Protective Effects of Curcumin on Cadmium-Induced Renal Injury in Young and Aged Rats

Genç ve Yaşlı Sıçanlarda Kadmiyumun Yol Açtığı Böbrek Hasarına Karşı Kurkuminin Koruyucu Etkileri

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ABSTRACT

Objective: We aimed to investigate the protective effects of curcumin (Cr) against cadmium (Cd) toxicity on the kidneys of both young and aged rats.

Methods: Forty-eight young and aged female Spraque–Dawley rats were divided into control, Cd, Cr, and Cd+Cr groups. We investigated kidney damage using a histopathological scoring system and measured total antioxidant status (TAS) and total oxidant status (TOS) and interleukin-6 (IL-6), procalcitonin (PCT), and C-reactive protein (CRP) levels.

Results: Kidney tissues of Cd groups showed acute histopathological alterations. Cr improved Cd-induced histopathological changes (p<0.05). The highest mean TAS was recorded in both the Cr groups. The highest mean TOS was recorded only in the aged Cd group. Cr decreased IL-6 levels in both the Cd+Cr groups (p<0.05). PCT levels in the Cd groups were higher than those in the control groups. Significance was detected only between the young Cd and control groups (p<0.05). PCT levels were reduced in both the Cd+Cr groups (p<0.05). CRP levels in the aged Cd group were higher than those in the other groups (p<0.05). CRP levels in the aged Cd group were higher than those in the other groups (p<0.05). Cr reduced CRP levels only in the aged Cd+Cr group (p<0.05).

Conclusion: Our results suggest that Cr prevents Cd-induced renal oxidative damage in both young and aged rats.

Keywords: Cadmium, curcumin, oxidative stress, interleukin, procalcitonin, C-reactive protein

ÖZ

Amaç: Bu çalışmada, genç ve yaşlı sıçanlarda kadmiyumun yol açtığı böbrek toksisitesine karşı kurkuminin koruyucu etkilerinin incelenmesi amaçlanmıştır.

Yöntemler: Çalışmamızda 48 adet genç ve yaşlı Spraque-Dawley cinsi sıçan kontrol, kadmiyum (Cd), kurkumin (Cr) ve kadmiyum+kurkumin (Cd+Cr) gruplarına ayrıldı. Böbrek hasarı histopatolojik skorlama sistemine göre değerlendirildi. Total antioksidan seviyesi (TAS), total oksidan seviyesi (TOS), interlökin 6 (IL6), prokalsitonin (PCT) ve C- reaktif protein (CRP) seviyeleri ölçüldü.

Bulgular: Kadmiyum gruplarının böbrek dokularında akut histopatolojik değişiklikler görüldü. Kurkuminin kadmiyum kaynaklı histopatolojik değişiklikleri iyileştirildiği tespit edildi ($p \le 0,05$). En yüksek ortalama total antioksidan seviyeleri genç ve yaşlı Cr gruplarından, en yüksek ortalama total oksidan seviyesi ise sadece yaşlı Cd grubunda kaydedildi ($p \le 0,05$). Kurkumin her iki Cd+Cr grubunda interlökin 6 seviyesini düşürdü ($p \le 0,05$). Genç Cd grubunun PCT seviyesi kontrol grubuna göre oldukça yüksekti ($p \le 0.05$). Genç ve yaşlı Cd+Cr gruplarında PCT seviyelerinin düştüğü belirlendi ($p \le 0,05$). CRP seviyesi yaşlı Cd grubunda diğer gruplardan daha yüksekti ($p \le 0,05$). Kurkumin sadece yaşlı Cd+Cr grubunda CRP seviyesini düşürdüğü tespit edildi ($p \le 0,05$).

Sonuç: Hem genç hem de yaşlı sıçanlarda kurkuminin kadmiyum kaynaklı renal oksidatif hasarı önlediğini düşünmekteyiz.

