ISSN: 1343-4292
Volume 140, Issue 01, April, 2022

The Effect of Repaglinide on the Liver and Kidney Histology of alloxan induced diabetic albino rats.

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ABSTRACT— The antihyperglycemic medication Repaglinide (RG) is used to treat non-insulin-dependent diabetic mellitus., that stimulates insulin release from pancreatic beta cells by binding to and ultimately activating ATP dependent potassium channels. The purpose of this study was to investigate the protective effect of Repaglinide on liver and kidney tissue of diabetic albino rats that had been induced by alloxan. In this investigation, 20 male white adult albino rats were separated into two groups (10 rats) were applied to produce diabetes mellitus (type II) using alloxan monohydrate, and the second group (10 rats) were administered normal saline intraperitonealy. These animals were divided in to four groups: Group 1 Normal control non-diabetic rats were only administrated distilled water; Non-diabetic rats in Group 2 were given 4 mg/kg/day of repaglinide; Group 3 Diabetic control who were given alloxan i.p. and administrated distilled water orally but were not given any medications; Groups 4 Diabetic rats treated with repaglinide 4mg/kg/day. According to the histological sections all of non-diabetic control, non-diabetic rats treated with repaglinide and in diabetic rats treated with repaglinide had normal histology of the liver and kidney, whereas diabetic control had hepatocytes degeneration and lymphocyte infiltration in both liver and kidney. On the other hand, rats treated with repaglinide showed a noticeable recovery of liver and kidney tissues, suggesting that (RG) might be a useful treatment for treating and avoiding harmful alterations in these tissues.

KEYWORDS: Repaglinide, alloxan-induced, albino rats, liver, kidney, histology

1. INTRODUCTION

Diabetes mellitus is a complicated metabolic illness described by high blood glucose levels, pancreatic beta cell insufficiency, and disturbed lipid profile, all of which are caused by metabolic disturbances, decreased insulin production and action, and excessive glucose consumption [1]. People's lifestyles and eating habits are contributing to the growing prevalence of this disease [2].

Complications of this condition have been shown to increase morbidity and death in people who are afflicted, resulting in major direct and indirect expenses [3].

Because alloxan causes damage to pancreatic cells, it can raise blood glucose levels, disrupting insulin synthesis. Disturbance of glucose entry into cells results in elevated blood glucose levels [2]. Study by Lucchesi et al. demonstrated that rats with type I DM produced by injected ALX exhibited chemical abnormalities in their blood as well as morphology and microscopic alterations in the liver that were very similar to chronic liver disease in people. The alterations in the liver ranged from fatty liver cell degeneration to steatohepatitis and periportal fibrosis [9]. Also, reported that Histopathological alterations

in the kidneys of alloxan-injected rats revealed kidney glomerular compression with expanded urinary gap, tubular epithelial vacuolar destruction, and damaged tubules [10].

Diabetes mellitus (type 2) has been treated using anti-diabetic medications. The majority of currently used hypoglycemic medications, such as thiazolidinediones, biguanides, meglitinides, and sulfonylureas, as well as benzoic acid derivatives (repaglinide), are taken orally as monotherapy or in conjunction with other drugs to manage blood sugar levels [4]. Repaglinide (RG) is a novel amino acid-structured oral hypoglycemic medication. It seems to have nonsulfonylurea insulin release–enhance hypoglycemic drug and antidiabetic effects [5]. It has a short half-life (1 hour), limited bioavailability (50%) and poor absorption in the upper intestine. It is completely digested after an IV or oral dosage by oxidative transformation and subsequent conjugated with glucuronic acid [6]. It has been reported that Repaglinide treatment has been shown to lower lipid hydroperoxide (LPO) levels and increase superoxide dismutase activity in diabetic nephropathy kidneys [7].

[7], [8] suggested that RG has antioxidant effects that are unrelated to its hyperglycemic impact. The direct antioxidant characteristics of RG create stronger benefits at therapeutic levels, which might help it be more helpful in the treatment of type 2 DM.

