Original Article

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Website:
www.carcinogenesis.com
DOI:
10.4103/jcar.jcar_22_02_07

The Effect of Ochratoxin A on Kidney Function Parameters of Patients with Chronic Kidney Disease in Kerbala

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Abstract

Objective: Investigating ochratoxin A (OTA) contamination in various countries and its health risks, particularly in chronic kidney disease (CKD) patients in Karbala, Iraq. Methods: A case-control study conducted from December 2022 to April 2023 assessed OTA exposure in CKD patients and healthy controls in Karbala. OTA levels were measured using thin-layer chromatography and high-performance liquid chromatography. Kidney function parameters were also evaluated. Results: OTA was found in 99% of CKD patients' blood plasma compared to 32% in healthy individuals, with higher prevalence in females (56%) than males (43%). Unidentified CKD cases showed links between OTA exposure, lower GFR, higher urea, and creatinine levels. Conclusion: OTA exposure in CKD patients suggests unidentified toxin sources. Kidney function markers were affected. Further research should investigate underlying causes of CKD rise and broader national impacts.

Keywords:

CKD, OTA, U, Cr, GFR.

Introduction

Fungi, particularly those of their harmful form, are one of the numerous origins of food contamination. It's well recognized for the poison it releases. According to their pharmacological activity, mycotoxins, which are categorized as the secondary metabolites created by fungi, put humans at risk for a range of health issues, including mycoses and even mortality. Fungi can contaminate agricultural products, which can cause a variety of changes both during the growing season and after harvest, When mold grows on specific plants, such as apples, wheat, coffee beans, nuts, and dried fruits, mycotoxins are formed, Mycotoxins can be eaten directly or through the meat and byproducts of animals that consumed contaminated feed. According to the World Health Organization in 2018, specific climatic factors, like high temperatures and humidity, encourage the production of these poisons by fungi [1]. When an animal or human consumes these mycotoxins, they may experience an acute or chronic illness, a condition known as mycotoxicosis, which is caused by the mycotoxins. Scientific research has shown that OTA has teratogenic, nephrotoxic, immunotoxic, neurotoxic, and hepatotoxic effects, among others. OTA's toxicological effects, such as its teratogenicity, neurotoxicity, and carcinogenicity, have been connected in the past to several harmful health outcomes, such as nephrotoxicity, immunotoxicity, neurotoxicity, and hepatotoxicity.

Additionally, it aids in the growth of endemic kidney disease in the Balkans [2]. Experts are increasingly convinced that OTA is the primary factor causing Balkan endemic nephropathy (BEN), a fatal kidney disease connected to the advanced stage of urothelial cancer [3].

Due to the severe toxicity of mycotoxins and the fact that OTA is a stable component that does not break down when prepared using common culinary procedures, guidelines on the maximum OTA level in food products have been established. The European Food Safety Authority (EFSA) has also defined a maximum tolerated weekly intake (TWI) for ochratoxin A at 120 ng per kg of body weight.

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Submitted: 16-Dec-2022
Revised: 08-Aug-2023
Accepted: 23-Sep-2023
Published: 11-Oct-2023

How to cite this article: Falayh O R, Ali S A R. The Effect of Ochratoxin A on Kidney Function Parameters of Patients with Chronic Kidney Disease in Kerbala. J Carcinog 2023;22(2):58-63

Chronic kidney disease, a degenerative disorder that affects both the structure and operation of the kidneys, is brought on by a variety of different factors. Chronic kidney disease is typically indicated by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1 73 m2 or by symptoms of kidney impairment, such as albuminuria, hematuria, or abnormalities discovered through laboratory tests or imaging and present for at least three months.

One of the biggest projected rises of any major cause of mortality is chronic renal disease, which is projected to rise to the fifth most common cause of death worldwide [4]. The causes of CKD are as follows: Type 2 diabetes mellitus (30% to 50%), high blood pressure (27.2%), Type 1 diabetes mellitus (3.9%), Chronic tubulointerstitial nephropathy (3.6%), Inherited or cystic diseases (3.1%), Primary glomerulonephritis (8.2%), Vasculitis or secondary glomerulonephritis (2.1%), Neo plasma cell dyscrasias and neoplasms (2.1%) [5]. The aim of the study, detect the correlation between Ochratoxin A and its effects on chronic kidney disease.