Anahtar Kelimeler: Kadmium, kurkumin, oksidatif stres, interlökin, prokalsitonin, c-reaktif protein

Introduction

Cadmium (Cd) is a heavy metal that is one of the most toxic environmental pollutants (1). It was classified as a "group I carcinogen" by the International Agency for Research on Cancer. Humans and animals are exposed to Cd via contaminated soil, food, drinking water, and air as well as dust and smoke (2, 3). It is known that it causes time- or dose-dependent toxicity in multiple organs of humans and animals. Cd causes oxidative tissue damage by accumulating mainly in the kidney, bone, brain, lung, and liver cells (4, 5). The effects of Cd on various cell types include chromatin condensation and damage to cell membranes, including the mitochondrial cristae membrane, resulting in an increase in their permeability (6). Cd exposure results in the impairment of the antioxidant defense system in the kidney and liver (7-9). As a

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matter of fact, the kidney is the most sensitive organ against Cd. Thus, chronic Cd exposure through inhalation or oral ingestion leads to renal dysfunction (10). In particular, with aging, renal functions are impaired and the activity of antioxidant enzymes is decreased; thus, exposure to toxic agents is expected to be more injurious to organs in aged individuals.

Curcumin (Cr) is the active component of turmeric (*Curcuma longa*) derived from rhizomes. Recent studies have reported various characteristic of Cr, including antioxidant (11), antiinflammatory (12), immunomodulatory, antiatherogenic, antiviral, and antifungal actions (13). In fact, Cr is a potent inhibitor of various reactive oxygen species. It exhibits protective effects against oxidative damage as a scavenger for free radicals and prevents lipid peroxidation. Cr binds to heavy metals such as Cd and lead and thus has a detoxificating effect against heavy metals (13).

The aim of the current study was to compare the effects of Cr against Cd-induced toxicity between the kidney tissues of young and aged rats.

Materials and Methods

Experimental design

Forty-eight young (age, 6 months) and aged (age, 16 months) female Spraque-Dawley rats weighing 250-300 g were randomly divided into the following groups: control group (n=6, 10 days), Cd-treated group (Cd, n=6, 10 days), Cr-treated group (Cr, n=6, 10 days), and cotreated group (n=6, Cd, 10 days+Cr, 10 days). The animals were kept at 25°C under a 12-h light/12-h dark cycle, with free access to water and food. The rats received Cd (Merck Millipore, Billerica, Massachusetts, United States) intraperitoneally (ip.) at a dose of 0.5 mg/kg/ day and Cr ip. at a dose of 50 mg/kg/day for 10 days. Cr (Sigma-Aldrich, St. Louis, Missouri, USA) was administered for 10 days after the administration of Cd in the cotreated group. At the end of the study, all rats were anesthetized with 80 mg/ kg ketamine (Ketalar, Pfizer, Brooklyn, New York, USA) and 5 mg/kg xylazine HCl (Rompun, Bayer, Barmen, Germany), blood samples were collected from the heart, and later the kidneys were removed. The study procedure was approved by the Local Ethics Board for Animal Experiments, Bezmialem Vakif University, Istanbul, Turkey (Decision No. 2013-231).

Histopathology

For histopathological analysis, kidney tissues were fixed in 10% neutral buffered formaldehyde and embedded in paraffin, 5 μ m longitudinal cross sections were obtained and stained with hematoxylin–eosin (H–E) and Masson's trichrome staining methods. Samples were examined and scored by a blinded observer using the Nikon Eclipse i5 light microscope with Nikon DS-Fi1c camera and the Nikon NIS Elements version 4.0 image analysis system (Nikon Instruments Inc., Tokyo, Japan).

Kidney damage was scored considering the tubular degeneration (including dilatation, squamation of the tubular epithelial cells, and necrosis), tubular vacuolization, glomerulosclerosis, hemorrhage, and interstitial fibrosis. Each data was scored as follows: 0: absent, 1: minimal, 2: moderate, and 3: severe with a maximum score of 15.