2. Materials and Methods

In this investigation, twenty male white adult albino rats, aged 2-3 months and weighing between 155-170 g, were employed. These animals were separated into two groups after a period of adaption. The first group of ten rats was used to induce diabetes mellitus (type II) by injecting alloxan monohydrate as a single dosage of 130 mg/kg body mass intraperitoneally after 72 hours, and fasted blood sugar levels were evaluated using a glucometer after 9-12 hours of fasting. The second set of ten rats got intraperitoneal injections of normal saline. Male albino diabetic and normal rats were separated into four groups: Group 1: Control group Non-diabetic rats were administered DW orally through an orogastric tube as an alternate to the therapy provided to the other groups. Group 2 non-diabetic animals were treated with repaglinide 4mg/kg/day, administrated orally by oral gavage tube. 3rd Group animals in the diabetic control group were given alloxan i.p. and administrated distilled water orally but have not been given any medications. Groups 4 Diabetic rats with Repaglinid after seven days of DM induction, diabetic rats treated with Repaglinide 4mg/kg/day orally. The animals were sacrificed after a 6-week treatment period, and their liver and kidneys were collected for histological analysis.

2.1 Histological sections examination

According to Bancroft's idea (11), histological sections of the liver and kidney (5 thick) were generated to evaluate the alterations that may be discovered in the treatment animal groups compared to the control group.

3. Results and Discussion

As demonstrated in the figures (1, 2,4) all of non-diabetic control, non-diabetic rats received repaglinide and in diabetic rats treated with repaglinide had normal histology of liver. While, Liver section of diabetic control showed some hepatocytes degeneration in addition to the presence of inflammatory cells infiltration (lymphocyte infiltration) as shown in the figure (3).

The kidney section of non-diabetic control, non-diabetic animals treated with repaglinide and in diabetic animals treated with repaglinid (figures 5, 6,8) showed normal renal construction. While, in the kidney of diabetic control (figure 7) showed lymphocyte infiltration.

ISSN: 1343-4292
Volume 140, Issue 01, April, 2022

Many studies have shown lesions in the livers and kidneys of alloxan-treated diabetic rats that demonstrate significant hepatocyte degeneration with many vacuolations that may affect all organ tissues, involving portal regions and sinusoids, as well as hepatocytes, nuclei, and intracytoplasmic organelles [9], [12], [14]. The kidneys of alloxan-induced diabetic rats reveal significant glomerular degeneration, glomerular atrophies, and extensive vacuolations [12]. The harmful effects of alloxan on the body are commonly noticed within the first two weeks of diabetes induction [14]. [10] found cellular infiltration and renal hypertrophy, as well as tubular damage and Bowman's space bleeding owing to glomerular injury. Our results showed no deleterious effects of alloxan induced diabetic rat on the liver and kidney histology of all DM groups. There was only lymphocytic infiltration, some hepatocytes degeneration in liver which might be due to the direct influence of alloxan on the body's inflammatory processes, or it could be linked to another factor that causes infiltration in the diabetic rat's liver and kidney. However, rats treated with repaglinide illustrated a noticeable recovery of liver and kidney tissues.

According to published data on the effect of repaglinide administration that has antioxidant properties independent of its action on hyperglycemia, repaglinide's significant antioxidant activities create good effects at therapeutic levels and also it can make a significant contribution to its efficacy in the treatment of type 2 diabetes [7], [8], [13], due to its insulinotropic action, which is referred to as insulin exocytosis and an increase in the sensitivity of its receptors [15]. Furthermore, RG therapy has been shown to reduce the levels of lipid hydroperoxide (LPO) and enhance the activities of superoxide dismutase (SOD) in diabetic nephropathy kidneys [7]. Repaglinide, according to [16] has a favorable safety and efficacy benefit in type 2 diabetes patients with impaired renal function, and is a suitable therapy option, especially for those with more severe degrees of renal impairment.

Our study demonstrated that repaglinide's antioxidant activity was connected with its protective effect on liver and kidney lesion of alloxan induced diabetic rats, suggesting that it might be a suitable agent for treating and preventing the deleterious changes in diabetic rats' liver and kidney tissue.

