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Teratogenic effect of hydroxychloroquine on the histological structure of adult rabbit Kidneys *Orectolagus cuniculus*

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ABSTRACT

Hydroxychloroquine (HCQ) is an effective drug for the treatment of various autoimmune disorders. It has appropriate pharmacological properties that show its effectiveness in improving the control of parasitic infections such as malaria. It is rapidly absorbed into the plasma and excreted through the kidneys. This study was designed to investigate the effect of hydroxychloroquine (HCQ) at two concentrations of 25 and 50 mg/kg/day on the histological structure of the kidney in an adult rabbit (*Orectolagus cuniculus*). The study was conducted on 18 rabbits, it was divided randomly and equally to three groups included a control group and a group that was treated with a concentration of 25 mg/kg/day of the drug, while the animals of the third group was injected with a dose of 50 mg/kg/day. The results of the histological study showed the occurrence of pathological histological changes to the kidneys in the group of animals treated with the drug of 25 and 50 mg/kg/day concentration, the most prominent of which was a clear congestion of blood in some blood vessels in the cortex area and between the epithelial cells lining the glomeruli. It also showed a clear cellular infiltration near the blood vessel. Degeneration of the lining of the epithelial cells of some renal tubules, especially the proximal convoluted tubules, and the separation of tubule cells from the detached basement membrane and their gathering in the lumen of the tubules in most tissue sections was observed. It was also found that the glomerulus was enlarged and that treatment with this drug led to a decrease in Bowman's space, in addition to an increase in the thickness and density of the basement membrane of the urinary tubules. Glomerular cells suffered from accumulation, shrinking, enlargement capsular space, and cell death. It can conclude from the above results that the hydroxychloroquine drug has clear effects on the histological structure of the kidneys.

1. Introduction

Since ancient times, humans have been exposed to many different pathogens, pollutants and chemicals, such as food additives or drugs used to treat a specific disease, as these drugs can have different origins obtained and manufactured from them. They are either chemicals of natural origin obtained from plants, fungi, or microorganisms, or these drugs are analogues of chemicals naturally present in biosynthetic pathways. These analogues include the intermediate compounds and end products of these pathways. One of these drugs is hydroxychloroquine, which is one of the drugs used in the treatment of malaria [24]. 4-aminoquinolonehydroxychloroquine (HCQ) was first made in 1946, [13]. Its structural formula is (C18H26ClN3O). This drug was known by several names, including Plaquenil, Oxichloroquine, Oxychlorochin, which is derived from chloroquine and differs from it only by the presence of a hydroxyl group and the half-life of the drug in the body is about 50 days. Hydroxychloroquine belongs to the class of drugs (AQs4)-aminoquinolines-4 [16]. It is considered a weak base due to the presence of an essential side chain that is believed to contribute to the accumulation of these drugs in intracellular compartments, in particular lysosomal compartments, which appears to be important for their potential interaction with nucleic acids [22]. It is considered a weak base due to the presence of an essential side chain that is believed to contribute to the accumulation of these drugs in intracellular compartments, in particular lysosomal compartments, which appears to be important for their potential interaction with nucleic acids [22]. HCQ has been used in the treatment of parasitic infections such as malaria, bacteria such as Q-fever, viral ones such as human immunodeficiency virus, and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis rheumatoid [6]. It has also been used to treat patients with Covid-19 who have symptoms of pneumonia [10]. On the other hand, many studies have confirmed that patients with rheumatoid diseases who are treated with HCQ sometimes suffer from arrhythmias. Other rare side effects of HCQ include gastrointestinal reactions, cramps cramps, liver dysfunction, itching, headache, dizziness, insomnia, and peripheral neuropathy [8]. Various common side effects of HCQ include gastro-intestinal upset, skin rash, headaches but the main concern is retinopathy with the consequent permanent vision loss. Ocular toxicity from hydroxychloroquine has become increasingly important due to the drug's increasing popularity and uses. Among the factors that increase the possibility of true retinopathy are: the daily excess dose, the cumulative increase in the dose, the duration of treatment and the age of the patient in addition to the presence of kidney disease or liver disease and the accompanying retinal disease [31]. Reports indicate that such drugs used to treat malaria lead to oxidative stress, especially in erythrocytes, leading to the formation of lipid peroxidation in the retina, which indicates that administration of these drugs increases NADPH, which produces lipid peroxidation [12]. [3] also reported cardiotoxic effects, including cardiomyopathy and heart rhythm disturbances, in which HCQ was found to cause electrical disturbance in the heart. Other possible side effects include loss of consciousness due to low blood sugar, suicidal behavior, and heart failure. Due to the lack of studies on the effect of the drug on the kidneys, the current study was designed to determine the teratogenic effect of hydroxychloroquine on the histological structure of the kidneys in the adult rabbit.