Biochemical analysis

Blood samples derived from the heart were collected in jelled serum tubes. Serum was separated from the cells by centrifugation at 3,000 × g for 5 minutes. Plasma samples were stored at -80° C until they were analyzed. Total antioxidant status (TAS) and total oxidant status (TOS) were determined by Erel's method (Rel Assay Diagnostics, Gaziantep, Turkey), which is automated and colorimetric. Erel's TOS method encompasses oxidizing ferrous ion to ferric ion in the presence of various oxidant species in an acidic medium and measuring ferric ion using xylenol orange. The results were explained in micromole H₂O₂ equivalent/L (H₂O₂ equiv./L). Erel's TAS method is based on the bleaching of the characteristic color of a more stable 2.2'-azino-bis (3- ethylbenz-thiazoline-6-sulfonic acid) radical cation by antioxidants. The results were expressed in millimole Trolox equivalent/L.

The percent ratio of the TOS value to the TAS value was defined as the oxidative stress index (OSI), which is an indicator of oxidative stress. The plasma OSI value was calculated using the following formula:

$$OSI= \frac{TOS (\mu mol H_2O_2 equivalent/L)}{TAS (mmol Trolox equivalent/L)x10}$$

Measurement of serum inflammatory factor levels

The serum was instantly separated by centrifuging at 3000 rpm for 5 minutes and then stored at -80°C. Interleukin-6 (IL-6) levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (Rat IL-6 Platinum ELISA, eBioscience, Bender MedSystems GmbH, Vienna, Austria). The plasma levels of procalcitonin (PCT) were measured by using ELISA kits (Rat PCT Elisa Kit, Eastbio Pharm, Hangzhou Eastbiopharm Co., Hangzhou, China). The plasma levels of C-reactive protein (CRP) were quantified using ELISA kits (Rat CRP Elisa Kit, Assaypro, St. Charles, MO, USA) according to the manufacturer's instructions.

Statistical analysis

Statistical analyses were performed and bar charts were plotted using SPSS version 20.0 (IBM, New York, USA), MS Office Excel, and GraphPad Prism 6. The data about biochemical analysis and histopathological scores were statistically evaluated using the Mann–Whitney U test for non-parametric data. In all the tests applied, the p significance degree (confidence interval) was evaluated at 95%.

Results

Oxidative stress parameters

The highest mean TAS values were 0.97 ± 0.45 and 0.90 ± 0.24 in the young and aged Cr-treated groups, respectively. Mean TAS value in the young Cd group was lower than that in the

control group; however, the mean TAS value in the CD+Cr group was higher than that in the Cd group. In aged rats, the mean TAS values in the Cd and Cd+Cr groups were nearly equal. In terms of the TAS values, no statistical significance was detected.

Total oxidant status values in the young groups did not show statistical differences at all; however, the mean TOS value in the Cd group was higher than that in the control group. Interestingly, the mean TOS values in the Cr and Cd+Cr groups were higher than those in the Cd group.

In all the groups, the highest mean OSI values were detected to be 0.40 ± 0.12 and 0.39 ± 0.10 in the young and aged Cd groups, respectively. OSI values in the young and aged Cd group were higher than those in the control groups. Cr alone did not affect the OSI value in young rats; however, it reduced the OSI value in aged rats. Additionally, OSI values in the young and aged Cd+Cr groups were lower than those in the Cd groups.

Mean blood TAS, TOS, and calculated OSI values obtained from all groups are presented in Table 1. Distribution of data regarding TAS (Figure 1), TOS (Figure 2), and OSI (Figure 3) in all groups is shown as bar charts.

Inflammatory parameters

It was observed that IL-6 levels were increased in the young and aged Cd groups when compared with the control groups, whereas these levels were decreased after Cr administration in both the young and aged Cd+Cr groups. Significant differences were detected between the young and aged Cd and Cd+Cr groups (U=0.000, p=0.004 and U=5.000, p=0.003, respectively).

