C: Treatment group liver tissues; D: Treatment group; E: Multiple treatment groups; F: Focal cells

Comparing the control and treatment groups, Figure 4 shows the pathological histopathological alterations in the rat liver tissues following repaglinide administration. Key components were found, including the sinusoids (S), hepatocytes (HC), Kupffer cells (KC), and central vein (CV). Hematoxylin and eosin (H&E) staining under a 400x microscope revealed that the control group's liver structure was normal, with well-preserved hepatocytes and sinusoidal gaps. Significant pathological alterations were observed in the therapy groups, including inflammatory cell accumulation (IF) in the hepatic sinusoids, central vein narrowing (CON), and inflammatory cell accumulation around the hepatic artery (AR) and bile duct (BD). Additionally, there was significant congestion in the central vein and inflammatory cell accumulation in specific regions in some therapy groups, indicating inflammation of the liver and blood vessel issues. According to the findings, repaglinide may be hazardous to the liver, which calls for more research into the possible causes of liver injury.

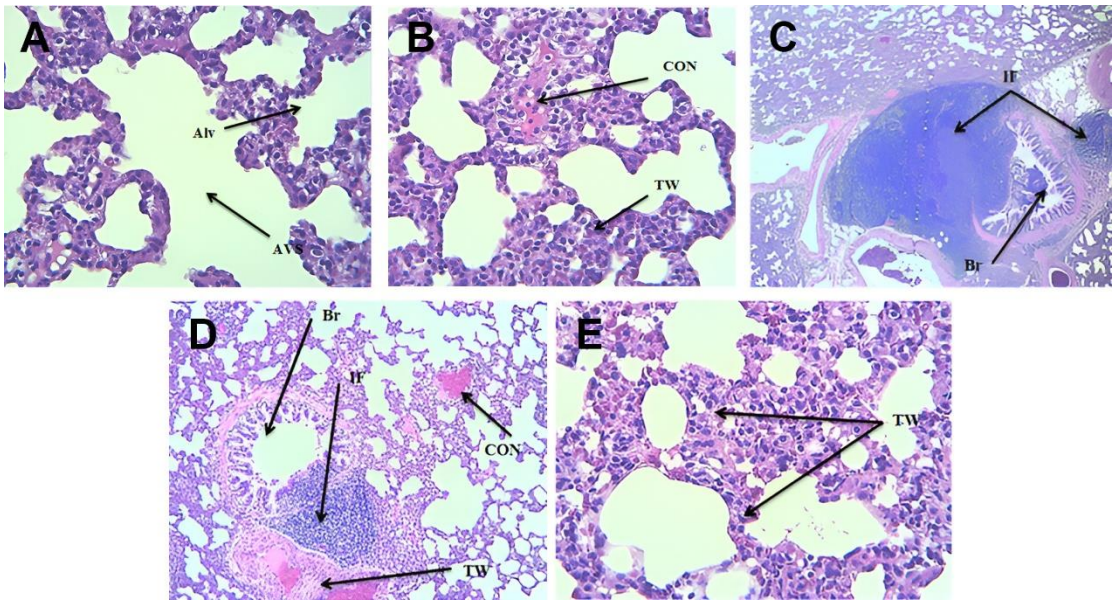

Figure 5. Pulmonary histopathology in rat treated with repaglinide (hematoxylin and eosin stain), groups A and B (400x); groups C and D (100x). A: control group; B: repaglinide-treated group; C: repaglinide-treated group; D and E: dual therapy-treated group

Microscopic examination of pulmonary tissue sections revealing histopathological alterations is presented in Illustration 5. Specimens from control subjects exhibit typical pulmonary architecture with well-delineated alveolar structures (Alv) and appropriately formed alveolar sacs (AVS). In contrast, specimens from subjects receiving repaglinide treatment show increased alveolar wall thickness (TW) and vascular congestion (CON). The comparative treatment group exhibited substantial inflammatory cellular infiltration (IF) within bronchiolar passages (Br). Notably, subjects receiving dual-dose therapy demonstrated more pronounced pulmonary pathology, characterized by vascular wall hypertrophy (TW), significant blood vessel congestion (CON), and peribranchial inflammatory cell accumulation (IF).

Administration of repaglinide, a rapid-onset insulin secretion stimulator employed in type 2 diabetes management, has been linked to significant pulmonary complications. Microscopic examination of pulmonary specimens from repaglinide-treated subjects revealed pathological alterations including alveolar wall hypertrophy, vascular engorgement, and bronchial region inflammatory cell aggregation (documented in Figure 5B-D). These architectural disruptions suggest parenchymal injury potentially compromising respiratory gas exchange and pulmonary function efficiency, as previously documented by García-Galicia and colleagues (2020). The observed elevations in erythrocyte count, hemoglobin concentration, and hematocrit values likely represent compensatory mechanisms addressing tissue hypoxia resulting from impaired alveolar-capillary oxygen transfer due to membrane damage. This adaptive physiological response, aimed at enhancing oxygen delivery to peripheral tissues during hypoxic states, parallels mechanisms well-documented in various chronic pulmonary pathologies (Chou et al., 2023).