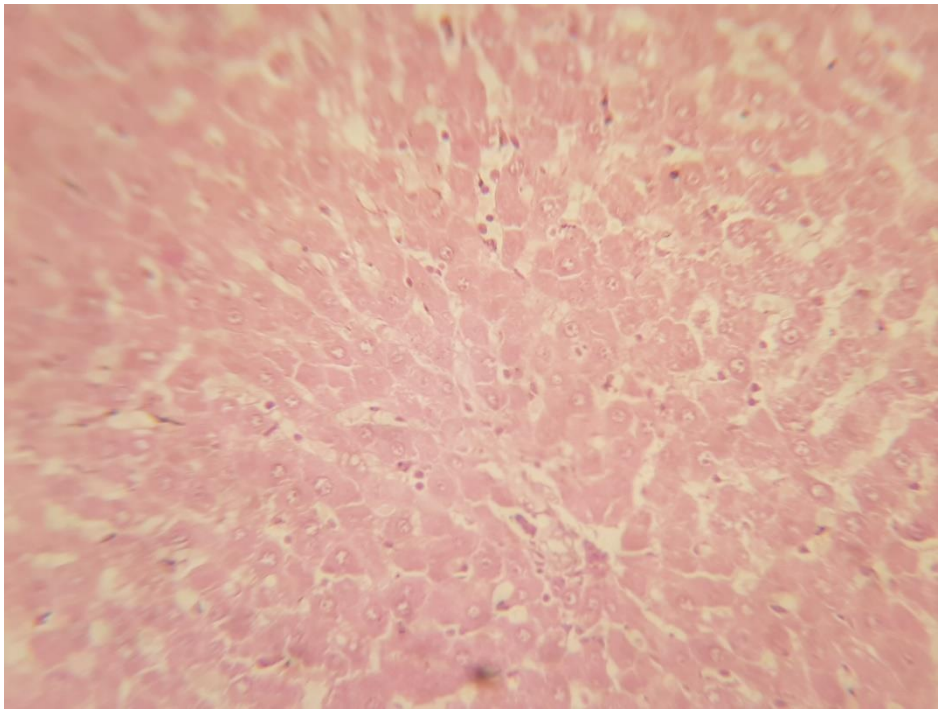

Figure 1: Cross Section of the Liver of Non-Diabetic Control Rats Showing Normal Histology, Stained with H&E 400x.

