Original Article

Evaluation of Kidney Injury Molecule -1(KIM-1) Quantitative Expression in Renal Tubule following Dose Dependent Chromium Administration

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ABSTRACT

Objective: To evaluate the histopathological alterations in renal tissue following chromium exposure, in different doses with particular emphasis on kidney injury molecule -1as a biomarker of renal damage.
Study Design: experimental study
Place and Duration of Study: This study was conducted at the College of Medicine, Al-Nahrain University, Baghdad, Iraq from 1st September 2025 to 30th November 2025.
Methods: This experimental group was exposed to different doses of chromium and compared with the control group. Histological analysis was performed and Kim-1 was assessed to evaluate tubular injury.
Results: Chromium exposure resulted in noticeable histological changes, treated groups showed enlargement of the urinary space and degenerative changes in proximal convoluted tubules. In addition, kim-1 expression was markedly elevated indicating early tubular injury based on dose dependent effect.
Conclusion: Chromium induces significant dose-dependent renal damage at both structural and cellular levels and the nephrotoxic potential of Chromium and support the utility of kim-1 as a sensitive biomarker for early detection of kidney injury.

Key Words: Chromium, Nephrotoxicity, Kim-1, Kidney, Oxidative stress, Histopathology

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INTRODUCTION

The kidneys are very important organs which control the regulation overflowed balance levels and elimination of metabolic wastes and the basic structural and functional unit of the kidney is called the nephron which is composed of renal corpuscle and a tubular system including the following: proximal convoluted tubule, loops of Henle, distal convolute tubule and collecting duct.[1]

The renal corpuscle contains the glomerulus surrounded by Bowman's capsule and is responsible for the filtration of a blood plasmas, filtrate then enters the proximal convolute tubule (PCT) which represents the most metabolic active segment of the nephron. The high metabolic activity and the filtrated substances make the proximal tubule more vulnerable to toxic injury from drugs, heavy metals and environmental toxins.[2]

Chromium supplement are widely used worldwide as a nutritional aids to support metabolic health despite it is a proposed beneficial effect, increasing evidence of prolonged intake of Chromium supplements may have toxic effect on different organs including the kidneys, since the kidneys are primarily responsible for the filtration and excretion of metal and xenobiotics, renal tissues may accumulate chromium following systemic exposure, This accumulation may induce oxidative stress, inflammatory responses, and cellular damage within renal structure.[3]

KIM-1, a type 1 transmembrane glycoprotein, is poorly expressed in normal kidney but is highly expressed in injured PT epithelial cells.[4] Due to its high sensitivity on the specificity of proximal tubular injury kim-1 immunohistochemical staining has been widely used in experimental nephrotoxicity studies to evaluate renal damage induced by drugs, environmental toxins and heavy metals.[5,6]

METHODS

This experimental group was exposed to different doses of Chromium and compared with the control group at College of Medicine, Al-Nahrain University, Baghdad, Iraq from 1st September 2025 to 30th November 2025 vide letter No. 341/Approval/SFGH dated July 12,

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2024. A total of 30 albino rats (males) were used in the present study and obtained from the animal house of the collage of science in Kufa University, which were already in experimental use. The rats have a body weight ranging between 250- 370 gm and age 8-12 weeks. The rats were divided into three groups: Control group, low dose group and high dose group (10 rats in each group). Oral Gavage Procedure: Homogenous powder was obtained by grinding Chromium tablets 200mcg with an electric grinding machine. The animals were anaesthetized with 80-100 mg/kg body weight of a combination of ketamine and xylazine (8:1). After 5 weeks underwent right kidney nephrectomy. Paraffin blocking and sectioning were done. The data was analyzed through SPSS-25.

