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Physiological and histological effects of the Repaglinide drug on kidney function in male albino rats

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Abstract :

This study aims to examine the detrimental effects of repaglinide on renal tissues. Fifteen male albino rats were randomly allocated into three groups: the Control and repaglinide administered orally, the double dose of repaglinide, with the treatment sustained for four weeks. The results of the biochemical test, the lipid profile, specifically, no significant change ($P \leq 0.05$) was observed in the concentrations of triglycerides, VLDL-C, and HDL-C in the groups treated with the drug compared to the control. However, there was a significant increase in LDL-C in the double-dose group relative to the control group. Kidney tests indicated a significant increase ($P \leq 0.05$) in urea levels and a significant decrease in creatinine levels in the therapeutic and double-dose groups receiving Repaglinide treatment

compared to the control group. The kidney was subjected to histopathological examination, revealing that the treatment group receiving repaglinide exhibited contraction of the renal glomerulus compared to the control group. Conversely, the treatment group administered a double dose of repaglinide displayed inflammatory cell infiltration, destruction of the renal glomerulus, sloughing of the lining of specific renal tubules, and hemorrhage within the kidney tissue, alongside notable infiltration of inflammatory cells and swelling of the renal glomerulus in comparison to the other group. We conclude that repaglinide treatment led to clear physiological and histological changes in kidney tissue in albino rats.

Keywords: Repaglinide drug, kidney function, Urea, Creatinine, and Lipid profile.

التاثير الفسيولوجي والنسجي لعقار Repaglinide على وظائف الكلى لدى ذكور الجرذان البيضاء

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مستخلص:

تهدف هذه الدراسة إلى دراسة الآثار الضارة لريباجلينيد على أنسجة الكلى. قُسِّم خمسة عشر جرذًا ذكرًا من الفئران البيضاء عشوائيًا إلى ثلاث مجموعات (خمس لكل مجموعة): (أ) مجموعة التحكم، (ب) مجموعة ريباجلينيد و(ج) مجموعة ريباجلينيد بجرعة مضاعفة ، واستمر العلاج لمدة أربعة أسابيع.

نتائج الاختبار الكيميائي الحيوي: لم يُلاحظ أي تغيير يُذكر ($P \leq 0.05$) في تركيزات الدهون الثلاثية، والكوليسترول منخفض الكثافة جدًا (VLDL-C)، والكوليسترول عالي الكثافة (HDL-C) في المجموعات التي عولجت بالدواء مقارنةً بالمجموعة الضابطة. ومع ذلك، لوحظت زيادة ملحوظة في الكوليسترول منخفض الكثافة (LDL-C) في مجموعة الجرعة المزدوجة مقارنةً بالمجموعة الضابطة. أشارت فحوصات الكلى إلى زيادة ملحوظة ($P \leq 0.05$) في مستويات اليوريا وانخفاض ملحوظ في مستويات الكرياتينين في المجموعة العلاجية والمجموعة ذات الجرعة المزدوجة التي تلقت علاج ريباجلينيد مقارنةً بالمجموعة الضابطة. خضعت الكلية لفحص نسيجي مرضي، وكشف أن المجموعة العلاجية التي تلقت ريباجلينيد بجرعة طبيعية أظهرت انكماشًا في الكبيبة الكلوية مقارنةً بالمجموعة الضابطة. في المقابل، أظهرت المجموعة العلاجية التي تلقت ريباجلينيد بجرعة مضاعفة تسللًا للخلايا الالتهابية، وتدميرًا للكبيبة الكلوية، وتسلخًا في بطانة بعض الأنابيب الكلوية، ونزيفًا داخل أنسجة الكلى، إلى جانب تسلل ملحوظ للخلايا الالتهابية وتورمًا في الكبيبة الكلوية مقارنةً بالمجموعة الأخرى. نستنتج أن علاج الريباجلينيد أدى إلى تغيرات فسيولوجية ونسيجية واضحة في أنسجة الكلى لدى الفئران البيضاء.

الكلمات المفتاحية : عقار ريباجلينيد، وظائف الكلى، اليوريا، الكرياتينين، مستوى الدهون.