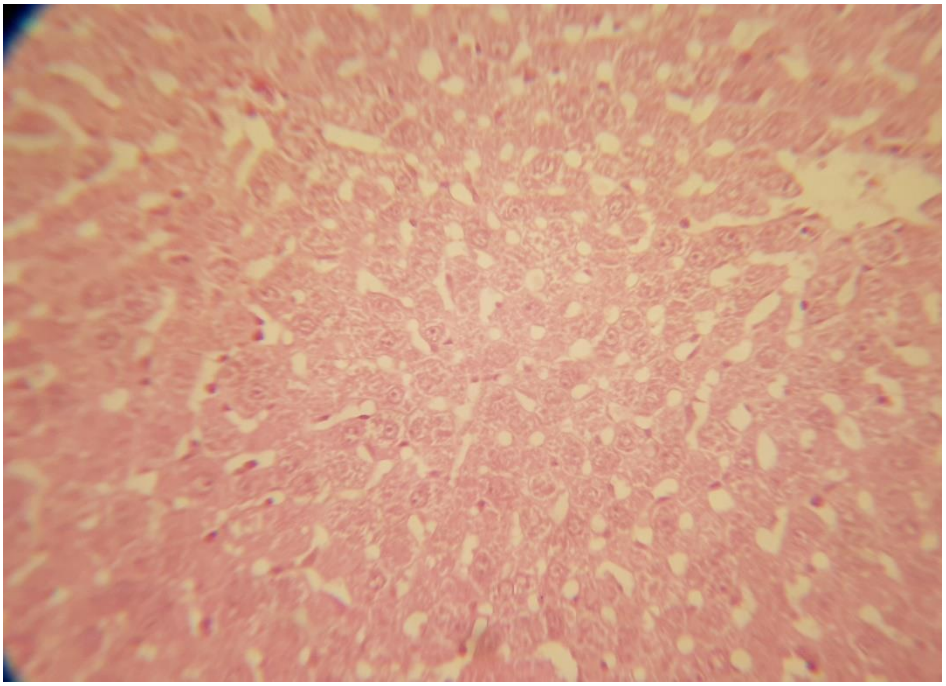

Figure 2: Cross Section of the Liver of Non-Diabetic Rats Treated with Repaglinide Showing Normal Histology, Stained with H&E 400x.

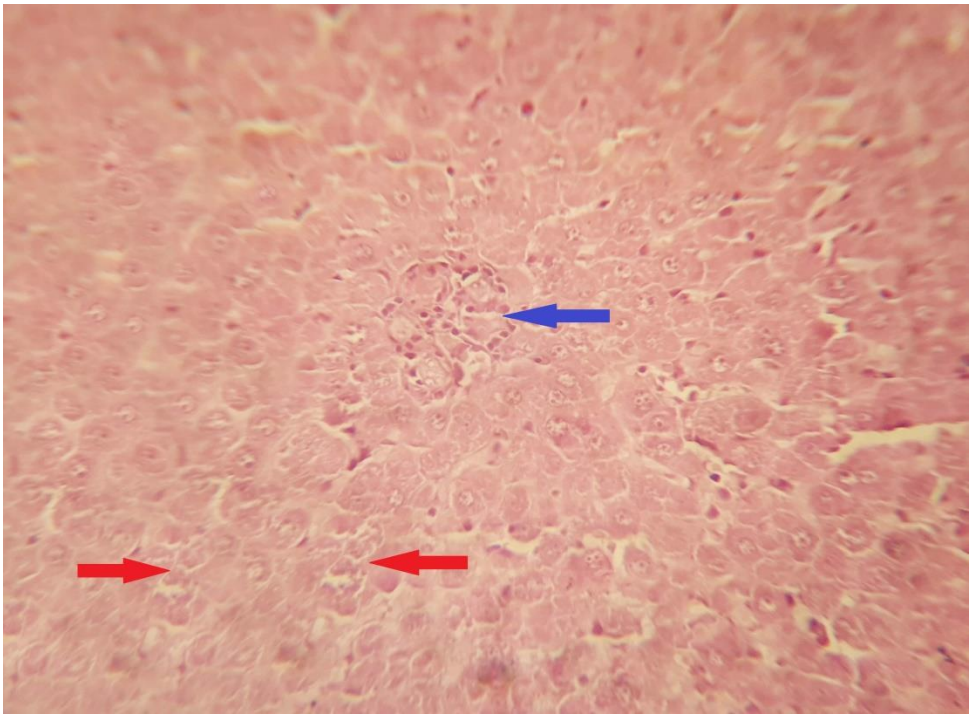

Figure 3: Cross Section of the Liver of Diabetic Rats Showing Lymphocyte Infiltration (blue arrow) and Hepatocytes Degeneration (red arrows), Stained with H&E. 400x