RESULTS

The antibody- antigen reaction appeared in PCT cells were assessed in all groups using Aperio software. Only strong positive staining was included in this statistical evaluation of the test, while positive and weak positive reactivity were deliberately excluded from this analysis to obtain the methodological precision and to minimize the background reactivity variability. Analysis of these measurements revealed highly statically significant differences between all groups. Mean of (kim-1) expression level in control group was 11941.3000±3761.37533 pixel/ μ^2 reflecting a base line protein expression and physiological expression while, the low dose group showed substantially elevated mean value of 63112.1000±5701.42797 pixel /μ^2, high dose group showed a striking rise of the mean which recorded 138773.1667±18679.70755 pixel/ μ^2(table 1).Statistical analysis evaluation confirm that this increase with the high significant p -value of (0.05) indicating that the differences is unlikely to be a due to random variation (Table 1).

General examination of the renal parenchyma in control group by light microscope showed that two distinct areas of the kidney were clearly demarcated. Notable, the proximal convoluted tubules were seen to be in greater number than the distal convoluted tubules near the renal corpuscles. The medullary area was less pigmented than the cortex and had fewer cells, with the presence of tubular structures consisting of parallel rays, which were composed mainly of collecting ducts and different parts of the loop of Henle. These medullary rays meet at certain points creating renal papillae which project into the lumen of the minor calyces (Fig. 1). Some variations were recorded in the experimental groups such as enlargement of renal corpuscle, decrease in the height of the cuboidal cells lining the lumen of the PCT with corresponding decrease in the number of microvilli in the lumen of the PCT in the experimental groups. The picture in high dose group is the same as that in low dose but more severe and deconfiguration of some PCT. At higher magnifications the experimental groups show more signs of vascular congestion, especially in the tuft (Fig. 2).

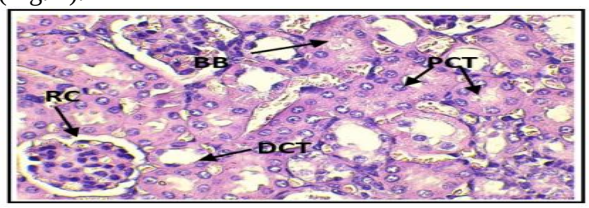

Figure No. 1: Section in the kidney of control group showing renal corpuscle (RC), proximal convoluted tubule (PCT) with high cuboidal epithelium and brush border (BB), distal convoluted tubule (DCT). control group, H&E,X40

Table No. 1: Difference in kim-1 expression between all groups

Groups		Mean Pixel μ^2	Standard Error	P value
Control group	Low dose group	63112.1000	5701.42797	0.006*
	High dose group	138773.1667	18679.70755	0.000*
Low dose group	Control group	11941.3000	3761.37533	0.006*
	High dose group	138773.1667	18679.70755	0.000*
High dose group	Control group	11941.3000	3761.37533	0.000*
	Low dose group	63112.1000	5701.42797	0.000*

Significant (P<0.05)

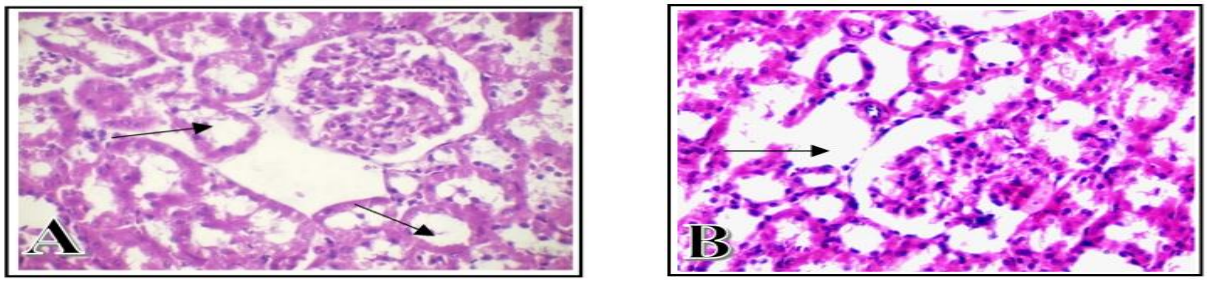

Figure No. 2: section in the kidney A: in low dose group increase in the size of renal corpuscles, loss of microvilli in lumen of PCT associated with decrease of the height of cuboidal cells lining it and increase in the size of the lumen (→) B: high dose group showing deconfiguration of some PCT (→). Experimental groups, H&E, X40