Introduction:

Drug-induced hypoglycemia presents a significant challenge for persons striving to attain glycemic objectives. Hypoglycemia may be severe, leading to confusion, unconsciousness, or seizures, necessitating aid from others. Substantial risk of hypoglycemia frequently requires less rigorous glycemic targets. The frequency and severity of hypoglycemia adversely affect quality of life [1]. It may result from excessive insulin administration, oral hypoglycemic medications, insufficient meal consumption, or extreme

physical exertion [2]. The glucose level that elicits hypoglycemic symptoms

differs among individuals and can fluctuate for the same individual under varying conditions [3]. Sweating, tremors, tachycardia, palpitations, nervousness, hunger,

confusion, slurred speech, emotional fluctuations, diplopia, drowsiness, and insomnia characterize it. It is frequently self-diagnosed, which may escalate to severe symptoms such as seizures, cognitive impairment, coma, and death [4]. All diabetic patients should be aware of the immediate treatment for hypoglycemia to prevent the necessity for hospitalization [5].

Hypoglycemia and its severity can be mitigated through early identification of risk factors, self-monitoring of blood glucose levels, selecting suitable treatment protocols, and implementing effective educational programs for healthcare professionals [6]

. Repaglinide is an antidiabetic medication utilized for the management of

type II diabetes mellitus. It is administered orally as monotherapy or in combination with other medicines to regulate blood glucose levels [7]. Repaglinide (RG) is a nonsulfonylurea hypoglycemic agent that enhances insulin release and exhibits antidiabetic properties [8]. It possesses a brief half-life (1 hour), restricted

bioavailability (50%), and inadequate absorption in the upper gut. It is fully metabolized following intravenous or oral administration through oxidative transformation and subsequent conjugation with glucuronic acid [9]. Repaglinide medication has been demonstrated to reduce lipid hydroperoxide (LPO) levels and enhance superoxide dismutase activity in kidneys

affected by diabetic nephropathy [10].

1- Materials and methods

Fifteen mature male albino rats weighing 155 170 - grams were employed in this investigation over four weeks. The animals were obtained from the animal house division of the College of Veterinary Medicine at Tikrit University. They were housed under standard ventilation settings, with a temperature of (25 ± 2)°C, humidity levels of (60-70)%, and a light/dark cycle of 12 hours each. The animals were fed tap water ad libitum and were administered standard commercial food.

Experimental Design

The animals were randomly assigned to three groups:

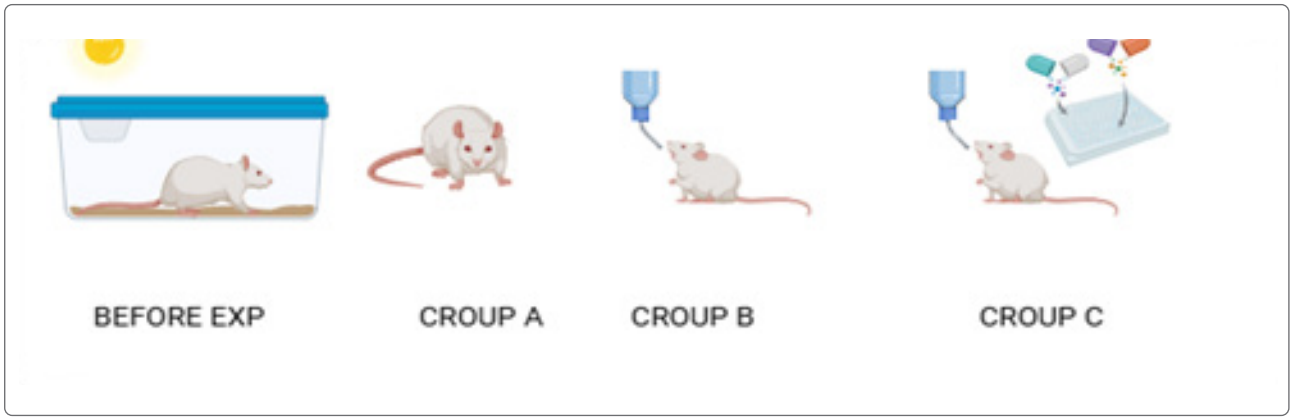
Group 1 - Animals were administered distilled water and functioned as the control group.

Group 2 - Animals received Repaglinide at a 0.07 mg/kg dosage.