The highest PCT levels were observed in the Cd groups. Cd affected mean PCT levels in young (U=0.000, p=0.004) and aged rats and not in the control groups. PCT levels were reduced with the administration of Cr after that of Cd in both the young (U=0.300, p=0.004) and aged groups.

The mean CRP level in the aged Cd group was found to be significantly higher than that in the control groups (U=5.000, p=0.037). CRP levels in both young (U=5.000, p=0.041) and aged Cd+Cr groups were lower than those in the Cd groups (U=5.000, p=0.003).

Mean values of IL-6, PCT, and CRP of all groups are shown in Table 2. Bar charts of IL-6, PCT, and CRP are presented in Figures 4, 5, and 6, respectively.

Histopathology of the kidney

The mean histopathological score in the aged control group was higher than that in the young control group. Kidney tissues of both young and aged Cd groups showed some histopathological alterations, including tubular degeneration and vacuolization (Figure 7a), glomerular collapse, tubulointerstitial fibrosis (Figure 7b), mononuclear cell infiltration (Figure 7c), hemorrhage, edema, and necrosis (Figure 7d). Mean histopathological scores (MHSs) in the young and aged Cd groups were higher than those in the control groups (U=0.000, p=0.004 and U=0.000, p=0.004, respectively). The histological appearance of the kidneys in the Cr groups was similar to that of the kidneys in the control groups in both young and aged rats (Figures

Table 1. Mean serum total antioxidant status (TAS), total
oxidant status (TOS), and oxidative stress index (OSI)
values in all groups

	Mean ± SD		
Groups	TAS (mmol Trolox equ./L)	TOS (µmol H2O2 equ./L)	OSI (TOS/ TAS×10)
Young Control	0.78±0.22	2.42±0.36	0.33±0.10
Aged Control	0.86±0.28	2.78±0.93	0.33±0.05
Young Cd	0.72±0.23	2.67±0.43	0.40±0.12
Aged Cd	0.88±0.35	3.21±0.79	0.39±0.10
Young Cr	0.97±0.45	3.04±0.86	0.33±0.08
Aged Cr	0.90±0.24	2.72±0.61	0.30±0.04
Young Cd+Cr	0.88±0.39	2.99±0.95	0.35±0.04
Aged Cd+Cr	0.80±0.29	2.82±0.90	0.36±0.07

SD: standard deviation; mmol: millimolar; µmol: micromolar; L: liter; equ: equivalent



Figure 1. Bar chart of mean total antioxidant status (TAS) in all groups



Figure 2. Bar chart of mean total oxidant status (TOS) in all groups

8a, b). It is obvious that in terms of MHSs, kidney tissues of the young groups were affected by Cd more severely than those of the aged groups (Figure 9).

Cr significantly improved Cd-induced histopathological changes. In young and aged cotreated groups, minimal cellular changes such as tubular degeneration, mononuclear cell infiltration, and necrosis were observed whereas glomerular collapse, tubulointerstitial fibrosis, and hemorrhage were not obvious. Significant differences were detected between Cd







Figure 4. Bar chart of mean interleukin-6 (IL-6) levels in all groups

Table 2. Mean serum interleukin 6 (IL-6), procalcitonin(PCT), and C-reactive protein (CRP) levels in all groups

	Mean±SD		
Groups	IL6 (pg/mL)	PCT (pg/mL)	CRP (µg/mL)
Young Control	55.40±39.24	480.90±321.48	0.38±0.23
Aged Control	106.07±74.70	542.68±403.41	0.38±0.37
Young Cd	66.96±20.57	1750.20±250.38	0.30±0.11
Aged Cd	121.93±69.70	819.22±327.79	0.89±0.39
Young Cr	87.50±59.72	681.10±342.87	0.31±0.25
Aged Cr	115.47±106.22	796.88±256.49	0.37±0.32
Young Cd+Cr	53.96±29.59	694.14±434.54	0.20±0.13
Aged Cd+Cr	89.98±56.49	645.41±241.83	0.41±0.36

SD: standard deviation; pg: picogram, µg: microgram, ml: milliliter

and Cr young and aged groups in terms of MHSs (U=0.000, p=0.004 and U=0.000, p=0.004, respectively). Same results were valid for the comparison between Cd and Cd+Cr groups (U=0.000, p=0.004 and U=0.000, p=0.004, respectively).