2. Materials and methods

The present study was designed based on the half lethal dose (LD50) of HCQ, which is measured by mg of HCQ/kg of body weight of rabbit. Two doses of the drug were chosen to test its toxic effect, which are 25 and 50 mg/kg. It was possible to calculate the amount of drug injected into rabbits used in this study based on the following equation:

$$\boxed{\frac{x}{D} = \frac{W_{rabbit}}{1000}}$$

Where: x: the injected amount of HCQ drug into rabbits measured by mg, D: the specified dose of the drug

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Volume 62, Issue 01, March, 2022

measured by mg/kg, W_{rabbit}: the weight of the rabbit used in the experiment measured by g.

In this study, 18 white male rabbits were used, supplied from the animal house in the department of biology - College of Education for Pure Sciences / University of Diyala. The average weight of rabbits used ranged between 1.210-1.350 kg. The animals were monitored for a week, and then divided into three groups: the first group was the control group that was not injected with the drug. The second and third groups were injected by 25 and 50 mg of HCQ/kg of rabbit weight, respectively. The intramuscular injection process lasted for 30 days, after which all the animals were dissected and the kidneys were removed and prepared to make tissue sections. 10% formalin solution was used to fix the samples for 24 hours, and then all the steps required for tissue sections were performed, as described in [27]. Hematoxylin-eosin dye was used to stain the slides to investigate the effect of HCQ drug on the histological structure of kidney.

3. Results

The results of the current study show that the kidneys of white rabbits treated by 25 mg/kg of HCQ for 30 days suffering of pathological changes such as congestion of blood vessels in the renal cortex, in addition to the presence of cellular infiltration near the blood vessel as represented in Figure (1).

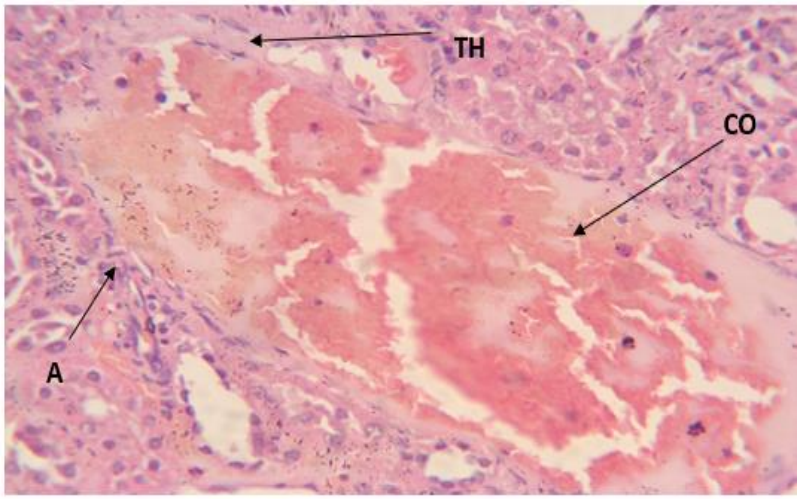

Figure (1) A cross-section of the kidneys of rabbits of the experimental group treated with a dose of 25 mg/kg of the drug, showing the enlargement of the vascular wall located in the cortex area within the kidney TH, vascular congestion CO, infiltration A. (H&E 40X).

