



Effect of Perfluorooctanoic Acid on Kidney Function in Diabetic and Non-Diabetic Male Guinea Pigs

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A B S T R A C T

Perfluorooctanoic acid (PFOA) is a synthetic fluor-surfactant chemical used widely in products that resist oil, heat, grease, stains, and water. It is also used in producing other fluoropolymers. The main sources of exposure to PFOA are water, soil, and animal-origin food (meat, fish, and dairy products). The aim of this study to evaluate the renal function following oral gavage of sub-lethal dose of PFOA in diabetic and non-diabetic guinea pigs. The experiment run for 4 weeks, total of 40 male guinea pigs, (*Cavia porcellus*), were randomly selected and grouped into four equal groups. The first group (G1) served as the negative control; 2nd group (G2) alloxan induced diabetic, 3rd group (G3) non-diabetic was exposed to PFOA at 100 mg/kg BW orally/daily and 4th Group (G4) was diabetic guinea pig exposed to PFOA at 100 mg/kg BW orally/daily. Serum creatinine and histopathological alterations in the kidney tissue were evaluated. Serum creatinine concentrations were significantly increased ($P<0.05$) in G3 and G4 exposed to PFOA. High serum creatinine levels were suggesting impairment in kidney function. Impaired kidney function was confirmed through histopathological changes such as glomerular atrophy, severe necrosis, and degeneration of renal tubular epithelium in guinea pigs that received PFOA in G3 and G4. In conclusion, the results confirmed that PFOA was associated with renal damage and elevated creatinine concentrations in diabetic and non-diabetic animals since PFOA itself can contribute to diabetes.

Keywords: perfluorooctanoic acid, guinea pigs, renal toxicity, diabetes

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INTRODUCTION

The perfluoroalkylated substances (PFAS) are a large group of chemical compounds that consist of a completely fluorinated hydrophobic alkyl chain with different carbon atoms (from 4 - 16 carbon atoms) and a hydrophilic end (1). The most prominent member among the perfluoroalkylated substances is perfluorooctanoic acid (PFOA) with eight carbon chain (2). Perfluorooctanoic acid used in industrial sites and commercial products as carpeting, clothing, fire-fighting foam, non-stick cookware

and fast-food packaging (3, 4). Perfluorooctanoic acid is also used for the production of fluoropolymer, as surface treatment agents, and for the synthesis of other fluorinated polymers (5). Manufacturing and industrial sites that discharge PFOA into wastewater are considered as the major contamination source in environment (6). Despite phasing out of PFOA production in North America and Europe, the developing countries of Asia, Africa, and Latin America are still producing PFOA. In addition, China is considered the largest fluorochemical producer and consumer in the world (7, 8). In recent years, there is an

increase in concern about the potential harmful effects of PFOA and its salts on both the environment and living organisms (9, 10). Researchers revealed that PFOA accumulate mainly in the kidney and causes nephrotoxicity with impairment kidney functions (6). Moreover, diabetes (DM) is one of the health conditions which can be caused by Perfluorooctanoic acid (PFOA) (11).

