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Revealing histological changes within renal components in treated mice (*Mus musculus*) with one of anti-diabetic drugs

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ABSTRACT

The present study was conducted to determine the effect of some anti-obesity drugs on the histological structure of the kidney in Swiss mice (Mus musculus) for 30 days. Twenty mice were used and each group was placed in a separate cage and divided into two groups, each group containing 10 mice. The first group was the control group where its animals were injected by distilled water, while the second group was the first experiment group where its mice were injected by the Saxand drug at a concentration of 0.3 mg/mL day. On the last day, the treated animals were sacrificed, their kidneys were extracted very carefully, and tissue sections were prepared by embedding in paraffin wax. The sections were then stained using two types of dyes which were hematoxylin and eosin (H&E). Finally, the histological sections were tested using a light microscope equipped with a digital camera, and the required information was recorded. Several histopathological changes were recorded in the kidneys tissue of animals treated with saxenda drug. Histopathological examination showed an enlarged vascular wall in the cortex area, along with vascular congestion and infiltration of inflammatory cells. In addition, had indications of, bleeding inside the glomerulus and cell separation from the basement membrane. Furthermore, degenerative changes in the medullary region of the kidneys. Some cells broke down and vacuolation was also observed, Deposition of colloidal fibers around blood vessels. Saxenda caused various changes in tissue structure, such as inflammation, bleeding and increased blood flow. It also led to a decline and deterioration of specific cells in the kidneys, with more significant effects observed at higher doses. The results of this study also showed that the weights of animals treated by the previously mentioned concentrations of saxenda drug were affected, as the weight rates of all experimental groups decreased and the average weights of animals dosed for 30 days were (25.5 - 28) g.

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1. INTRODUCTION

Humans administer medications to alleviate the manifestations of diseases. Nevertheless, various pharmaceuticals may elicit adverse side effects that undermine general health or produce toxicological consequences. Conversely, the consumption of drugs without professional prescription can trigger critical complications and occasionally mortality, whether acutely or chronically. Moreover, the bioaccumulation of chemical agents may exert toxicological effects on the organism across time, depending on biological variables including species, age, sex, and overall body weight [1]. A growing body of public interest in fitness and physical well-being is increasingly evident, encouraging individuals to pursue diverse nutritional supplements, pharmaceuticals, or therapeutic agents that promote weight reduction while safeguarding overall health. Within this context, considerable emphasis is placed on slimming products, which assist in reducing excess weight [2]. Slimming pills are described as a category of formulations or dietary supplements designed to assist individuals in reducing body weight, sustaining an optimal weight, or reaching a desirable and balanced body mass.

These pills differ widely in composition and modes of administration, generally encompassing reduced-calorie preparations, dietary additives, pharmaceutical agents, and herbal derivatives reputed to produce weight-reducing benefits. Slimming pills are frequently incorporated within structured and scientifically guided weight management approaches [3]. The demand and widespread utilization of slimming products are steadily rising because of their accessibility and enhanced recognition of the significance of weight control and preserving general health. Numerous slimming formulations are employed to assist in regulating body weight and minimizing obesity, a disorder that may contribute to several medical complications, including hypertension and diabetes mellitus [4]. The consumption of slimming pills represents an appropriate option for individuals seeking to avoid surgical operations, thereby minimizing dependence on invasive medical interventions. Furthermore, certain slimming pills are administered orally, offering an additional method for individuals who prefer oral pharmaceutical treatment rather than undergoing surgical procedures [5]. Nevertheless, the consumption of slimming supplements is not wholly advantageous; instead, it represents a two-edged sword. Although slimming supplements provide certain health advantages, their use requires caution, with precise dosages and appropriate timing, and always under medical or nutritional supervision to prevent possible adverse health consequences [6]. Using diet slimming without the supervision of a doctor or nutritionist can cause several health problems, including side effects such as high blood pressure, headaches, irritability, insomnia, and others. Some diet pills may also be low in essential nutrients such as proteins, vitamins, and minerals, which can lead to malnutrition. In addition, the unbalanced use of diet pills can have negative effects on mental health such as anxiety, depression, and nervous tension. Some diet pills can also cause gastrointestinal disturbances such as constipation, diarrhea, or intestinal irritation. Finally, they can affect cardiovascular function, increasing the risk of heart disease and stroke[7]. Two of the most commonly prescribed anti-obesity drugs are Saxenda and Rybelsus. These medications represent promising choices for individuals pursuing weight reduction, due to their minimal caloric impact and proven ability to promote fat metabolism without impairing normal weight [8]. Saxenda is a medication employed in the treatment of obesity and weight management. It incorporates the active compound liraglutide, a hormone that modulates appetite and satiety through action on the brain's appetite center. Saxenda's formulation promotes insulin secretion from the pancreas during elevated blood glucose levels. Additionally, it delays gastric emptying and potentially suppresses appetite, supporting weight reduction [9]. This medication is usually administered via subcutaneous injection once daily and should be combined with a calorie-restricted diet and consistent physical activity. Saxenda is mainly indicated for individuals with severe obesity (grade 2 or 3) who have been unsuccessful in losing weight through conventional approaches such as lifestyle modification, diet, and exercise. Saxenda may also provide advantages for individuals with obesity-associated health conditions, including hypertension and diabetes [10].