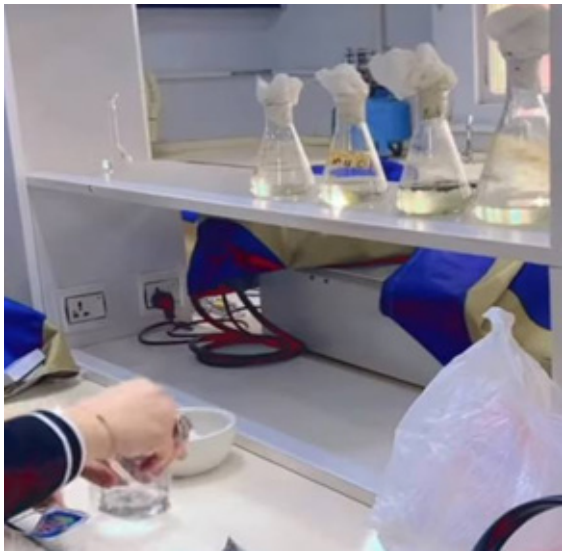
Group 3 - Animals were administered Repaglinide at a dosage of 0.14 mg/kg.

All experimental animals received oral administration.

The animals were randomly assigned to three groups Obtaining blood samples .



After the 30-day experiment, the animals were deprived of food for 24 hours and subsequently anesthetized with chloroform while confined in a sealed glass container. Blood samples were obtained via cardiac puncture using a syringe and transferred to gel tubes. The samples were then subjected to centrifugation at 3000 rpm for 10 minutes. Serum was aliquoted into Eppendorf tubes and stored at -80 °C until the necessary biochemical analyses were conducted.



Images (1),(2) illustrate the procedures and progress of the scientific experiment.

Preparing histological sections

Kidney tissue specimens were preserved in 10% formalin for 24 hours; after that, they were rinsed with water and dehydrated using ethyl alcohol in increasing concentrations.

(70%, 80%, 95%, and 100%). The specimens were subsequently cleaned with xylene and embedded in paraffin. All paraffin-embedded tissue was sectioned to a thickness of five micrometers and stained with hematoxylin and eosin. The specimens were examined with a light microscope at 400X magnification. Digital images were acquired for further study [11].

Statistical analysis:

Substantial differences were identified using the one-way ANOVA test, with these differences corroborated by standard deviation analysis. The ethical distinctions were established based on Duncan's multiple range test at a significance level of ($P \leq 0.01$) [12].

Result and discussion

1- Biochemical variables:

Table 1 indicates no significant change ($P \leq 0.05$) in the concentrations of triglycerides, VLDL-C and HDL-C in the groups treated with the medication compared to the control group. However, there is a significant rise in LDL-C in the double group relative to the control group.

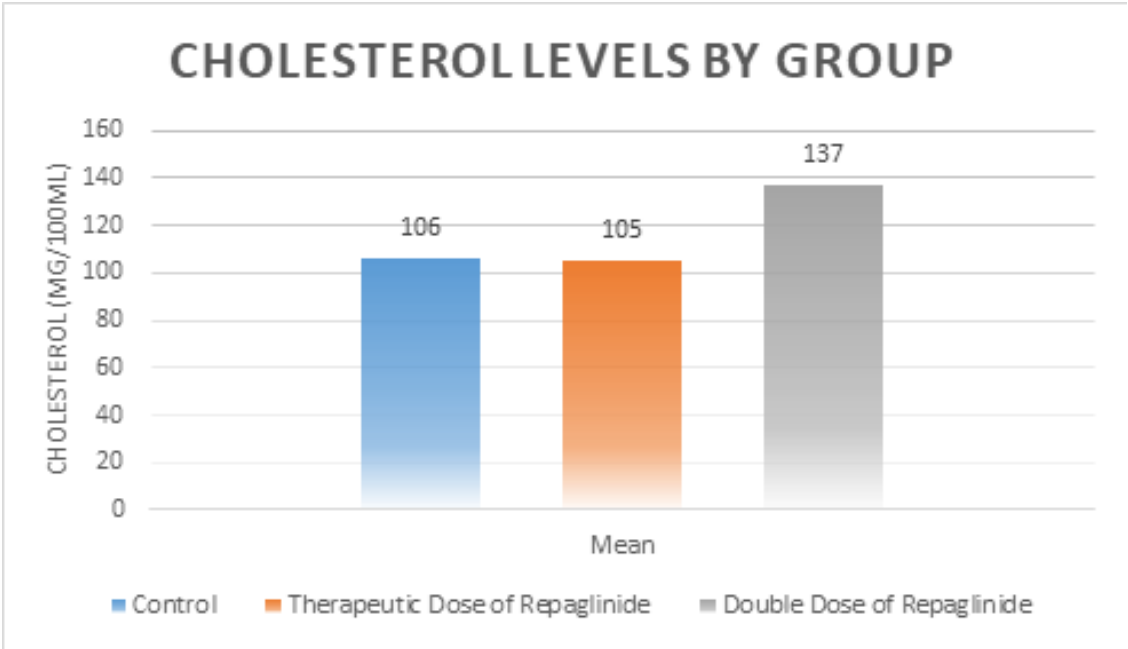


Figure 1: Serum Cholesterol Levels in Study Participants

Each group has five creatures.