The results of the study also elucidated the occurrence of degenerative changes such as swelling of the epithelial cells lining some renal tubules, especially the proximal convoluted tubules, causing narrowing of the lumen of some tubules. While it was observed that the wall of some tubules was destroyed, part of the tubule cells were separated and collected inside the lumen, necrosis of some urinary tubule cells, hemorrhage between the renal tubules, and glomerulus enlargement was also observed, which led to a reduction in the area of Bowman's space and the appearance of edema between the tubules as shown in the Figures 2 and 3.

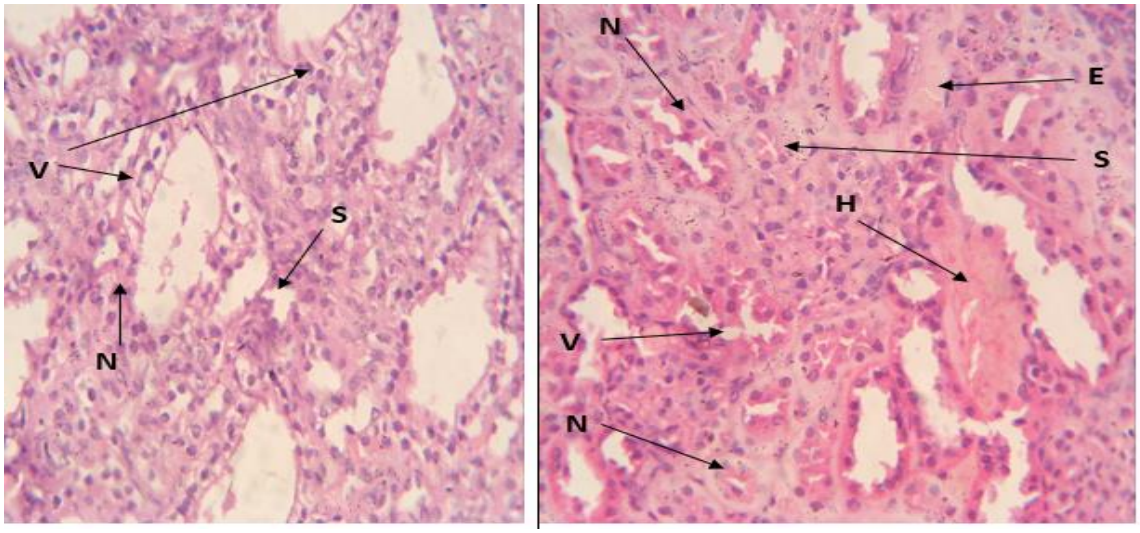

Figure (2) A cross section in the kidneys of rabbits of the experimental group treated with a dose of 25 mg/kg of the drug, showing the occurrence of necrosis N of cells of some urinary tubules, swelling S, edema E, hemorrhage H, detachment of cells from the basement membrane SB(H&E 40X).

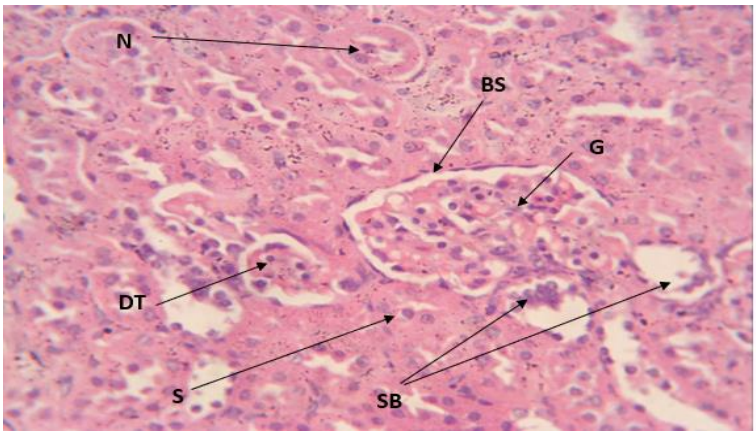

Figure (3): A section of rabbit kidneys injected with 25 mg/kg showing histological changes such as swelling of cells lining the tubules S, necrosis N, enlargement of glomerulus G, small Bowman space BS, detachment of cells from the basement membrane SB, aggregation of cells inside the lumen DT (H&E 400X).