2. MATERIALS AND METHODS

Drug Doses & Method of Administration: In developing this study, the sublethal dose (LD50) of ligaglutide, or Saxenda, was used. LD50 is determined by multiplying milligrams of mouse by kilograms of mouse weight. To test the toxicity of the drug, a single dose of 0.3 mg/mL was chosen. A specific equation was used to calculate the dose of drug administered to mice in this research.

$$x/D=W\text{mouse }/1000 \quad (1)$$

Where: x: is the weight to be injected into the mice in the experiment, measured in mg,: is the specified dose of saxenda, which is 0.3 mg/mL , W.mouse: is the weight of the mice used in the experiments, which ranged between 28-43 g. Preparation of animals: 20 Swiss white mice of both sexes, male and female, aged 3-4 months, weighing 19-43 grams, were prepared and raised in the animal house, by placing them in plastic cages covered with metal mesh covers, measuring 30 × 50 × 20 cm. The cage floors were covered with sawdust, and they were cared for and provided with water and feed. The animal cages were cleaned every day and sterilized with disinfectants. The animals were then placed in suitable laboratory conditions in terms of ventilation and lighting at a temperature of 23-26 C.

Dissection of Animals and Preparation of Histological sections: The mice were dosed for thirty days with saxenda , after which their kidney were removed for tissue section analysis and the animals were dissected. The tissue sections were prepared using the method described by [11] after the tissues were fixed for 24 hours in a 10% formalin solution. The slides were colored using hematoxylin-eosin dye in order to evaluate how saxenda impacted the histological makeup of the kidney.

The treatments were repeated three times, and each replicate included 50 worms. The number of fatalities was calculated after 24 hours, 48 hours, and one week from the treatment, and the lethal concentrations and the median lethal concentration (LD50) were calculated according to the [15].

The statistical program was used to analyse the data, and analysis of variance and the least significant difference test were employed to determine the essential differences between the means of the transactions at a significance level of 0.05. To assess fertilizers' effect on worms' biological indicators, the measurement of hemoglobin levels was chosen according to the method [16]. Additionally, the worms' activity, movement, and shapes were observed, recorded, and photographed.

3. RESULTS AND DISCUSSION

The results of the current study of the kidneys of mice treated with a concentration of 0.3 mg/ml of Saxenda for 30 days showed pathological tissue changes, the occurrence of Bowman's space expansion and the occurrence of hemorrhage inside the glomerulus, as in Figures (1). The results obtained also showed the occurrence of congestion of blood vessels, hemorrhage of blood vessels, and the formation of a blood clot inside the blood vessels, as in Figure (2), and the death of some cells and the occurrence of degeneration in the tubule lining, as in Figure (3).

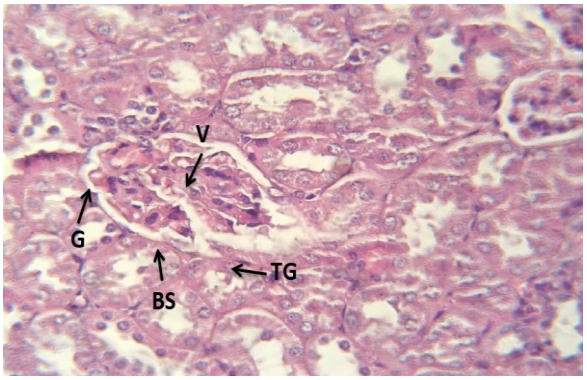

Figure (1) Cross section of the kidney of mice in the experimental group treated with 0.3 mg/ml Saxenda for 30 days, showing the occurrence of inflammatory changes in the glomeruli inside the kidney. (BS) Bowman's space, (TG) thickness and density of the glomerular basement membrane, (CO) vascular congestion, (DT) destruction of some cells, (V) cell rupture in the parietal region of the glomerulus. Stained (×H&E 40)