ISSN: 1343-4292
Volume 140, Issue 01, April, 2022

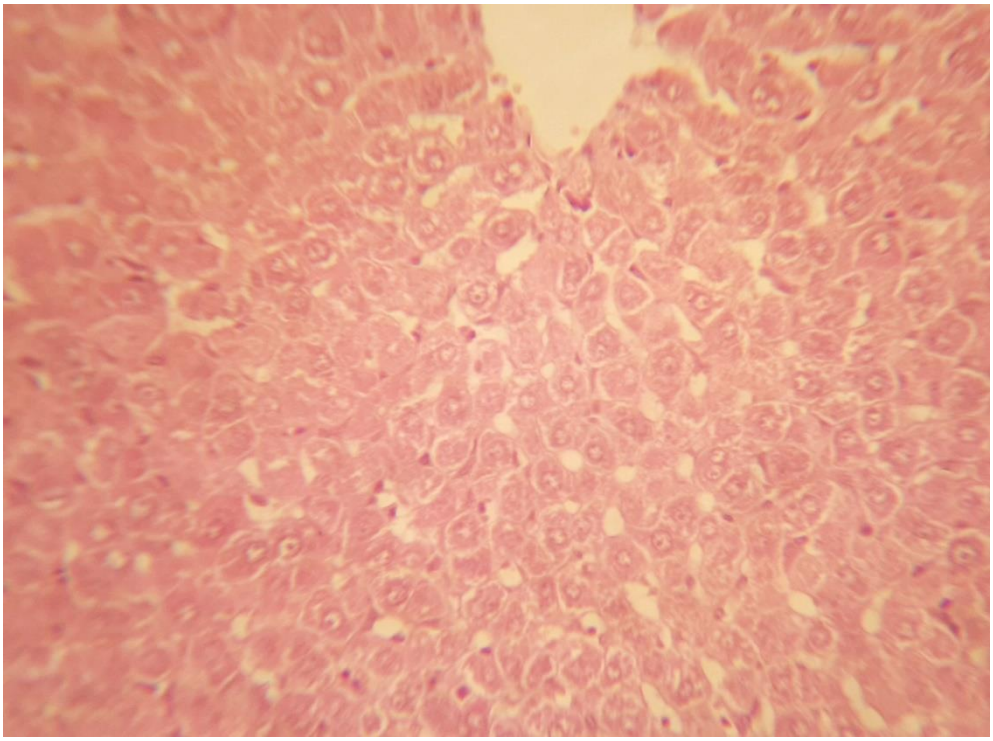

Figure 4: Cross Section of the Liver of Diabetic Rats Treated with Repaglinide Showing Normal Histology, Stained with H&E 400x.

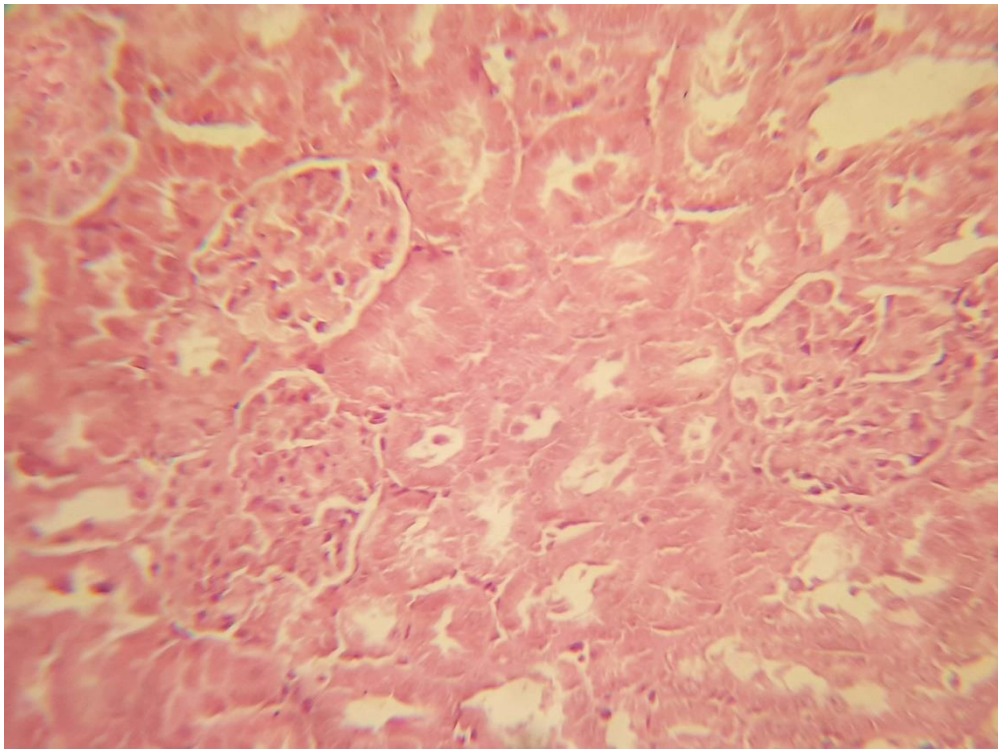

Figure 5: Cross Histological Section of the Kidney of Non-Diabetic Control Rats Showing Normal Histology, Stained with H&E 400x.