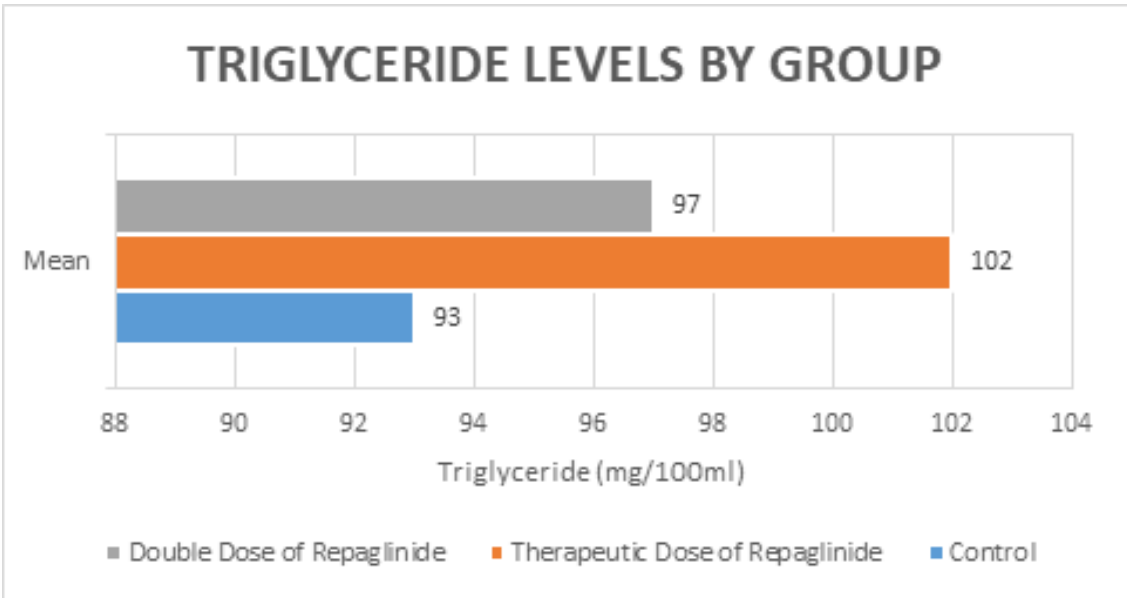
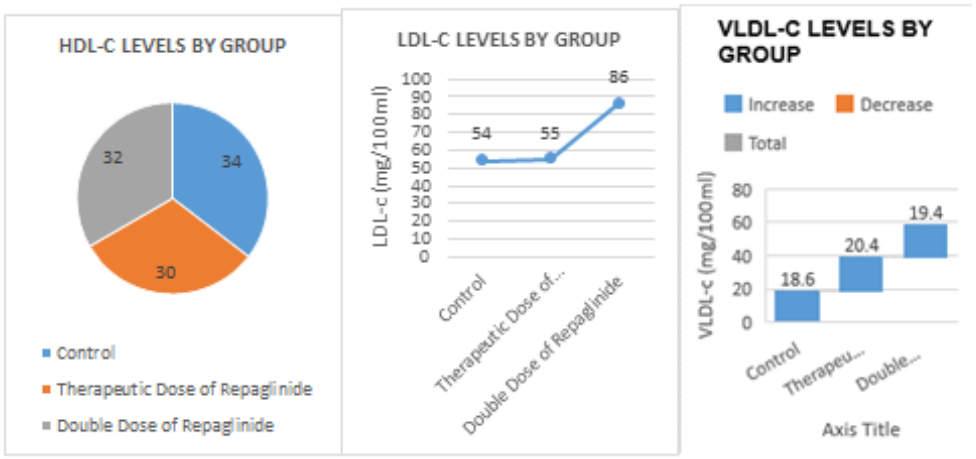