Materials and Methods

Case-control studies were undertaken between December 2022 and April 2023. The samples were submitted by patients from the Dialysis Division of the Internal Medicine Department at Imam Hassan Medical City and the Consulting Nephrology Department at the AL-Hussain Teaching Hospital in Kerbala. In the study, 100 individuals with nephropathy and 100 healthy controls took part. At the Department of Environment and Water of the Ministry of Science and Technology and the Department of Analytical Laboratories at the College of Applied Medical Sciences in Karbala, blood samples were examined in private laboratories, and ochratoxin was extracted and detected using high-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC), respectively.

A sterile syringe was used to take ten milliliters of blood from each participant's vein; two milliliters were put in a gel tube, and eight milliliters were put in an EDTA tube before being shipped in a container to the lab's main facility. After the samples had rested for 15 minutes, the serum was separated by centrifuging them for 15 minutes at 4000 rpm. Each serum sample was divided in half with a micropipette and stored at - 20 Cc until analysis was possible in a sterile container (an Eppendorf 1.5 ml tube).

The evaluation process then used serum samples that had already been obtained. OTA in blood serum was examined using TLC, measured (qualitatively and quantitatively) using HPLC, and the kidney function tests (U), (Cr), and (GFR) were performed[6]. The phases described by AL-Musoui [7] were followed for the qualitative analysis of serum Ochratoxin A by TLC. The procedure used by milićević [8]. for the qualitative and quantitative analysis of serum ochratoxin A by HPLC was followed.

Using an American hormone analyzer (Abbott i1000), the results of the Level Kidney Function Test (U), (Cr), and (GFR) were examined in private laboratories in Ireland. The experiments were conducted according to the complete design and results analysis by using ANOVA and mean comparison according to T-test and X^2.

Results and Discussion

The results showed that serum collected from a CKD patient exist the toxin in 99 (99%) samples where one patient was without OTA. Another hand the number of blood serums collected from the healthy, the toxin exists in 32 (32%) samples, while 68 (68%) samples are without OTA. When compared to the healthy the number of samples taken from patients shows a highly significant difference in the result stable (Table 1).

Table (1): Distribution of the number of patients with OTA and without OTA toxins compared to the number of healthy with OTA and without OTA toxins according to the TLC test

Cases	With OTA	Without OTA	Total	*P value*
Patients	99 (99%)	1 (1%)	100	0.0000**
Healthy	32 (32%)	68 (68%)	100	0.00032**
Total	131	69	200	0.0000**
P value	0.00001**	0.0000**	NS	

* Means significance differences (p<0.05)

** means high significance differences (p<0.001)

The findings revealed that the levels of OTA in the blood serum of male and female patients were 23.943 and 23.475 ng/ml, respectively, whereas the levels of male and male healthy subjects were 2.171 and 2.075 ng/ml, respectively, with highly significant differences between healthy and patients (Table 2).

Table (2): Duncan's test for measuring the concentration of OTA in patients and healthy blood serum using HPLC

Groups	Mean ng/ml	SD	Duncan Test	P value
Patient Females	23.943	2.413	a	
Patient Males	23.475	2.592	a	0.0015*
Healthy Females	2.171	0.121	b	
Healthy Males	2.075	0.124	b	

* Means significance differences (*p<0.05*)

** Means high significance differences (*p<0.001*)

The European Commission estimated OTA exposure in European Union member (states to range from 0.13 to 3.55 ng/kg bw/day on a total diet basis).The researcher's study also agrees [9] the study's findings showed a statistically significant rise in the concentrations of (OTA) in both the control group and all patients with renal failure who were also taking OTA, with P values of

(1.298 ng/ml) and (0.543 ng/ml), respectively .The above results are also similar to the research conducted by Özçelik, Koşar, and Soysal [10] Where were his results, the healthy group's average OTA concentration was 0.40ng/ml.

The group of patients receiving hemodialysis had the highest mean concentration, measuring 2.11ng/ml. All patient groups had greater average toxin concentrations than the control group. The concentration of the toxin varies because patients with renal failure had undergone dialysis, while in our study the condition of patients without dialysis .This study is not in agreement with the study of Hassan and Ali [11] who found the concentration range of OTA in the blood serum of female and male patients with CKD was 7.015 ng/ml and 7.071 ng/ml respectively.

Breitholtz-Emanuelsson [12] illustrated that the healthy group's mean and median ochratoxin A values were 0.53 and 0.44 ng/ml serum, respectively. The group of patients receiving dialysis had the highest mean levels, which was 1.4 ng/ml serum. The dialysis group had a greater frequency of samples with >0.44 ng ochratoxin A/ml serum .The concentrations of (OTA) in the male and female kidney failure patients were significantly higher at (1.136 ng/ml) and (1.231 ng/ml), respectively, compared to the control group, which had concentrations of (OTA) of (0.573 ng/ml) and (0.48) ng/ml, respectively. However, the results of the sex differed, with the results being found to be significantly higher. Agrees with our study, as it proved that ochratoxin poison is associated with connected to malignancies of the urinary system and has been hypothesized to play a role in the development of Balkan endemic nephropathy (BEN).