The study also showed an increase in the severity of the negative effects resulting from the drug by increasing the dose of the drug, and that the histological sections of the kidneys of rabbits dosed with a concentration of 50 mg / kg of the drug showed more severe histological changes than the previous group. The results showed, by testing the sections under light microscope, an increase in the thickness and density of the basement membrane of the glomeruli and an expansion in Bowman's space. Shrinking was also observed in some glomeruli, leading to a decrease in the diameter of the glomerulus, while vacuolation was observed in some glomeruli, necrosis and hemorrhage in the glomerulus and the parietal region of it, and an increase in the infiltration of inflammatory cells around it as clarified in Figures 4 and 5.

ISSN: 0005-2523
Volume 62, Issue 01, March, 2022

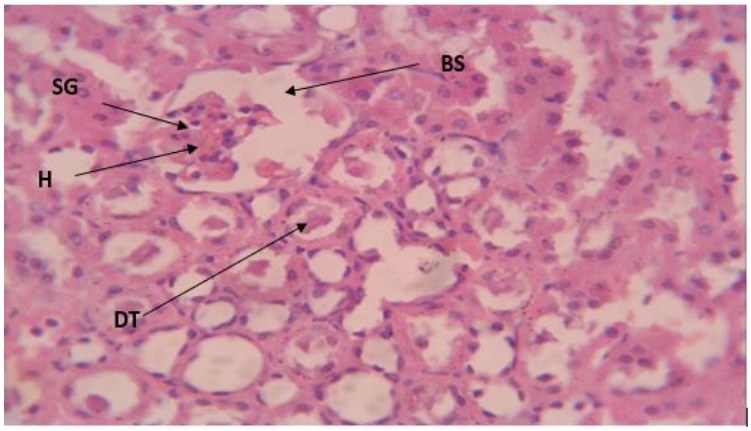

Figure (4): A section in the kidneys of rabbits of the second group injected with 50 mg/kg showing shrinkage of glomerulus SG, increase of Bowman space distance BS, and occurrence of intraglomerular hemorrhage H, collection of cell debris inside the tubules DT (H&E 40X

Sections also showed congestion of blood vessels and the presence of bleeding in them, as well as infiltration of inflammatory cells and the appearance of fibrosis around the blood vessels as shown in Figure 6. The results of the study noted an increase in the thickness and density of the basement membrane of the renal tubules and the degeneration and damage of the cells and their separation from the basement membrane and their collection in the lumen of the tubules in most of the tissue sections, in addition to the thickening of the nuclei of some renal tubules, necrosis and vacuolation in some of the proximal and distal tubules with the appearance of edema and hemorrhage between cells and infiltration of inflammatory cells between the tubules as shown in Figure 7.

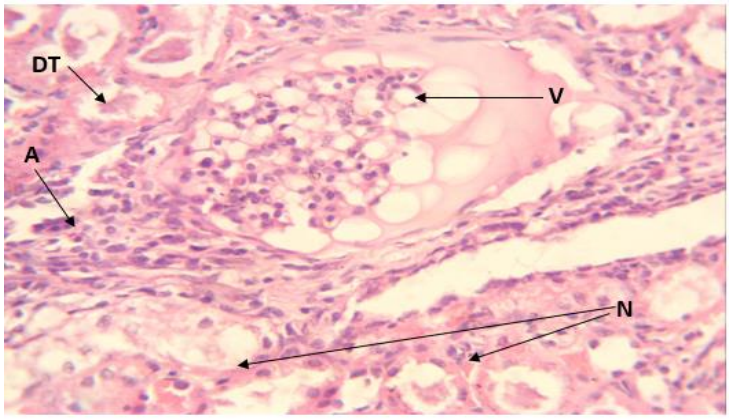

Figure (5): A section of the kidneys of the second group dosed with 50 mg/kg showing the most important histological changes, including necrosis N, intra-tubule debris collection DT, rupture V, infiltration of inflammatory cells A, (H&E 40X).