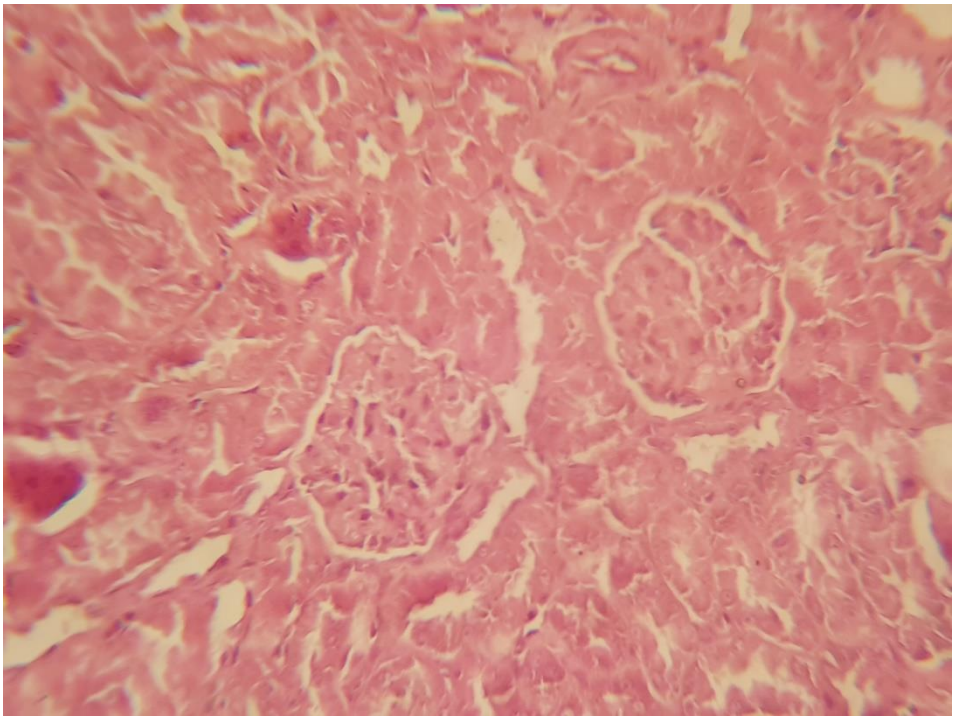

Figure 6: Cross Histological Section of the Kidney of Non-Diabetic Rats Treated with Repaglinide Showing Normal Histology, Stained with H&E 400x.