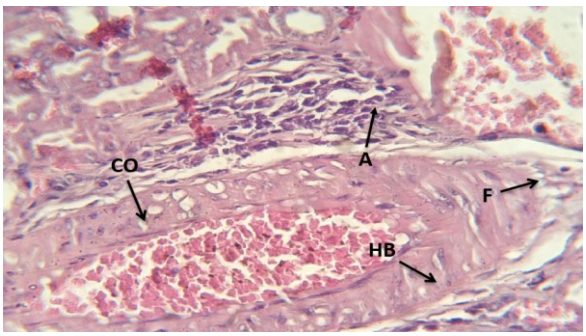

Figure (2) Cross section of the kidney of mice in the experimental group treated with 0.3 mg/ml Saxenda for 30 days, showing the occurrence of intrarenal vascular congestion. (F) Perivascular fibrosis, (CO) Vascular congestion, (HB) Vascular wall hyperplasia, (A) Infiltration of inflammatory cells. Stained (×H&E 40)

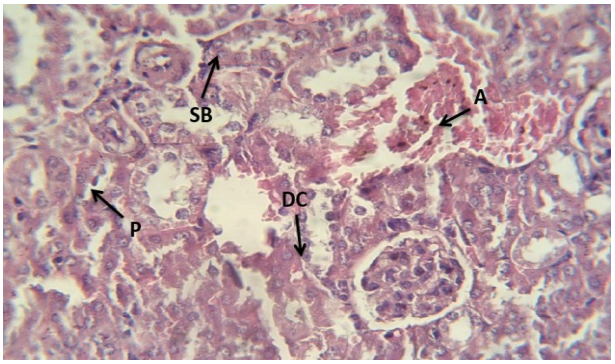

Figure (3) Cross section of the kidney of mice in the experimental group treated with 0.3 mg/ml Saxenda for 30 days. Note (P) thickening of the nuclei in the renal tubules within the kidney. (SB) detachment of some tubule cells from the basement membrane. (DC) small cell size. (E) edema. Stained (×H&E 40)

It has been shown through this study that prolonged use of some medications can cause harm and may lead to a malfunction in them, and it is necessary for health care professionals to be aware of the effects and negative effects that may occur as a result of the use of some medications on the kidneys and to monitor the patient well and monitor its functions [12]. Kidney of all patients need to learn how to use medications to avoid kidney damage and should be reminded to report any unusual symptoms to their physician [13]. Current studies are focusing on developing safer medications that have little effect on kidney function. The results of the current study revealed thickening of the nuclei in the renal tubules and degeneration of the epithelial cells, as well as necrosis and rupture between some proximal and distal tubules, decreased cell size, damage to the lining epithelial cells in most histological sections, and detachment from the detached basement membrane. Edema appeared between the cells, as shown in Figure (4). Histological sections passing through the medulla region revealed some pathological histological changes, such as the presence of inflammatory cell infiltration, necrosis and rupture of the cells forming the collecting tubules and other tubules within this region. Swelling of some cells, indicating hydropic degeneration, and thickening of the nuclei of others, were also observed, as shown in Figure (5).

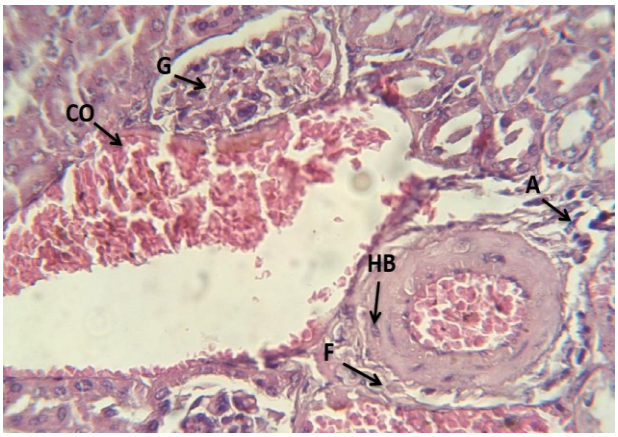

Figure (4) A cross-section of a kidney from mice in the experimental group treated with 0.3 mg/ml Saxenda for 30 days, showing the appearance of perivascular fibrosis within the kidney. Note (F) perivascular fibrosis, (CO) vascular congestion, (HB) vascular wall hyperplasia, (A) inflammatory cell infiltration, (G) glomerulus. Stained (×H&E 40)