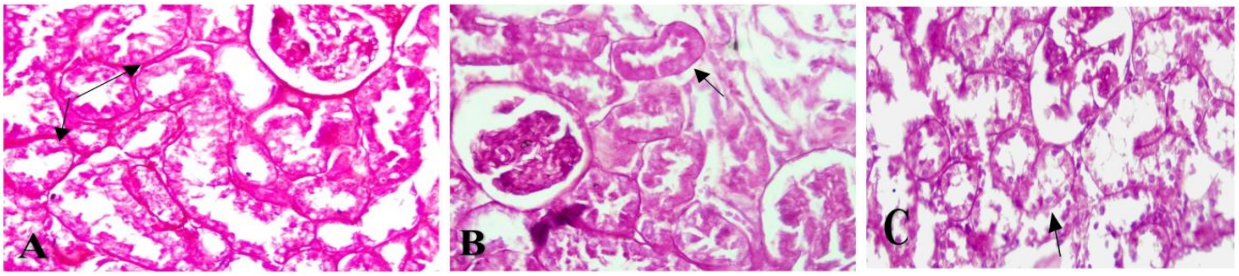

Figure No. 3: section in the kidney A: in control group showing thick basement membrane (⟶) B: with decrease thickness of B.M (⟶). C: high dose group showing with decrease thickness of B.M with some tubules showing loss of continuity of B.M (⟶). Experimental groups, PAS stain, X40.

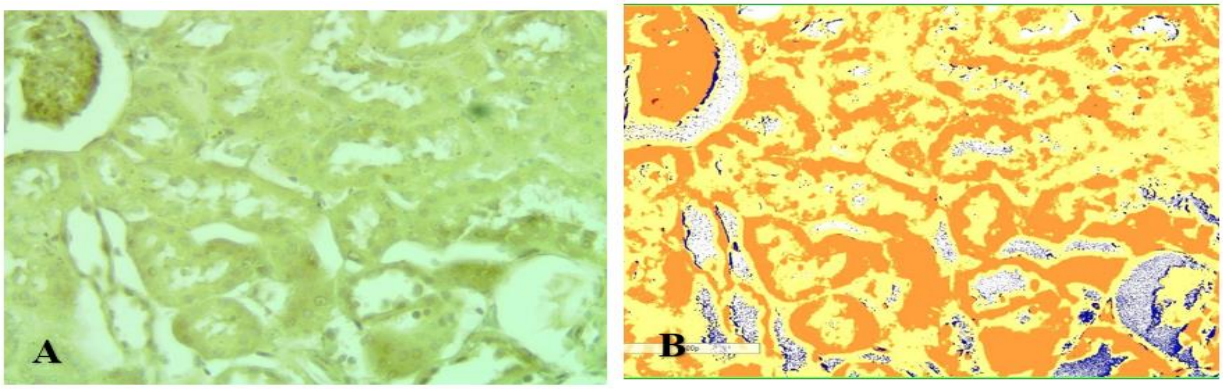

Figure No. 4: Cross-section in the kidney of control group showing A: distribution of DAP with no strong reactivity for KIM1 Ab reactivity B:, snapshot picture seen with aperio-software , (control group , KIM1 Ab, X40)