The toxicokinetic of diverse PFAS members are influenced by their chemical composition, chain length and branching (12). PFOA is easily absorbed orally, as well as inhalation and cutaneous routes (13). Animal studies have found that both long- and short-chain PFAS are rapidly absorbed when given orally to the animal model. In toxicokinetic studies, substances are evaluated based on the time that required for 50% of the chemical to fall of its initial concentration half-life ($t_{1/2}$). For example, the rate of absorption in the digestive tract of rats has been calculated to be < 2 h. Notably, female rats absorbed PFOA at a rate faster than in male rats about 1.1 h vs. 10 h. The mechanisms underlying the differences in toxicokinetics variables between males and females is unknown, but it is supposed to include hormonal variations influencing the absorption of these chemical materials (14) PFOA is easily absorbed following oral exposure and is mostly present in liver, kidney and blood of rats. It can easily cross the blood-placenta barrier and pass to the fetus, where it is mainly present in the liver (15). PFAS bind to the serum albumin and proteins in plasma such as gamma globulin, transferrin, alpha-globulin, beta-lipoproteins and alpha-2-macroglobulin in both rat and human plasma, but the affinity for albumin to binding in rats is more than in human (16, 17). The absorbed PFAS distributed extensively from plasma into the soft tissues. The variance in PFAS plasma half-lives between species is most likely due to changes in the density, nature and the activity of renal tubular organic anion transporters (OATs) among species, as well as the differences in affinity of PFAS (17, 18). PFOA is not broken down within the body (not metabolized) (19, 20). PFAS are mostly excreted in urine, with minor levels expelled in the feces and in breast milk. The elimination half-life of PFAS compounds has shown to be quicker in females than in males rats (14) The association between serum PFOA and diabetes prevalence was documented (21). Based on the biodegradability and bioaccumulation properties of PFOA in animals and human tissues, concerns are increasing about the harmful effects of PFOA on kidney function. The aim of this study is to investigate PFOA effects on the kidney of diabetics and non- diabetics guinea pigs.

MATERIALS AND METHODS

Ethical Approval

Ethical approval was granted through the local committee of the animal care and use at the College of Veterinary Medicine in the University of Baghdad (Number 828 at 9/4/2023) before starting this study.

Animals

The experimental animal model selected for this study was *Cavia porcellus* guinea pigs. Forty male guinea pigs about 12-14 week of age with range weight 500-550 g, were obtained from the animal house of College of Veterinary Medicine, University of Baghdad. A standard diet of commercial pellets, vegetables, vitamin C and tap water were available. The animals apparently healthy and kept under hygienic environment at 22 ± 4 °C in air-conditioned room, a relative humidity of $50\pm 10\%$, and the light system was 12/12 h. light/dark cycle (22, 23). The air of the place was continuously changed by the ventilation vacuum (24). The place was cleaned every three days to avoid any stress and all animals were observed daily for clinically apparent signs of disease or injury.

Chemicals

Perfluorooctanoic acid (PFOA), 95% purity, CAS No. 335-67-1 and alloxan monohydrate 98%, CAS No. 2244-11-3 were purchased from Sigma-Aldrich (Saint Louis, USA). Creatinine kit was obtained from SPINRAC (Spain) and normal saline 0.9% was purchased from Marksans pharma Ltd. (India). Xylazine and ketamine were purchased from Kepro company.

Induction of Diabetes in Guinea Pigs

Following overnight fasting, guinea pigs were injected intraperitoneally (IP) with 200 mg/kg of alloxan monohydrate in 24 h. intervals for three days, respectively in order to induce diabetic and maintain the increasing blood sugar levels in the experimental diabetic guinea pigs. Blood glucose test was performed before and after the injection as described in (26, 27) with modification. Following restraint of the animal, a blood drop from the ear is placed on the strips, and the sugar is measured with a glucometer. Diabetes mellitus was induced in twenty guinea pigs represented in Group 2 and Group 4, respectively. Guinea pigs with fasting blood glucose concentrations over 200 mg/dL were considered as diabetic (28) and involved in this study.

Experimental Design

The experimental animals (40 male guinea pigs) were divided randomly and equally into 4 groups. Group 1 (G1) was represented as a negative control treated with DW. 1 mL orally for 4 weeks. Group 2 (G2) induced diabetic male guinea pigs using alloxan monohydrate served as a positive control. Alloxan induce hyperglycemia which can be sustained for less than month. The sub-lethal toxicity of PFOA dose was calculated below the literature reported LD50 200 mg/kg in guinea pigs (25). Non-diabetic animals in Group 3 (G3) received 100 mg/kg BW of PFOA. Group 4 (G4) diabetic male guinea pigs received 100 mg/kg BW of PFOA orally by using stomach gavage. The duration of the experiment was 4 weeks.