The researchers also indicated their results as follows. In France, two individuals with chronic renal failure had blood levels of OTA that were extremely high (205 ng/ml and 367 ng/ml, respectively) Fuchs and Peraica [13] found that in Egypt, patients with nephropathic syndromes had a highest OTA level of 10.15 ng/ml compared to 0.91 ng/ml in healthy controls.

Assessment of urea level:

Urea levels in patients' groups increased to (140.34 and 121.53) mg/dl in the blood serum of (the PM with OTA) group and (PF, with OTA) respectively without significant difference between them. While the levels of urea in healthy groups (HM, without OTA) and (HF without OTA) were (28.47) mg/dl and (24) mg/dl respectively with significantly different patient groups that were borne of OTA (table 3).

Table (3): Comparison between urea for study groups by Duncan's test

Groups	Mean mg/dL	SD	Duncan Test	P value
PM, with OTA	140.34	86.98	a	0.00029**
PF, with OTA	121.53	64.89	a	
PF, without OTA	74.00	0.00	ab	
HM, with OTA	25.20	3.46	b	
HF, with OTA	24.63	4.89	b	
HM, without OTA	28.47	5.09	b	
HF, without OTA	24.00	6.40	b	

* means significance differences ($p<0.05$)

** means high significance differences ($p<0.001$)

We analyzed the functional nephrotoxicity indices, such as BUN and CREA. The increase in BUN is often associated with renal insufficiency. The resulting agreement with Hassan and Ali [11] who found that increased levels of urea in patients with nephropathy get 115 mg/dl in male patients while the level was (99.1) ng/dl compared to the levels in healthy persons which were (21.6 mg/dl).

Many studies found a significant positive relationship between urea and creatinine in progress chronic kidney disease as a result of the loss of glomerular filtration rate [14]. Also, increased levels of urea in blood serum are considered greater, whereas protein levels are significantly lower than in the healthy group indicating that the kidney is impaired and has toxicity. This finding is consistent with Sharma et al.'s findings that the concentrations of urea and creatinine change in an opposite manner. As they are correlated with differences in glomerular filtration rate, they are useful in evaluating the level of renal impairment. When renal function drops to roughly 25–50% of normal levels, blood urea levels rise, which is a particularly sensitive sign of renal failure [15].

The blood's urea levels were significantly higher, which suggested severe kidney impairment. The results are consistent with kidney histopathology sections. Biochemically, blood levels of urea are significantly higher than in the control group, although protein levels are significantly lower, indicating that kidney function is compromised. According to MIR and Dwivedi [16], elevated blood urea levels are a significant marker of kidney damage and toxicity [17].

Assessment of creatinine level

The result illustrated those levels of creatinine in the blood serum of the patient's groups (PM, with OTA) and (PF, with OTA) was (3.65) mg/dl and (3.68) mg/dl respectively with significantly different creatinine levels in blood serum of other groups which of them were normal levels (table 4).

Table (4): Comparison between creatinine for study groups by Duncan's test.

Groups	Mean mg/dL	SD	Duncan Test	P value
PM, with OTA	3.655	2.64	a	0.00018**
PF, with OTA	3.680	2.44	a	
PF, without OTA	1.620	0.00	b	
HM, with OTA	0.700	0.141	b	
HF, with OTA	0.500	0.083	b	
HM, without OTA	0.739	0.161	b	
HF, without OTA	0.536	0.113	b	

* means significance differences ($p<0.05$)

** means high significance differences ($p<0.001$)

The results of this study were in agreement with Hassan and Ali [11] who found that level of creatinine in female patients was 3.73 mg/dl compared with the level in the blood serum of the female control was 0.571mg/dl. Also, the result approached of result that by Kareem [18] reported that the level of creatinine in the blood serum of patients with chronic kidney diseases was 3.92 mg/dl compared with healthy levels (0.66 mg/dl).

The increase in the concentration of serum creatinine indicates the development of kidney disease. also, increase creatinine live in blood serum consider a marker of renal damage [19]. This outcome is consistent with the blood creatinine levels, which were significantly increased and indicated severe kidney injury. The findings are in line with kidney histological sections and biochemical data, which show a significantly increased blood creatinine level. demonstrating a decline in liver and renal function. According to experiments, the kidneys have a higher concentration of OTA. A prominent marker of kidney damage and toxicity is an elevated blood creatinine level [16].