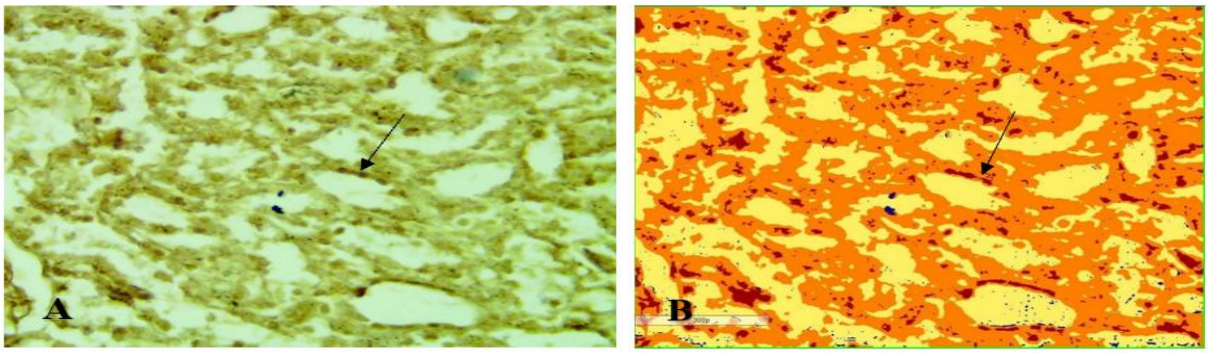

Figure No. 5: Section in the kidney in lower dose group showing A: positive reactivity of KIM1 in the apical cytoplasm of some PCT (⟶). B: snapshot of the same figure showing the reactivity as small reddish brown granules in the apical surface of PCT (⟶). Low dose group, KIM1 Ab, X40)

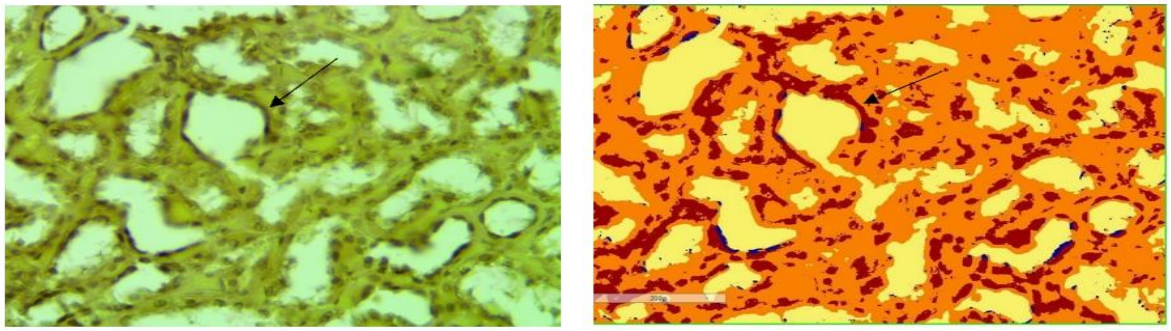

Figure No. 6: Section in the kidney in lower dose group showing A: increased positive reactivity of KIM1 in the apical cytoplasm of some PCT (⟶). B: snapshot of the same figure showing the reactivity as small reddish brown granules in the apical surface of PCT (⟶). Low dose group, KIM1 Ab, X40).

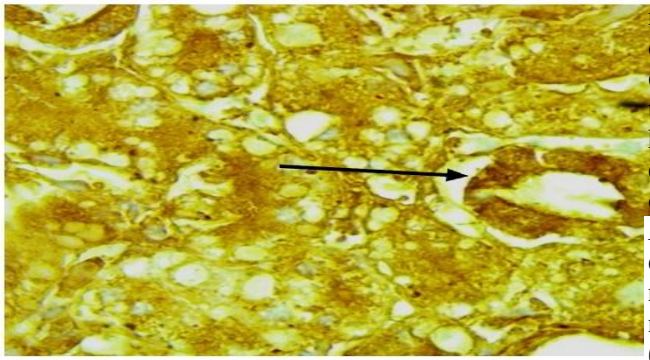

Figure No. 7: Kidney section in experimental group at high magnification indicating dark stained brown granules (⟶) in the cytoplasm of the PCT. (high dose group, KIM1, X100)

Basement membrane is a critical barrier that's found in all parts of the nephron assessment of renal corpuscle and proximal convoluted tubule, basement membrane was done using PAS stain. The overall picture showed differences in the thickness of basement membrane both in glomeruli and PCT. Basement membrane was thick and dense continuous in control group, thin and delicate fine line around the corpuscle and PCT in low dose group and it was also continuous. High dose group basement membrane was not easily detectable with a striking feature of lost continuity of the basement membrane which was seen mainly in some PCT more than renal corpuscles. Glycocalyx was easily seen in control and low dose groups, but was not seen in high dose groups, which could be because of the loss of brush border. Using PAS stain enables easy distinguishing between PCT and DCT by showing densely eosinophilic Glycocalyx inside the lumen (Fig. 3).