Figure 6. Bar chart of mean C-reactive protein (CRP) levels in all groups



Figure 7. Kidney sections from young and aged Cd groups. (a) Tubular degeneration in young groups (hematoxyline-eosin: H-E) (b) Glomerulosclerosis (blue arrows) and fibrosis (black arrows) in young groups (Masson's trichrome). (c) Mononuclear cell infiltration (H-E) in aged groups (d) Necrosis, edema, and mononuclear cell infiltration in aged groups (H-E)

Mean data of histopathological scores of kidney tissues in all groups are showed in Table 3. Bar chart of MHSs are presented in Figure 9.



Figure 8. (a-d). Kidney sections from young and aged Cr groups. (c) Normal histological view of tubules and glomerulus from young Cd+Cr group (H–E). (d) Minimal changes are shown in kidney sections from aged Cd+Cr group (blue arrows: mononuclear cell infiltration around the glomerulus)





 Table 3. Mean histopathological scores (MHSs) of the kidney tissue in all groups

Groups	MHSs ((Mean±SD)
Young Control	5.33±1.36
Aged Control	6.16±1.94
Young Cd	13.33±0.81
Aged Cd	11.83±1.47
Young Cr	4.66±1.63
Aged Cr	5.83±2.13
Young Cd+Cr	7.66±1.51
Aged Cd+Cr	7.75±3.37

Discussion

Acute Cd exposure through inhalation causes pulmonary edema and respiratory tract irritation, whereas chronic Cd exposure causes renal impairment, anemia, and bone defects (14). Chronic Cd exposure through inhalation or ingestion also causes renal dysfunction (10). The kidney is one of the most vulnerable organ against the toxic effects of Cd (15). Intoxication of Cd results in common transport defects of the proximal tubules (9, 16, 17). In the present study, Cd caused severe renal damage in both the aged and young groups. Both glomeruli and tubules were reported to be more sensitive against acute Cd toxicity than chronic toxicity (18). However, we observed prominent histopathological alterations within tubules and glomeruli following chronic Cd exposure. We detected tubular degeneration, necrosis, glomerular collapse, mononuclear cell infiltration, hemorrhage, edema, and tubulointerstitial fibrosis. Surprisingly, although MHS in the aged control group was higher than that in the young control group, MHS in the aged Cd group was lower than that in the young Cd group. We suggest that aged renal tissues are more resistant to the damaging effects of toxic agents than young ones. We recently showed that liver tissues of the aged rats against chronic Cd exposure were also more resistant to the oxidant effects of Cd than those of the young rats (unpublished data). Additionally, in another study, we showed that renal tissue of aged rats exposed to ischemia and reperfusion was more resistant to the damaging effects of the process than that of young rats (unpublished data).

Interestingly, Cd administration caused higher damage in the young Cd group when compared with the aged Cd group. Although Cr significantly improved Cd-induced histopathological changes in the young and aged cotreated groups, Cr administration was more effective in young Cd+Cr group than aged Cd+Cr group. Significant differences were detected between the young and aged Cd and Cr groups in terms of MHSs (p<0.005). Same results were valid for the comparison between the Cd and Cd+Cr groups (p<0.005). Similarly, Cr has been shown to protect the renal structure in cisplatinexposed rats (19). Chronic Cr treatment also significantly attenuates both renal dysfunction and oxidative stress in diabetic rats (20, 21). Cr also prevented renal oxidative damage mediated by gentamicin; thus, it was suggested that it can be a potent protective agent (22). Similarly, in the present study, Cr treatment significantly improved the Cd-induced histological changes.