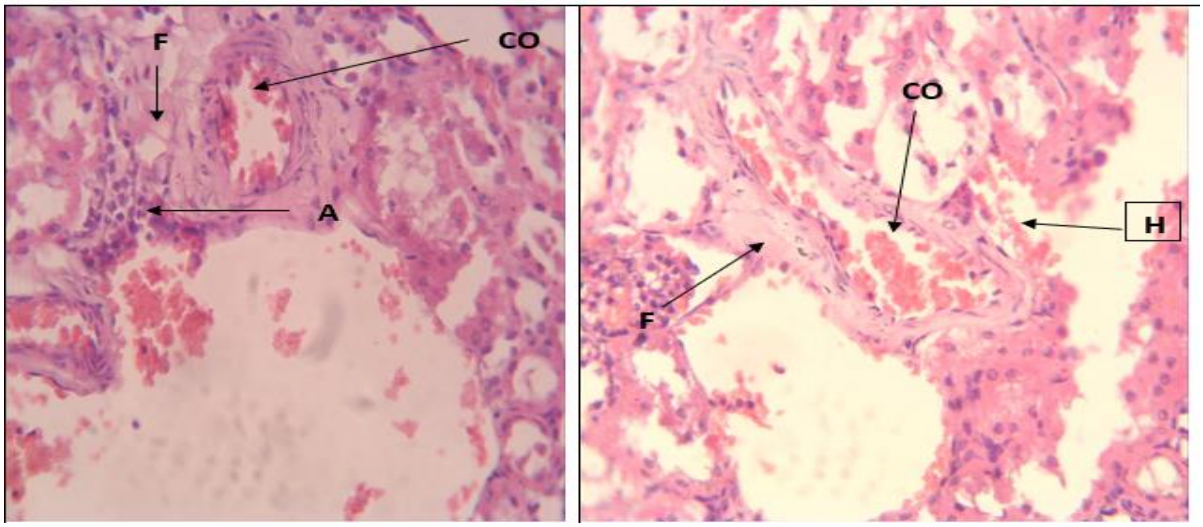

Figure (6): A section of rabbit kidneys dosed with 50 mg/kg shows the occurrence of congestion CO, hemorrhage H, inflammatory cell infiltration A, fibrosis F (H&E) 40X).