The quantitative and qualitative expression of the histochemical product in renal cortex was examined in detail in all the groups by using polyclonal antibody (Kim-1); it was observed as multiple structural chromogenic expression, dark brown color tiny granules and extended in different ranges between light pale yellow, light orang to deep dark brown redish. The chromogenic expression signals were mainly observed around the renal corpuscles, and the site of reactivity was only observed in proximal convoluted tubules; the pattern of distribution of this expression was observed as deep intense brown-red colour in the cell cytoplasm in all three groups, the reaction of PCT to (kim-1) was not observed in other tubules. Evaluation of this chromogenic signal objectively was mainly qualitative including the distribution and localization of Ab-Ag reaction. From an objective point of view, the intensity of this reaction of PCT cytoplasm had different degrees in the three groups (Fig. 4).

In both experimental groups (low and high) Kim-1 reactivity showed significant upregulation of expression as the immune reaction was found as strong brown reddish cytoplasmic granules in the apical portion of the cytoplasm cells in the PCT. This upregulation of the cortical granules in the apical cytoplasm resulted in thicker granules as well as increased intensity in the high dose groups, where the intensely appeared as thick dark brown large granules occupying most of the cytoplasm PCT cells (Figs. 5-6).

At higher magnification the intensity of reaction was so deep that obscuring the nuclei, intensity was seen mainly in the high dose group the obscuring of the nuclei appeared partially and sometimes completely (Fig. 7).

DISCUSSION

The human kidney is the bilaterally located excretory organ. Histologically, the renal cortex is the site of the larger number of renal corpuscles and the proximal and distal convoluted tubules while the renal medulla is composed primarily of loops of Henle and collecting ducts contained within renal pyramids.[7] The renal corpuscle is made up of the glomerulus and Bowman's capsule, which constitute the filtration unit of the nephron.[8] The sample is present on the proximal convoluted tubule, which has a cuboidal epithelium with a prominent brush border to increase the reabsorption surface area.[9]

Exposure to chromium showed some significant structural damage in renal tissue as revealed by the data in the present study which was a reflection of toxic and antioxidant activity of trivalent chromium and has a toxic effect on renal cells and tissues. Chromium compounds have been linked to the development of toxicity in the cells by the mechanism of causing oxidative stress. Reactive oxygen species (ROS) are formed during intracellular reduction of hexavalent and trivalent chromium, which can attack cellular proteins, lipids and DNA.[6] The results obtained by Soudani[10] who reported that rats fed potassium dichromate exhibited histopathological changes such as tubular degeneration, necrosis and vascular congestion in renal tissues were similar. In this present study, Heavy metal like chromium causes a glomerular injury by causing oxidative damage to the glomerular cells and results in a distortion of the glomerular tuft. Glomerular changes were also noted by Goodarzi et al[11] who reported glomerular degeneration and disruption of the renal architecture in rats treated with chromium.

This experimental group showed that degenerative changes in the proximal convoluted tubules. Hasan et al[12] found necrosis damage in the renal tubules of rats after chromium exposure. The progressive renal change noted with the higher doses of chromium in the present study indicates a dose-dependent toxicity. Experimental studies have also shown dose-dependent nephrotoxic effects of chromium, as renal damage was found to be increasingly severe with increasing doses of chromium.[13]

In the present study, high doses of Chromium compounds may cause morphological changes in renal tissues, especially in tubular epithelial cells, the proximal convoluted tubule is regarded as one of the most susceptible parts of the nephron to toxic damage. As it is actively transported and has high metabolic rate, the proximal tubular cells are good targets of toxicity and when damaged by nephrotoxic agents, they can undergo tubular degeneration, cellular swelling, loss of the brush border integrity and impair the absorptive function.[14]

The changes are probably the result of oxidative stress–mediated degradation of proteins at the basement membrane, such as type IV collagen and laminin. These findings were corroborated by experimental nephrotoxicity studies that demonstrated that disruption of the integrity of the basement membrane was linked to tubular injury.[15]