Figure 2: Serum Triglyceride Levels in Study Participants



Figures (3),(4),(5) Distribution of Lipoprotein Cholesterol Levels (HDL, LDL, and VLDL) in Study Participants

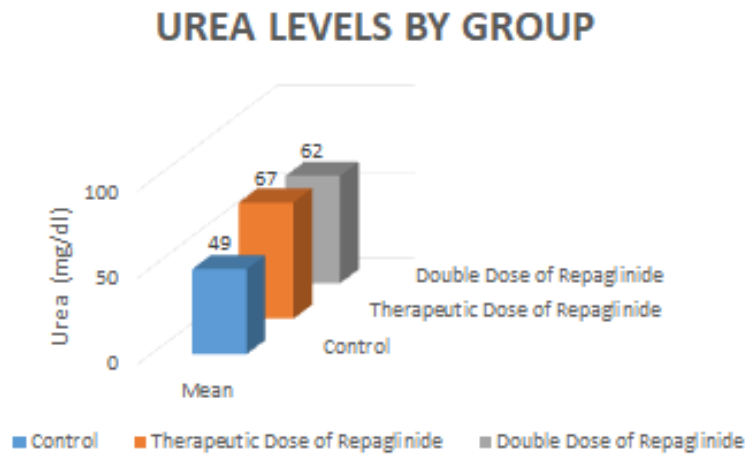


Figure 6: Serum Urea Levels in Study Participants

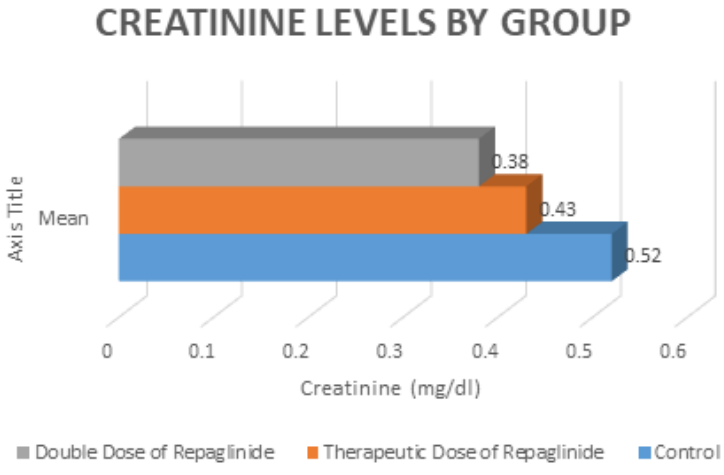


Figure 7: Serum Creatinine Levels in Study Participants

2- Study of Histology:

The outcomes of the histological analysis for the cohort administered Repaglinide at a dosage of 0.07 mg/kg. There is bleeding in the majority of the renal cells, accompanied by infiltration of inflammatory cells, and it exhibits desquamation of the renal tubule lining (Images 1, 2, 3). Compared to the control group, the double dosage group with Repaglinide exhibited collapse of the renal glomerulus and shedding of the lining of specific renal tubules, together with apparent histological necrosis, and showing glomerular swelling (Images 4.5, 6, 7, 8).

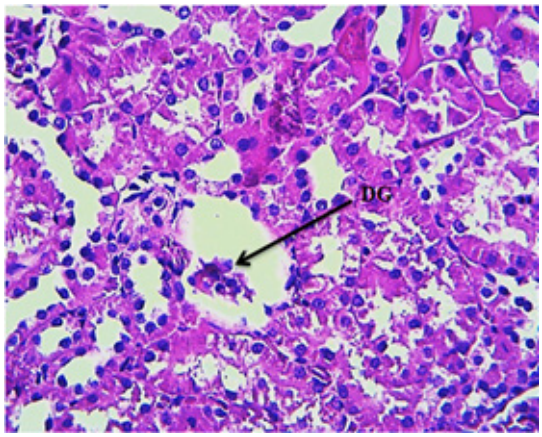


Image (1) A section of the kidney of the control group showing the renal glomerulus (G), the proximal convoluted tubule (PCT), the distal convoluted tubule (DCT), and the per glomerular space (C) normally. H & E 400X,