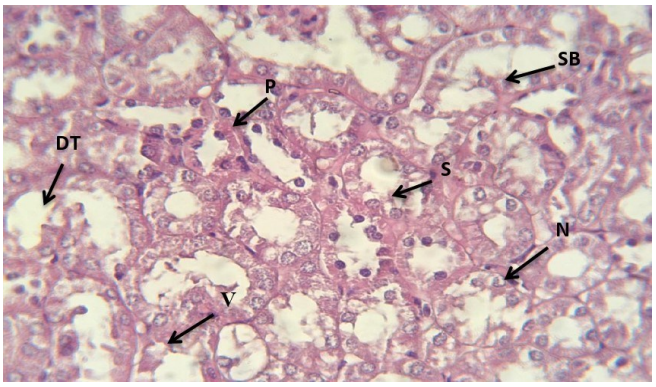

Figure (5) A cross-section of a kidney from mice in the experimental group treated with 0.3 mg/ml Saxenda for 30 days, showing degenerative changes occurring in the medullary region within the kidney. Note: (S) swelling of some tubule cells, (SB) detachment of some tubule cells from the basement membrane, (P) thickening of the nuclei, (V) vacuolization of cells, (DT) destruction of some cells, (N) cell necrosis. Stained (×H&E 40)

Collaboration between doctors, researchers and pharmaceutical companies is essential to ensure patient safety and improve outcomes for people who are at risk of kidney failure resulting from damage caused by drugs [14]. This study indicated that mice treated with drugs for a month showed significant changes in kidney tissue due to the large amount of drugs affecting kidney cells. Excessive medication can be harmful to the kidneys because they are exposed to a large amount of chemicals, which can lead to problems such as aneurysms, obstruction in the blood vessels, and inflammation [13]. In addition, inflammatory cells were detected in the tubules and glomeruli of treated animals, suggesting inflammation or drug accumulation. Existing kidney damage can attract immune cells [1], which may lead to worsening of the condition in the future [15]. These results are consistent with previous studies on drug effects on rat kidneys, suggesting that high concentrations of drug from renal transport and reabsorption can lead to necrosis and collapse [16]. Medications play an important role in the changes observed in kidney tissue [17].

4. CONCLUSION

The findings of the present study demonstrated that administration of Saxenda (0.3 mg/mL) for 30 consecutive days induced marked histopathological alterations in the renal tissue of experimental mice. These changes included vascular wall hypertrophy, vascular congestion, inflammatory cell infiltration, intraglomerular hemorrhage, degenerative changes, and separation of tubular cells from the basement membrane, in addition to perivascular fibrosis. Such alterations indicate that prolonged exposure or higher doses of Saxenda may lead to significant renal impairment and functional deterioration. Therefore, the clinical use of this drug should be approached with caution and under strict medical supervision, with continuous monitoring of renal function to minimize potential complications. Further investigations are recommended to elucidate the underlying molecular and physiological mechanisms responsible for these alterations and to explore safer therapeutic alternatives.

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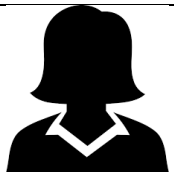	**Dr. Thekra Atta Ibrahim** is Professor at College of Education for Pure Science, University of Diyala, Iraq. She received the B.Sc. degree and M.Sc. degree in biology science from the University of Diyala, IRAQ. She Holds a PhD degree in biology Science with specialization in Histological Analysis Tissue Preparation Paraffin Embedding Anatomic Pathology Immuno-histology Immunocytochemistry Tissue Fixation Tissue Dissection Cryostat Sectioning and Ultrastructure. Her research areas are embryology and histology. She has published several scientific papers in national, international conferences and journals. She can be contacted at email: thekraatta@uodiyala.edu.iq.
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