Samples and Laboratory Tests

The first blood collection from the heart was performed immediately before the 1st dosing and then animals in each group had blood collecting every week after exposure at 1, 2, 3 and 4 weeks. After manual restraint of guinea pigs, blood samples (2.5 mL) were collected from each animal by cardiac puncture. Blood was deposited into tubes without anticoagulant then, blood samples were centrifuged at 3000 rpm for 15 min (29). The serum samples were kept in polyethylene Eppendorf tubes at -20 °C (30) which were used for assessing creatinine concentrations.

Histopathological Examination

After the completion of dosing for 4 weeks, guinea pigs were euthanized by using an overdose of ketamine (95 mg/mL) with xylazine (5 mg/mL, 1.5 mL/kg BW) (31) and then necropsies. Samples for histopathology collected from the kidney and kept in 10% formalin (32). The samples were processed for paraffin embedding. Then, sectioning was performed using microtomy. Finally, the sections were stained by hematoxylin and eosin (H&E). The slides were examined as described by (33). All the micro-pathological changes in treatment groups were assessed and compared with the control group.

Statistical Analysis

The data of the experiment were analyzed using the GraphPad Prism Statistical (version 8.0.2). Two-way ANOVA and Tukey's multiple comparison test were performed to evaluate significant differences among means

of the groups. The results were expressed as mean \pm standard errors and $P \leq 0.05$ was considered statistically significant (34).

RESULTS

Clinical Signs

Guinea pigs that exposed to PFOA represented by G3 and G4 showed signs of emaciation, hypoactivity and unhealthy hair appearance. Alloxan induces diabetes in G2 shows polyuria, polydipsia and excessive water drinking.

Serum Creatinine Concentration

Figure 1 illustrates serum creatinine concentrations in control and treated guinea pigs. There were no significant differences between positive control (G2) (1.02 ± 0.05 , 1.13 ± 0.1), PFOA treated group (G3) (1.07 ± 0.1 , 1.02 ± 0.09) and diabetic animals treated with PFOA (G4) (1.25 ± 0.1 , 1 ± 0.1) compared with the negative control group (G1) (1.01 ± 0.1 , 0.97 ± 0.08) after 1st and 2nd week of the experiment. After the 3rd and 4th week of treatment, the results displayed a significant ($P < 0.05$) increase in serum creatinine levels in positive control (G2) (1.46 ± 0.1 , 2.46 ± 0.2), PFOA treated group (G3) (1.46 ± 0.3 , 2.45 ± 0.09) and diabetic animals treated with PFOA (G4) (1.5 ± 0.1 , 2.66 ± 0.2) respectively, compared with the negative control group (G1) (1.18 ± 0.1 , 1.18 ± 0.1). There were no significant differences between PFOA treated group (G3) and diabetic animals treated with PFOA (G4) after the 3rd and 4th weeks of the experiment.

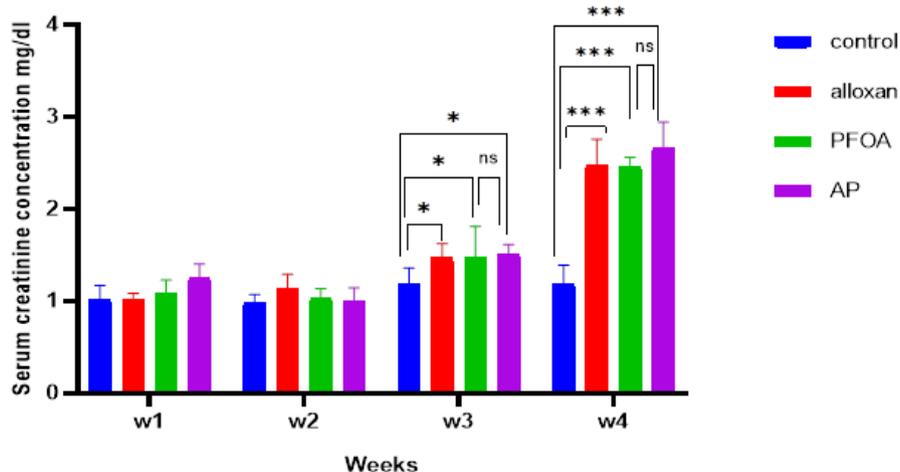


Figure 1. Serum creatinine concentrations in the control, alloxan induced diabetic, treatment animals with PFOA at 100 mg/kg BW and diabetic guinea pigs exposed to PFOA at 100 mg/kg BW during the experimental period of 4 weeks, n=10, * $P < 0.05$