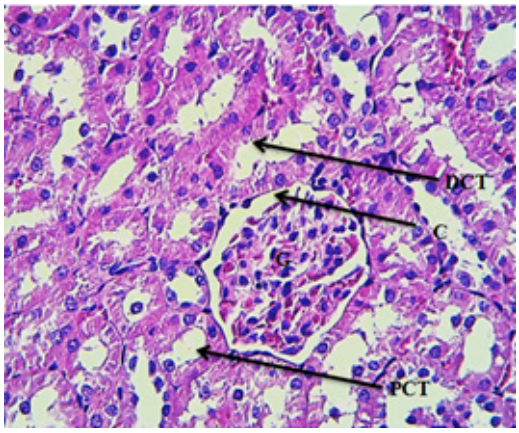


Image (2) of a kidney section of the treatment group showing contraction of the renal glomerulus (DG). H & E 400X,

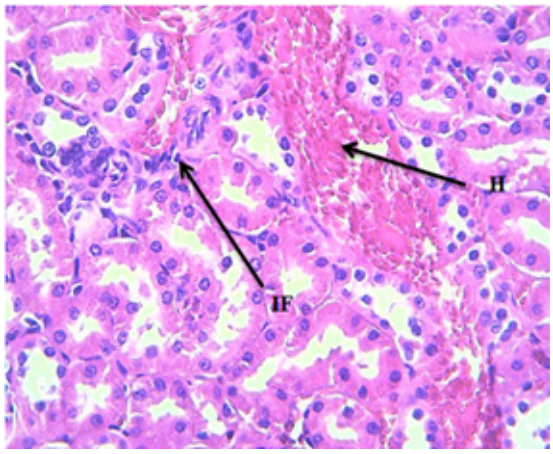


Image (3): A section of the kidney of the treatment group showing blood bleeding (H) within the kidney tissue, noting the infiltration of inflammatory cells (IF). H & E, 400X .

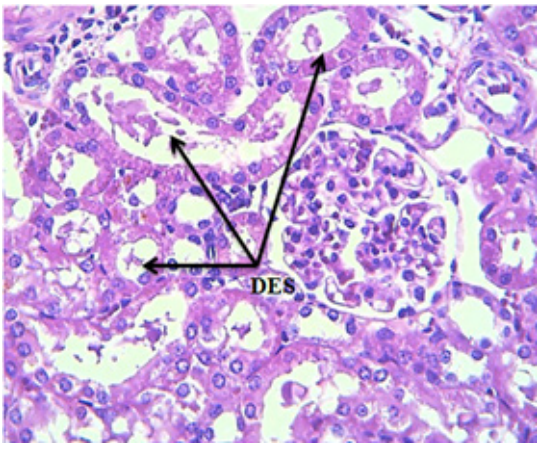


Image (4): A section of the kidney of the treatment group showing sloughing of the lining of the renal tubules (DES). H & E, 400X.

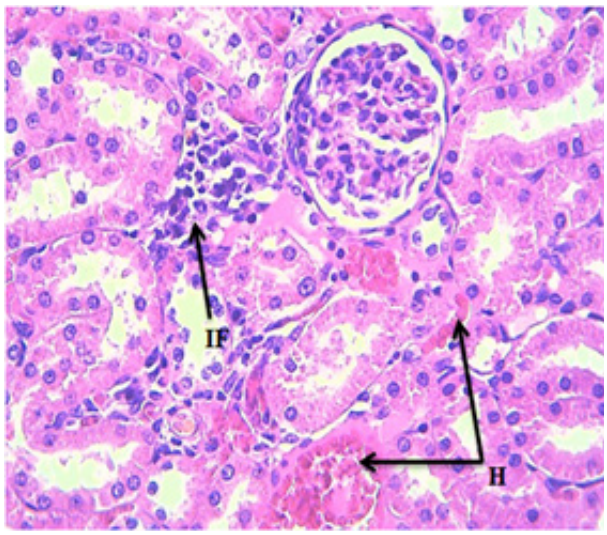


Image (5):
A section of the kidney of the treatment group showing infiltration of inflammatory cells (IF) and the presence of blood bleeding between the renal tubules (H). H & E, 400X .