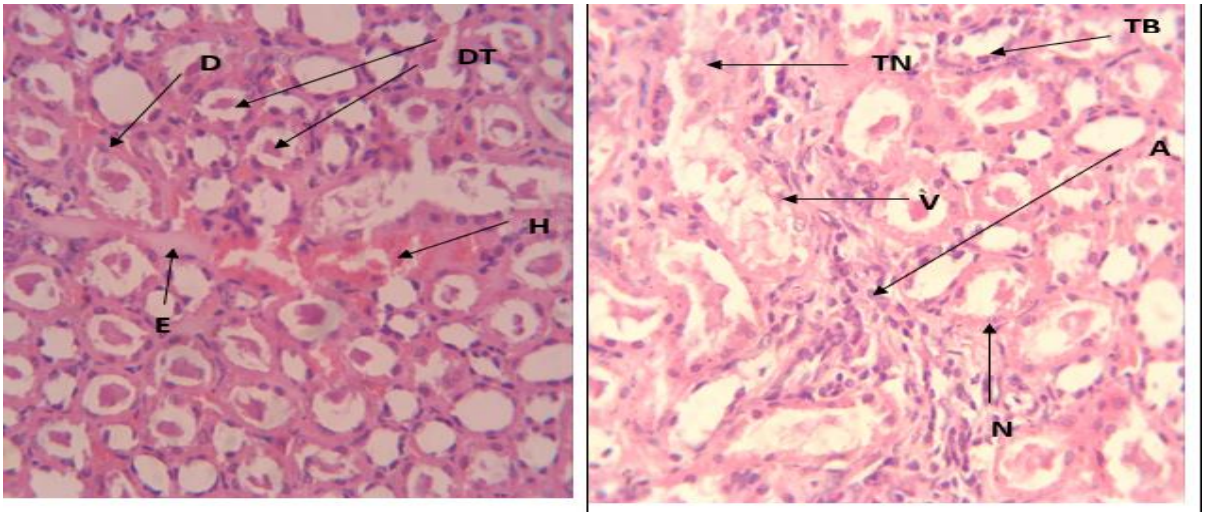

Figure (7) The section shows the changes represented by an increase in the thickness and density of the basement membrane of the urinary tubules TB, degeneration of cells D, detachment of cells from the basement membrane and their collection in the lumen of the tubule lumen DT, thickening of the nuclei Tn, necrosis N, vacoulation V, edema E, hemorrhage H, and infiltration of inflammatory cells A (H&E 40X).

4. Discussion

The number of drugs currently being marketed is innumerable, and the ever-increasing number of prescriptions is increasing the potential for adverse effects dramatically. And because the kidneys rid the body of many drugs through the excretion process, they may cause kidney damage. Some drugs may cause direct toxic effects on the glomeruli or even on the epithelial cells, the podocytes and the mesengial cells [5]. Acute kidney injury is a very common diagnosis, up to 60% of critically ill patients are found, and the third major cause is drug poisoning. Nephrotoxicity can be defined as any kidney injury resulting directly or indirectly from drugs [21]. Many therapeutic agents have nephrotoxic effects, especially when the half-life is prolonged and their levels in the blood rise due to decreased renal excretion [15]. The results of the current study, by examining the histological sections of rabbit kidneys after being injected with the drug for 30 days, showed the presence of histological changes in the kidney tissue. These changes included both glomerular cells and tubule cells, which may be due to the effect of the accumulation of the drug or its

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Volume 62, Issue 01, March, 2022

metabolic derivatives in the kidneys. Because the function of the kidneys is to eliminate waste, minerals, acids, drugs, or their metabolites, the excretion may expose blood vessels, tubules, and interstitial tissues to very high concentrations of these substances and may damage them) [19], [21]. Vascular congestion of blood vessels in the cortex area was observed as well as enlargement of the walls of these vessels, this could be due to the toxic effect of HCQ, which led to an inflammatory response that led to an increase in blood flow to the area of damage, which also resulted in damage to epithelial cells In the tubules and glomeruli of vaccinated animals when compared with the control group [1].

The change in pressure may be a cause of congestion, as these drugs are likely to have effects on blood vessel pressure. [19] indicated that the factors that control the regulation of blood circulation within the kidneys (such as prostaglandins and the renin-angiotensin system) are affected by many drugs and thus change the pressure in renal vessels. Other effects also appeared, such as swelling of the epithelial cells lining some tubules, especially the proximal convoluted tubules, vacuolation of the cytoplasm, which caused the narrowing of their cavities, the destruction of the wall of some tubules, and the necrosis of the renal tubule cells, and this is consistent with the results reached by [11], Where the same changes were observed in the kidneys of rabbits when using Relief drug, which resulted from the toxic effect of the drug or its metabolites that lead to a change in the permeability of cell membranes, which prevents the entry of some important substances such as glucose, which is an important energy source for the cell, or prevents the exit of harmful metabolites from inside the cell and thus its accumulation, and this leads to necrosis and gradually death of cells. The swelling of cells in the tubules is also caused by a lack of oxygen, and thus a lack of energy that the cell needs, and the effect of the sodium pump, which works to regulate the osmotic pressure, thus accumulating fluids inside the cell, leading to its swelling. These results also agreed with the results of the effect of Ritan-A drug on mice by researchers [4], and the effect of phenol on the kidneys of mice [30]. Transtubular transport and reabsorption processes in the tubules of the renal cortex may increase drug concentrations to levels much higher than those in plasma, which leads to the concentration of changes such as necrosis and degeneration in the renal tubules, and most clinical and non-clinical studies indicated that drugs are one of the most important causes of these changes [7].