Histopathological Findings of Kidney

To study the histopathological alterations of PFOA in normal and diabetic male guinea pigs, tissue sections from the kidney were examined microscopically to determine any changes following PFOA toxicity.

The first group (control negative group) shows no noticeable lesions (Figure 2). The second diabetic (control positive group) shows infiltration of inflammatory cells and

hemorrhage (Figure 3 A) with dilation of Bowman's space and sloughing of renal tubules (Figure 3 B). Guinea pig's kidney that treated orally with 100 mg/kg BW of PFOA (G3 and G4) shows necrotic changes with sloughing in the tubular epithelium lining, glomerular atrophy, vacuolar degeneration, infiltration of inflammatory cells (Figure 4 A, B, Figure 5 A-C). In addition, formation of hyaline casts in the renal tubular lumen (Figure 4 B).

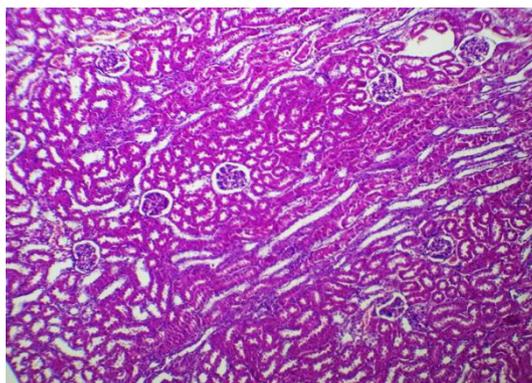


Figure 2. Histopathological section of male guinea pig kidney (G1, negative control) following 4 weeks shows normal histological appearance (H&E, 10 \times)

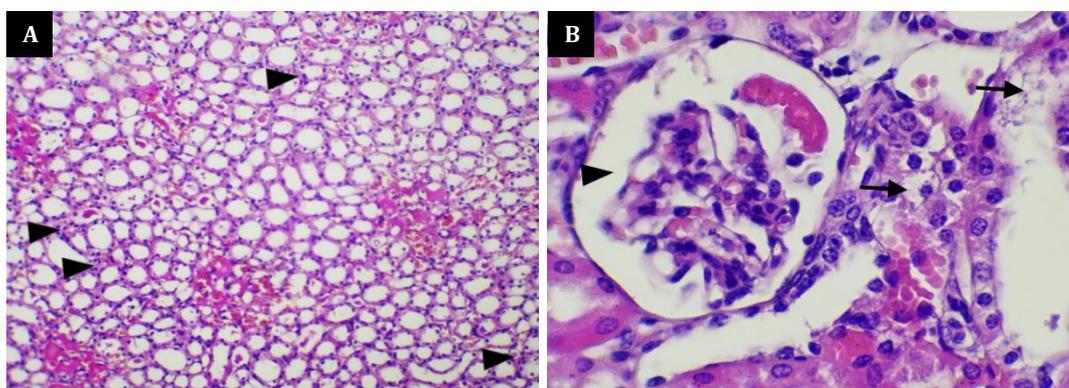


Figure 3. Histopathological sections of diabetic male guinea pig kidney (G2, positive control) following 4 weeks showing (A) infiltration of inflammatory cells (arrowheads) and hemorrhage (H&E, 10 \times), (B) dilation of Bowman's space (arrowhead), degeneration (arrows) with sloughing of renal tubules (H&E, 40 \times)