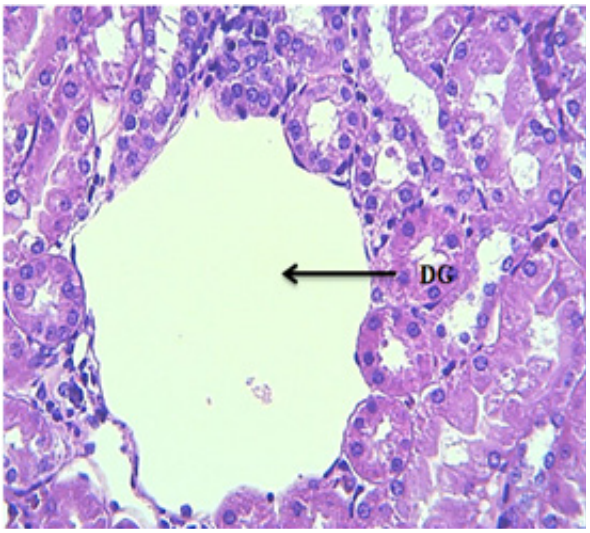


Image (6):
A section of the kidney of the double group showing the collapse of the renal glomerulus (DG). H & E 400X,

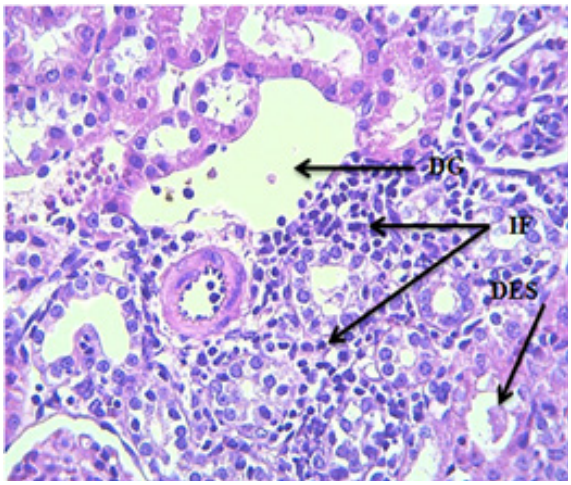


Image (7):
A cross-section of the kidney of the double group showing the infiltration of inflammatory cells (IF), the destruction of the renal glomerulus (DG), and the sloughing of the lining of some renal tubules (DES). H & E, 400X .

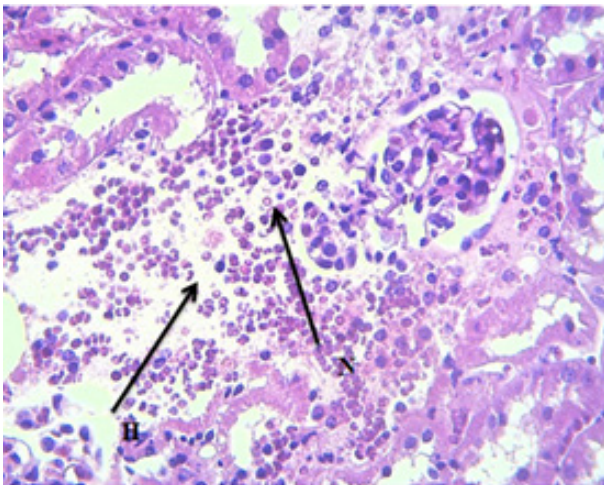


Image (8):
A section of the kidney of the duplicated group showing the presence of histological necrosis (N) filled with hemorrhage (H). H & E, 400X .

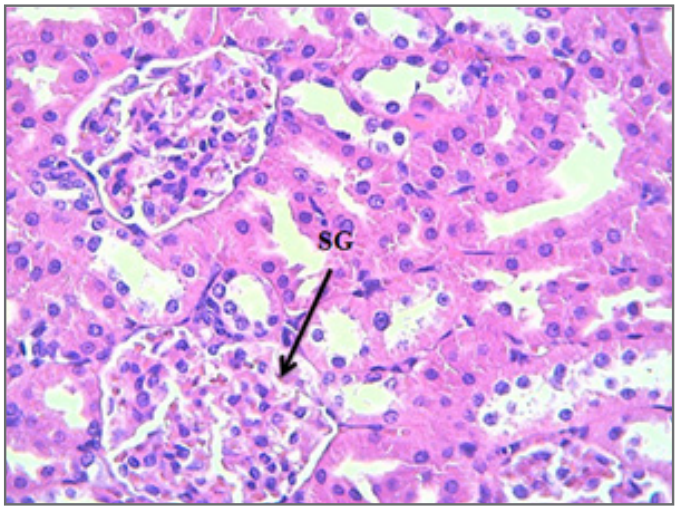


Image (9):
Image (8) Double subset showing glomerular swelling (SG).H & E 400X,

Discussion:

From the research results, we note that biochemical analyses of the lipid profile did not reveal any significant change at the probability level ($P \leq 0.05$) in the concentrations of triglycerides, VLDL-C, and HDL-C in the Repaglinide groups compared to the control. However, there was a significant increase in LDL-C and TC in the dual group compared with the control group.