The first stage in regulating the glomerular filtration rate (GFR) is the measurement of creatinine, which is frequently used to assess renal function.

Assessment GFR

The result showed that GFR decreased in (PM, with OTA), (PF, with OTA) groups to (25.69 and 21.48) ml/min/1.7m² respectively with high significantly different with healthy groups as compared with (HF, with OTA), (HM without OTA), (HM, with OTA) and (HF without OTA) which were (111.60, 114.64, 113.84 and 118.63) ml/min/1.7m² respectively (Table 5), the resulting agreement with Kareem [18] who found that OTA decreased GFR in serum of patients with chronic kidney disease and serum contamination with OTA.

Table (5): Comparison between GFR for study groups by Duncan's test.

Groups	Mean (ml/min/1.73m2)	SD	Duncan Test	P value
PM, with OTA	25.69	14.24	b	0.000017**
PF, with OTA	21.48	14.52	b	
PF, without OTA	36.00	0.00	b	
HM, with OTA	111.60	8.60	a	
HF, with OTA	114.64	11.40	a	
HM, without OTA	113.84	13.85	a	
HF, without OTA	118.63	11.44	a	

* means significance differences ($p<0.05$)

** means high significance differences ($p<0.001$)

OTA is a well-known mycotoxin that is widely distributed around the world and has harmful effects on both human and animal health [20]. Therefore, it is essential to research OTA's hazardous effects and take precautions against their harm. One of the target organs most susceptible to OTA-induced damage is the kidney [21].

OTA-induced nephrotoxicity has been addressed by a variety of treatments, however, the mechanism of action of this mycotoxin is still unclear and complex. But in recent years, numerous in vivo and in vitro investigations have acknowledged that one of the mechanisms behind the toxicity of OTA is the production of oxidative stress caused by its exposure [22, 23]. As a result, administering antioxidants that combat oxidative stress may shield the kidneys from harm. Studies on nephrotoxicity have validated the real functions of bioactive substances in reducing chronic renal failure [24, 25]. It is generally recognized that oxidative stress results from an imbalance between the oxidant and antioxidant systems, which may be brought on by higher levels of free radical production and lower antioxidant activity. Numerous studies indicate that OTA exposure causes an excess of free radicals to be produced both in vitro and in vivo [23, 26], causing lipids in membranes, one type of cell component, harm.The study Damiano [27], which proved that oxidative stress mediates the kidney toxic effects of OTA on a functional and histological level, serves as an example of this.

Actually, in this work, we discovered that OTA treatment increased MDA, a marker of membrane lipid damage, in the kidneys of rats, and that GPx activity was primarily decreased. Studies Dai et al [28] and Bertelli et al.[29], permit us to speculate that OTA's harmful effects are partly related to how it affects enzymatic activities and partially to how it directly affects the formation of ROS [30]. As the researcher explained Damiano [27] that the reduction in GFR, which is connected to the generation

of oxygen free radicals, and the increase in creatinine shown in rats treated with OTA are related.

In reality, oxidative stress can encourage the production of several vasoactive mediators that can directly impact renal functions by producing renal vasoconstriction or lowering the glomerular capillary ultrafiltration coefficient and, thus, lowering GFR[31].

The OTA nephrotoxicity mechanism involves oxidative stress, according to research on rats. Kidney function is negatively impacted by OTA exposure, which also causes significant alterations. The researcher's study Kareem [18] is consistent with the results of the current study, with a decrease in GFR due to the effect of mycotoxins.

Conclusions

The results of the current study, this study showed that the level of toxin concentration in chronic renal disease is much higher than the permissible levels in the blood, and the presence of the same toxin in the blood of healthy people indicates the presence of food contamination. The results also showed that patients' blood plasma levels of ochratoxin A were significantly higher than those of healthy people, with patient levels reaching (23.475 and 23.943 ng/ml, respectively), while healthy people's levels were (2.075 and 2.171) ng/ml, respectively. The results, on the other hand, showed that levels in healthy males and females were both within the normal range, whereas the presence of ochratoxin A was associated with an increase in urea levels in male patients to 140.34 ml/dl and in female patients to 121.53 ml/dl. Average creatine levels in male and female patients with chronic kidney disease increased to (3.655, 3.680) ml/dl, respectively, which I substantially higher than those in healthy individuals.

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