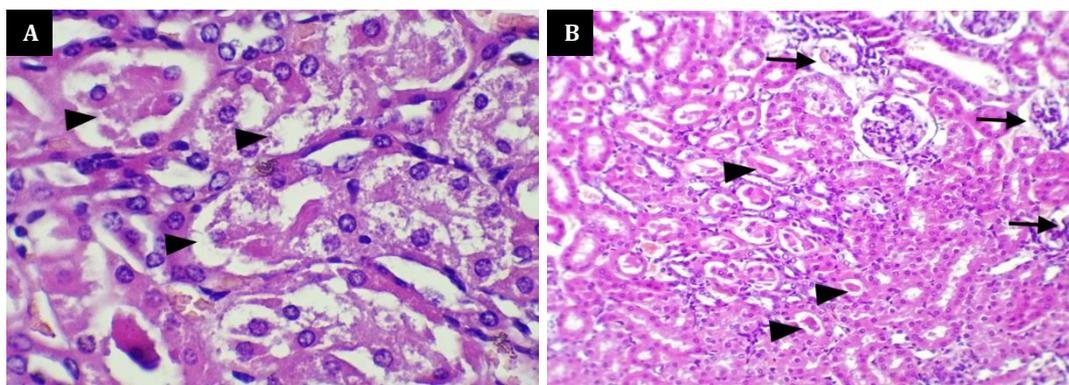


Figure 4. Histopathological sections of guinea pig kidney treated orally with 100 mg/kg/BW of PFOA (G3) following 4 weeks showing (A) necrotic changes with sloughing in the tubular epithelium lining (arrow head) (H&E, 40 \times), (B) glomerular atrophy (arrows), infiltration of inflammatory cells and hyaline casts present in the tubular lumen (arrowhead) (H&E, 20 \times)