In the present study, changes in the basement membrane were clearly observed in the renal corpuscles and PCT using the PAS stain. In control group, the basement membrane was seen to be thick, dense, continuous and strongly PAS positive, indicating that its structural integrity and glycoproteins and proteoglycans level were normal. The basement membrane is positive for the presence of carbohydrate containing components like type IV collagen, laminin and proteoglycans, hence its positivity.[16]

The basement membrane seemed to be noticeably thinned in the low dose group, but was continuous forming a fine linear border around both glomeruli and proximal tubules. This implies that physical changes occur, but the trucks are not completely destroyed and is similar to early nephrotoxicity, where components of the extracellular matrix are partially degraded or remodelled.[17]

High dose group has well preserved glycocalyx see by pasabsent, while control and low dose groups have well preserved glycocalyx. At the apical surface, the glycocalyx is important and its loss could contribute to damage of the brush border of the proximal convoluted tubular cells. Recently impaired function of the glycocalyx has also been linked to impaired epithelial barrier function and susceptibility to injury.[18]

The kidney injury molecule 1 (KIM-1) is a type I membrane protein that has two domains; an extracellular domain and a cytoplasmic domain. Also known as HAVCR1 (hepatitis A virus cellular receptor 1), also known as TIM1 (T-cell immunoglobulin mucin receptor 1), it is expressed in kidney, liver and spleen. KIM-1 acts via several molecular targets in immunological diseases and renal damage. In HAV infections, KIM-1 is involved, in autoimmunity, in immunological tolerance and in atopic disorders. The level of urine KIM-1 is closely correlated with its tissue level and, like renal tissue injury, is linked to renal tissue injury. KIM-1 is a sensitive biomarker for acute kidney injury (AKI), and might even be a predictive marker for long-term renal outcomes.[19]

The present investigation showed that there was a significant induction of the expression of kim-1 upon chromium exposure which was largely localized in the proximal convoluted tubules of the kidney cortex. Different degrees of staining reactivity were observed, from weak staining reaction in the control group to the highest staining reaction in the treatment group and most intense in the high dose group, staining being cytoplasmic in these groups. No staining was seen in the distal tubular segment or glomeruli. The selective localization is consistent with its known role as a marker of damage in the proximal tubule.[20] The immunoreactivity was seen as brown granules in the apical part of the cytoplasm and increased with the chromium exposure. The same type of staining has been seen in tubular injury models.[21]

The treatment groups report a significant increase in expression when it's compared with the minimal expression reported in the control group. Initial injury is reflected by mild staining in LDO and significant tubular damage is reflected by severe and diffuse staining in HDO. The level of kim-1 expression has been demonstrated to be linked to how bad the damage.[22]

There was a significant dose-dependent increase in expression. This suggests that there is a direct relationship between the severity of renal injury and exposure to chromium. Kim-1 over-expression has been reported with a wide variety of dose-response relationships.[23] These results were confirmed by quantitative analysis showing a significant difference and confirming the reliability of kim-1 as a marker for nephrotoxicity.[21] This agreement between the qualitative and quantitative results increases the validity of the current results.

CONCLUSION

Structural defects of the architecture of the kidneys have been shown by histological and macroscopic examination may be functional because of exposure to chromium. These changes including cortical thinning, discoloration was involved with underlying pathological processes (edema vascular disturbance and cellular degeneration). Histopathological analysis revealed renal damage in the form of both glomerular and tubular damage, particularly in the proximal convoluted tubules, the most sensitive part of the kidneys to toxic injury. The effects were dose-dependent, showing the greatest effects at high doses. The increase in kim-1 expression support it is role as reliable and early biomarker of the tubular damage. Importantly, these effects were dose-dependent with greater alterations seen as exposure levels increased.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Sajjad Jubair Kadhim, May Fadhil Majid AL-Habib
Drafting or Revising Critically:	Sajjad Jubair Kadhim, May Fadhil Majid AL-Habib
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

Conflict of Interest: The study has no conflict of interest to declare by any author.

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