This explains that the reason for this effect is due to the presence of free radicals that reduce the amounts of oxidative enzymes in the body, and this is consistent with the result in [7]. He explained that the results of his research indicated a significant decrease in the levels of antioxidant enzymes in the group of mice treated only with repaglinide. While it did not agree with the results of [8].

The prevalence of atherosclerosis in diabetes patients is associated with various variables, with high plasma lipid levels being the most significant. Dyslipidemia in type 2 diabetes is defined by elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) alongside reduced high-density lipoprotein cholesterol (HDL-C) [12]. This suggests that acute repaglinide treatment does not enhance postprandial lipaemia in individuals with type 2 diabetes[13].

The analysis of renal function revealed a substantial increase ($P < 0.05$) in urea levels and a significant decrease in creatinine levels in the thera-

peutic and double-dose groups receiving Repaglinide medication compared to the control group. Repaglinide is a fast-acting, short-term medication that lowers blood sugar levels by boosting insulin secretion, distinguishing it from other diabetic medications. This indicates that the kidneys will filter substantial quantities of sugar, imposing a strain on them [14]. This aligns with the result, where he elucidated. The findings of his investigation indicated a significant decrease in the levels of antioxidant enzymes in the group of rats treated just with repaglinide [7].

Additionally, in his article, it is said that the substance is primarily metabolized by the liver, with less than 10% excreted in urine. Renal impairment may marginally extend its half-life, and the pre-prandial dosage of 0.5–4 mg should be adjusted based on the postprandial blood glucose response. This suggests that a double dosage of the medication will result in renal impairment [15].

Histological results of the kidneys revealed substantial damage to the renal tissue in the groups administered RG at both the conventional and double doses. This signifies exposure to considerable oxidative stress. This aligns with [7]. The use of antibiotics in many studies had negative effects on kidney tissue in terms of physiological function through measuring the levels of urea and creatinine, and the negative histological effect also appeared clearly when dosing rats with treatments, for example, cefixime treatment [16]. The results were corroborated by histological alterations observed in the kidney and liver sections of the examined group. Necrosis of hepatic tissues is seen, accompanied by mononuclear cell aggregation in the liver. Moreover, there were hemorrhagic renal tubules and necrotic glomeruli in the kidneys of the group of rats administered just repaglinide. Given that the kidney tissue results indicated extensive damage, including impairment of the renal vasculature and loss of the renal tubules, these injuries will ultimately inhibit renal function and may result in renal failure [17]. The present study demonstrates that chronic administration of high doses of repaglinide induces significant renal toxicity in diabetic subjects. Histopathological examination revealed clear signs of tubular necrosis, glomerular damage, and interstitial inflammation. Furthermore, renal function tests showed elevated lev-

els of urea and creatinine, indicating impaired kidney function and These findings suggest that while therapeutic doses of repaginate are generally considered safe, repeated exposure to subtherapeutic doses may lead to structural and functional kidney damage. The observed nephrotoxicity may be attributed to increased oxidative stress and metabolic overload in renal tissues. Therefore, caution is warranted when using repaglinide in diabetic patients, particularly in cases where dose adjustments are necessary or when combined with other nephrotoxic agents. This observation is consistent with [17].

Conclusion: Treating rats with repaglinide at therapeutic and double doses showed physiological effects represented by lipid levels, kidney function, and histological changes in kidney tissue compared to the control group, but the effect was more pronounced in the group dosed with double treatment.

Thanks and appreciation:

Thanks and appreciation to the Department of Biology for agreeing to include the research within the department's plan, as well as thanks to the workers in the Animal House - College of Veterinary Medicine - Tikrit University.

Author contributions:

All researchers contributed to conducting the practical aspect and contributing to laboratory procedures, as well as organizing the writing of the research.

Conflict of interest:

All researchers confirm that there are no conflicts of interest within the content of the research.

Funding source:

The work was submitted to Tikrit University - College of Education for Pure Sciences, but was self-funded by the researcher

Ethical clearance:

The current study has been approved by the scientific research instructions of Tikrit University –Iraq, NO TUA00012, on 10/2/2025

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