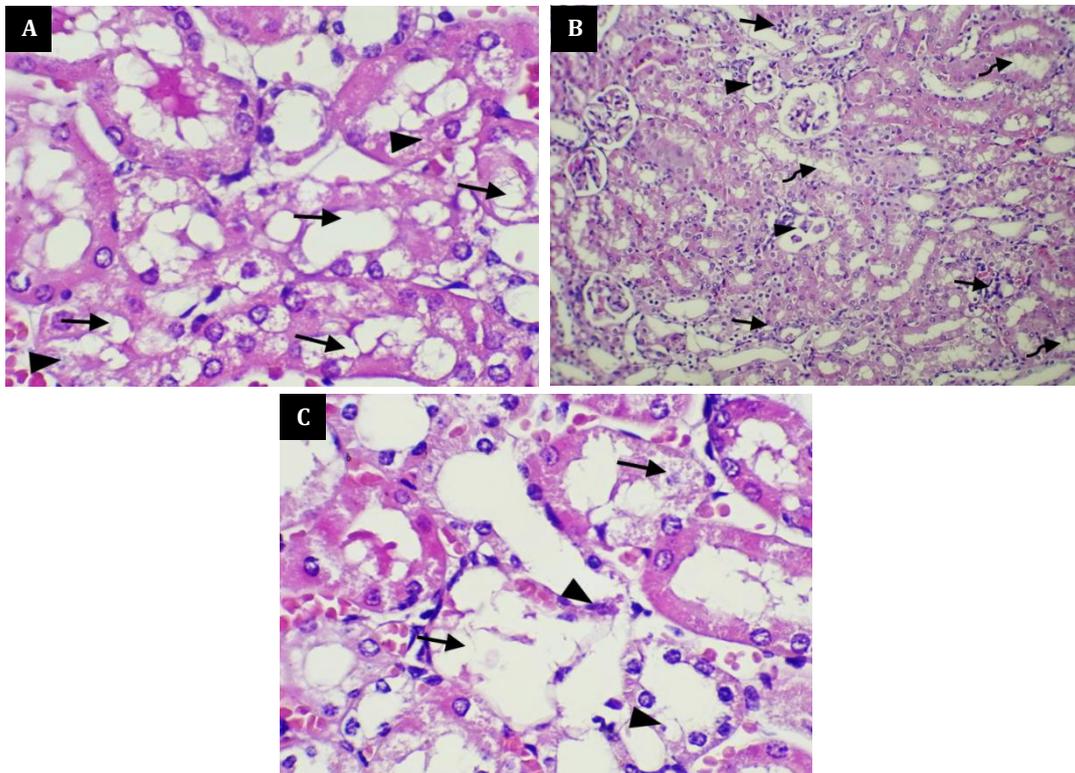


Figure 5. Histopathological section of diabetic male guinea pig kidney treated orally with 100 mg/kg BW of PFOA (G4) following 4 weeks showing **(A)** sever necrosis (arrowhead), vacuolar degeneration (arrows) and renal tubules damage (H&E, 40×), **(B)** infiltration of mononuclear cells (arrow), sever atrophy of glomerular tuft (arrowhead) with vacuolar degeneration (curved arrows) (H&E, 40×), **(C)** extensive areas of necrosis and sloughing of renal tubular lining (arrows), vacuolar degeneration and fragment nucleus of cells undergoing necrosis (arrowheads) (H&E, 40×)

DISCUSSION

This study investigates the renal histopathological changes associated with creatinine levels following oral gavage of sub-lethal dose of PFOA in diabetic and non-diabetic guinea pigs. Our results revealed that PFOA lead to rose in serum creatinine levels as show in Figure 1. These results are in accordance with (35, 36) which demonstrated that PFOA causes renal impairment and significant elevation of creatinine concentrations. Moreover, a study showing elevation concentrations of serum creatinine at dose 0.05 mg/kg of PFOA in rats (37). Furthermore, the presence of PFOA in the water at concentrations of (30 mg/L) for a period of 30 days in Nile tilapia (*Oreochromis niloticus*) caused a considerable rise in creatinine levels (38). PFOA caused alterations in renal microvascular endothelial-cell permeability by increasing production of reactive oxygen species (ROS) (39). When the oxidation processes of reactive oxidative species are stronger than the antioxidant response within the cell, the oxidative stress will occur (40).

In addition, diabetic rats treated with perfluorooctanoic acid showed extensive kidney damage with marked fibrosis and inflammation of glomerular mesangial cell due to disturbance metabolisms of amino acids and purines (41). Epigenetic alterations which promote expression of

fibroblast activation markers were reported in kidney tissues of mice exposed to PFOA (42)

The non-significant differences between non-diabetic group (G3) and diabetic group (G4) that both toxicated with PFOA indicated that PFOA is responsible for increasing creatinine concentrations with or without development of diabetes.

Several reports indicated the pathological effects of alloxan in renal tissues. Alloxan treated mice that caused kidney damage and degeneration to proximal and distal convoluted tubules and degeneration in glomerulus with increased capsular space (43). These results are in accordance with the current study in diabetic guinea pigs following the injection by alloxan monohydrate 200 mg/kg BW. Earlier it was reported that PFOA caused necrotic alteration in epithelial lining of renal tubules with accumulation of eosinophilic substance in tubular lumen in albino rats at dose 20-40 mg/kg BW by intragastric intubation daily for month (44). Exposure to PFOA changed numerous pathways that related to kidney diseases, including induction of oxidative stress, peroxisome proliferator activated receptor pathway, inflammatory pathway, autophagy pathway and DNA methylation (45). Moreover, the main nephrotoxicity mechanism in fish treated with 0.2 mg/kg PFOA was mediated by the oxidative damage and production of ROS (46). In addition,

to increased production of free radicals, disturbance in serum lipid and glucose concentrations following PFOA exposure in guinea pigs was reported (47).