Oxidative stress compromises both endothelial and epithelial cellular integrity through mechanisms researchers attribute to reactive oxygen species generation. This pathological process contributes to alveolar wall hypertrophy, tissue fibrosis, and interstitial fluid accumulation (Mari et al., 2024). During hepatic biotransformation of repaglinide, metabolic intermediates potentially generate reactive oxygen species that directly compromise pulmonary tissue architecture, thereby

amplifying inflammatory cascades and diminishing respiratory gas exchange capacity (Jomova et al., 2023). Histological examination revealing peribronchiolar neutrophil and macrophage accumulation suggests pronounced inflammatory pathway activation, consistent with oxidative stress-mediated tissue pathology (Al-Kraiel et al., 2020; Smith et al., 2022). Activated immunological cells secrete various pro-inflammatory mediators, notably interleukin-6 and tumor necrosis factor-alpha, which further perpetuate tissue damage and pathological remodeling processes (Laskin et al., 2019).

Contemporary research suggests repaglinide administration potentially disrupts pulmonary cellular mitochondrial homeostasis, thereby enhancing oxidative stress burden and promoting cellular apoptotic pathways. Mitochondrial organelles serve as critical regulators of cellular bioenergetics; their functional compromise frequently triggers release of pro-apoptotic factors, including cytochrome c, into cytoplasmic compartments. Research published in 2023 documents repaglinide-induced enhancement of mitochondrial membrane permeability in alveolar epithelial cells, consequently upregulating caspase-3 enzymatic activity and accelerating genomic DNA fragmentation processes (Gonzalo-Gobernado et al., 2023; Buniya et al., 2023). These molecular events align with histopathological observations of alveolar wall thickening, wherein fibrotic remodeling appears accelerated through programmed cell death mechanisms. Furthermore, mitochondrial dysfunction establishes a self-perpetuating pathological cycle wherein increased reactive oxygen species production further exacerbates inflammatory responses and oxidative cellular damage (Zorov et al., 2014).

The concurrent use of antioxidants or anti-inflammatory drugs may mitigate the damage caused by repaglinide. N-acetylcysteine (NAC), which is a building block for glutathione, reduces swelling and scarring in the alveoli of rat that were given repaglinide by taking in reactive oxygen species (Choi et al., 2022; Assi et al., 2024). According to Jamialahma di et al. (2023), the anti-fibrotic drug pirfenidone also blocks TGF-β signaling, which lowers the buildup of collagen in preclinical animals. These supplementary therapies necessitate clinical examination.

Notwithstanding repaglinide's effectiveness in diabetes control, regulatory bodies such as the FDA and EMA have failed to provide explicit warnings regarding pulmonary hazard. It has been found that repaglinide is linked to an increasing number of cases of drug-induced interstitial lung disease (EMA, 2023) the EMA. Clinicians must prioritize evaluations of respiratory symptoms (e.g., dyspnea, cough) and contemplate pulmonary function tests for patients at elevated risk. Adjusting the dosage or considering alternate therapy, such as DPP-4 inhibitors, may be advisable.

Comparison with Subacute/Subchronic Studies

The observed hepatic and pulmonary toxicities in this study align with previously reported subacute or subchronic exposure outcomes for repaglinide and similar agents. For instance, a subchronic study by Chukwunonso Obi et al. (2016) on diabetic rats treated with repaglinide for 8 weeks reported significant alterations in oxidative stress markers and antioxidant enzyme activity, especially in the liver and kidneys. While their results emphasized the antioxidative properties of repaglinide, our current findings diverge under non-diabetic conditions, particularly at higher doses, where hepatotoxic and pulmonary alterations dominate. This suggests that oxidative outcomes may differ between diabetic and non-diabetic models and under varying dosing regimens.

Similarly, Shaker et al. (2020) reported subacute toxicity from repeated dosing of another therapeutic agent (cefixime), highlighting elevated liver enzymes and inflammatory infiltration in hepatic tissues of albino rats. These findings mirror our histological observations of central vein

congestion and inflammatory cell accumulation, supporting the notion that prolonged exposure to pharmacological agents—even at therapeutic or slightly elevated doses—can induce subchronic hepatic stress. Moreover, Villanueva-Paz et al. (2021) emphasized that prolonged oxidative imbalance from drug metabolism is a key driver of tissue pathology in subchronic liver injury, consistent with our documentation of elevated AST and ALT, disrupted hepatic architecture, and evidence of mitochondrial dysfunction. These comparative findings suggest that **repaglinide, though effective for glycemic control, may contribute to dose-dependent systemic toxicity in subacute to subchronic exposure scenarios**, particularly through mechanisms involving oxidative stress and mitochondrial impairment. Further research utilizing longer durations and different models (e.g., diabetic vs. non-diabetic) would be valuable to delineate the therapeutic-toxic threshold of repaglinide more precisely.

CONCLUSION.

This study suggests that repaglinide effectively lowers blood glucose levels but may induce significant physiological and histological changes suggestive of liver and lung damage in rats. These results raise concerns about the possible bad effects of repaglinide, especially when taken in large amounts. They also stress the need for more research to figure out how these effects happen and what they mean for therapy. The differences between the results of this study and other studies about repaglinide's antioxidant properties show how complicated its drug effects are and how much more research needs to be done.

ETHICS APPROVAL.

Approval for the study was granted by the minutes of the Scientific Research Ethics Committee at Tikrit University, Iraq, No. TUA0003, dated 10/11/2024.

CONFLICT OF INTEREST

The authors assert that there are no conflicts of interest pertaining to the publishing of this research. All contributors have revealed any affiliations or engagements that may be interpreted as potentially influencing the results of this study.

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