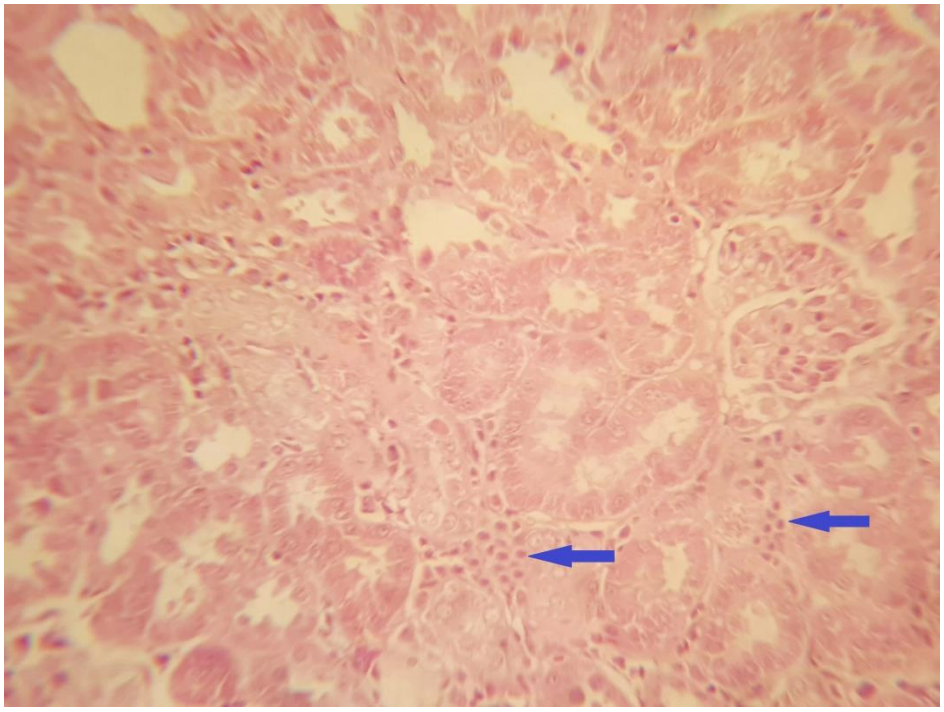

Figure 7: Cross Histological Section of the Kidney of Diabetic Rats Showing Lymphocyte Infiltration (blue arrow), Stained with H&E 400x.

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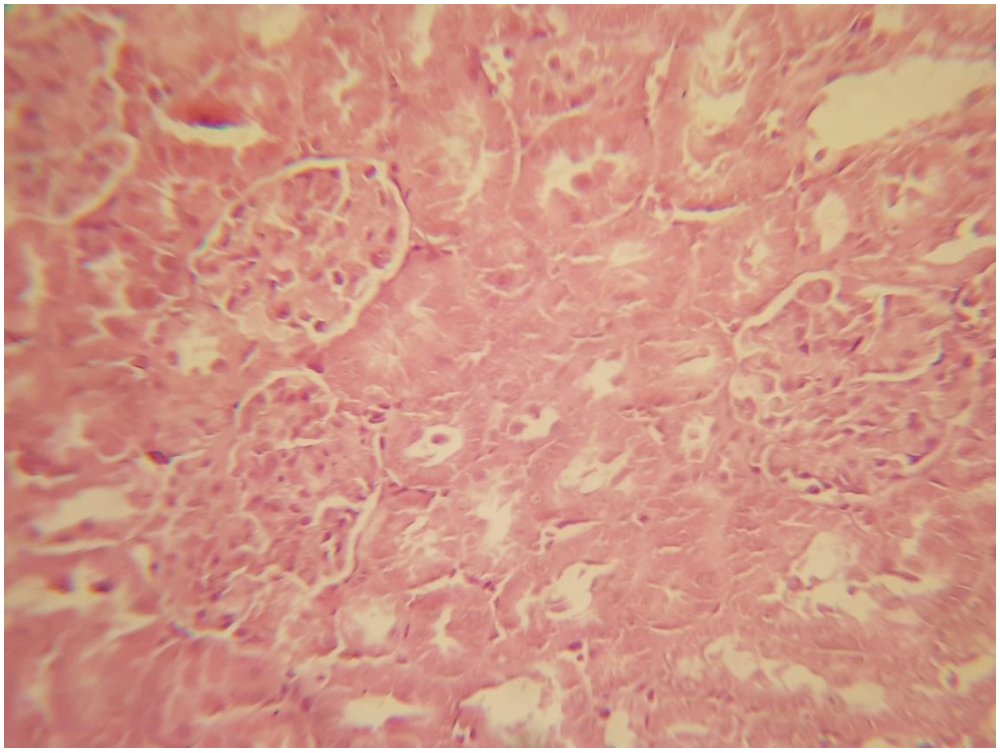

Figure 8: Cross Histological Section of the Kidney of Diabetic Rats Treated with Repaglinide Showing Normal Histology, Stained with H&E 400x.

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