The results of the microscopic examination also revealed an increase in the severity of histopathological effects with increasing the dose, in addition to the previously mentioned damages, the whole group dosed with 50 mg/kg showed changes represented by the infiltration of inflammatory cells, which may be caused by the effect of drug accumulation or the occurrence of inflammation, as [5] explained) that the drugs can cause systemic immune reactions, leading to inflammation and kidney injury. It is possible that an existing renal injury such as fibrosis is responsible for attracting immune cells to the kidneys [26]. The sections also showed the presence of necrosis and degeneration due to the same reasons mentioned above, the necrosis may be related to ATP depletion, which eventually leads to cell death [23]. The expansion of Bowman's space and glomerular contraction may be due to degeneration, death and atrophy of glomerular cells, and the reason may be the effect of the drug on the hormone Angiotensin I, which stimulates the mesangial cells to contract, resulting in a narrowing of the glomerular capillary blood vessels as these cells support the capillary blood vessels, and Its constriction leads to the contraction of the glomerular capillary blood vessels and thus increase the area of Bowman's space [1]. These changes agreed with the results of [18], which included the effect of taxol on the kidneys of rats, and the effect of fructose on the kidneys of rats [20]. The results of the examination also showed the separation of the renal tubule cells from their basal membranes, with the occurrence of hypertrophy and necrosis, and this may be a result of the effect of HCQ on the arteries, which reduces the supply of blood, which in turn affects the nutrition of cells leading to their death, and drugs may affect the enzymes secreted by the kidneys that regulate Arterial contraction and relaxation, such as prostaglandins. [3] note the toxic effects of HCQ to the heart, including cardiomyopathy

and heart rhythm, as well as causing an electrical disturbance in the heart. These disorders may reduce the efficiency of the heart in preparing organs, including the kidneys, with blood, leading to damage. As [2] reported that the functioning of the heart and kidney function are closely interrelated, and dysfunction in one of these organs often leads to deterioration in the function of the other, which is known as cardiorenal syndrome. Examination showed the presence of fibrosis between the cells and around the blood vessels. The emergence of fibrosis has several causes, the work of the immune system and the infiltration of immune cells may be a reason for this. It is known that renal inflammation is the fuel for the initiation of renal fibrosis, where the release of cytokines and infiltration of inflammatory cells leads to fibrosis. Repairs of damaged tubules include activation of the epithelial growth factor receptor (EPGFR), which stimulates the proliferation of myofibroblasts in the interstitium and the secretion of collagen and extra cellular matrix (ECM) proteins that lead to fibrosis [17]. Kidney fibrosis also appears to be related to the loss of nephrons and their replacement by scarring, or to be caused by inflammation and injury to the interstitium [28]. The main causes of renal injury are based on immune reactions, tissue hypoxia, ischaemia, exogenous factors such as drugs and endogenous substances such as glucose or proteins, etc. [14].

5. Conclusion

Hydroxychloroquine caused many histopathological changes, including hyperemia, hemorrhage, edema, and fibrosis. It also caused the degeneration and atrophy of the glomeruli and the epithelial cells that make up the tubules, and the severity of the effects increased with the increase in the dose.

Recommendations: It is important to be fully aware of the renal side effects of drugs because of its importance with regard to prevention and early diagnosis of damage, and further studies are required to clarify the effect of this drug on the histological structure on the kidneys and other organs.

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