The histopathological changes in the kidney such as necrosis, diffuse vacuolar degeneration and glomerular atrophy following PFOA administration (100 mg/kg BW, daily for 4 weeks) were related strongly with serum creatinine elevation (Figure 1). In fish, PFOA exposure influence on both the excretory and hemopoietic parts of the kidney with dilated glomerular capillary bed and loss of typical folding pattern (48). Furthermore, different doses of PFOA (0.05, 0.1, 0.5, and 1 mg L⁻¹) for 7, 14, and 21 days lead to swelling of mitochondria, hydropic endoplasmic reticulum and vacuolization in zebrafish kidney (49). PFOA also has been identified as a kidney carcinogenic that may have significant effects on public health for many individuals exposed to this widespread and extremely persistent chemical worldwide (50). It is believed that PFOA induces kidney carcinogenesis by activation signaling pathway of Peroxisome proliferator-activated receptors (PPAR α) (51, 52). Another hypothesis supposed that PFOA induced epithelial-mesenchymal transition in the kidney by increasing the expression of genes correlated with epithelial-mesenchymal transition with promotion of cell migration (53).

In vitro studies are recommended to well-known the impact of long-term PFOA exposure on the kidney including the toxicological information and mechanism of toxicity under stressed conditions (54, 55)

In conclusion, after 4 weeks, positive associations of PFOA with serum creatinine, have been observed in non-diabetic and diabetic guinea pigs exposed to PFOA. Furthermore, PFOA lead to disturbances in the kidney performance and nephrotoxicity in diabetic and non-diabetic animals.

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N/A

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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تأثير حمض بيرفلوروأوكتانويك على وظائف الكلية في خنازير غينيا المصابة وغير المصابة بالسكري

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الخلاصة

حمض البيرفلوروكتانويك (PFOA) هو مادة صناعية كيميائية فلورية خافضة للتوتر السطحي تستخدم على نطاق واسع في المنتجات التي تقاوم الزيت والحرارة والشحوم والبقع والماء. كما أنها تستخدم في إنتاج البوليمرات الفلورية الأخرى. المصادر الرئيسية للتعرض لحمض البيرفلوروكتانويك هي من الماء والتربة والأغذية حيوانية المنشأ (اللحوم والأسماك ومنتجات الألبان). الهدف من هذه الدراسة هو تقييم وظائف الكلية بعد التعرض الفموي للجرعة تحت القاتلة من حمض بيرفلوروأوكتانويك (PFOA) في خنازير غينيا المصابة بداء السكري وغير المصابة بالسكري. استمرت التجربة لمدة ٤ أسابيع، وتم اختيار ٤٠ ذكرًا من خنازير غينيا بشكل عشوائي وتم تقسيمها إلى أربع مجموعات متساوية. كانت المجموعة الأولى (G1) بمثابة مجموعة السيطرة؛ المجموعة الثانية (G2) المصابة بداء السكري بواسطة الألوكتسان، المجموعة الثالثة (G3) تعرضت لـ PFOA بجرعة ١٠٠ ملجم / كجم من وزن الجسم عن طريق الفم / يوميًا، المجموعة الرابعة (G4) كانت خنازير غينيا مصابة بداء السكري تعرضت لـ PFOA بجرعة ١٠٠ ملجم / كجم من وزن الجسم عن طريق الفم / يوميًا. تم قياس الكرياتينين في المصل والتغيرات النسيجية المرضية في الكلية. زاد تركيز الكرياتينين في المصل بشكل معنوي ($p < 0.05$) في G3 و G4 التي تعرضت لـ PFOA. مستويات الكرياتينين المرتفعة في المصل تشير إلى وجود خلل في وظائف الكلية. تم تأكيد اضطراب وظائف الكلية من خلال التغيرات النسيجية المرضية مثل الضمور الكبدي والنخر الشديد وتكس الطهارة الأنبوبية الكلوية في خنازير غينيا التي تلقت PFOA في G3 و G4. الاستنتاج، أكدت النتائج أن حمض بيرفلوروأوكتانويك (PFOA) مرتبطًا مع تلف الكلية وارتفاع تراكيز الكرياتينين في الحيوانات المصابة بداء السكري وغير المصابة بالسكري لأن حمض بيرفلوروأوكتانويك (PFOA) نفسه يمكن أن يساهم في الإصابة بمرض السكري.

الكلمات المفاحية: حمض البيرفلوروكتانويك، سمية كلوية، خنازير غينيا، سكري