We detected that the mean TOS values in the aged control group were naturally higher than those in the young control group, and perhaps as a result of higher oxidative stress status, the mean TAS values in the aged control group were higher than those in the young control group. Higher antioxidant enzyme levels or activities should increase the tolerance of aged tissue against the hazardous toxic agents.

A previous study has reported oxidative stress in Cd-induced acute toxicity (21). Protection against these acute actions of

Cd can be achieved through the antioxidant systems (21, 22). Cr has many beneficial features, including antioxidant and anti-inflammatory actions (11, 12). We tried to investigate antioxidant and anti-inflammatory efficacy of Cr against renal toxicity in our study. Thus, Cr administration alone affected the mean serum TAS value in both the young and aged rats versus the controls. Cr also affected the TAS value in Cd-administered young rats but not that in aged rats. On the other hand, OSI (mean TOS/mean TAS×10) in both the young and aged Cd groups were higher than those in the Cd+Cr groups. Because higher values of OSI represent higher oxidative stress status, we suggest that Cr inhibits oxidative stress.

Because acute Cd exposure causes severe inflammation, it activates inflammation markers depending on the severity of stress within the cells. IL-6 is a proinflammatory cytokine that plays a critical role in the human defense system (23-25). Many toxic agents and pathological conditions, such as bacterial and viral infections, trauma, and autoimmune diseases, induce production or affect the function of cytokines, including IL-6 (26). In the present study, although extensive inflammation was not detected in renal tissue of the groups, IL-6 levels in the young and aged Cd groups were increased probably as a result of the inflammation of other affected organs, including the liver, heart, pancreas, etc. On the other hand, Cr administration reduced IL-6 levels of young (p=0.004) and aged (p=0.003) rats of the Cd groups.

Cytokines synthetized by neutrophils and macrophages stimulate the production of acute-phase proteins, including Creactive protein (CRP) and procalcitonin (PCT). Procalcitonin, a precursor of the hormone calcitonin, is synthetized by C cells of the thyroid gland and neuroendocrine cells of the lungs, pancreas, intestine, and liver during infection and inflammation (27, 28). CRP is synthesized by the hepatocytes. CRP levels in serum increase in response to IL-6 during infection and inflammation (29). Cr has considerable inhibitory effects on the production of TNF- α (30). It was stated that Cr administration reduced serum levels of TNF- α and IL-6 in cisplatin-exposed rats (19, 31). Cr had protective effects against liver fibrogenesis via reducing TNF- α and IL-6 levels in the liver and serum (32-35).

C-reactive protein is a marker, which appears during the late phase of infection, whereas IL-6 and PCT are affected in the early phase (36-38). In the present study, increased PCT levels of Cd-administered young (p=0.004) and aged (p=0.004) rats were reduced by Cr administration. On the other hand, mean CRP levels in the young Cd group were reduced probably as a result of liver failure. As we mentioned before, CRP is mainly produced by the hepatocytes. As a matter of fact when we examined the liver section of Cd-administered young rats, we observed extensive necrosis (unpublished data). In aged rats, increased levels of CRP were reduced by Cr administration presenting its anti-inflammatory function (p=0.003). It was known that Cr exhibits anti-inflammatory activity, so it was determined to levels of pro-inflamatory markers.

Conclusion

We suggest that inflammation and oxidative damage induced by Cd is inhibited by Cr. Cr prevents Cd-induced renal oxidative damage in both young and aged rats and should be considered as a therapeutic agent against toxic oxidative stress.

Ethics Committee Approval: Ethics committee approval was received for this study from Bezmiâlem Vakıf University Ethics Committee of Experimantal Animal.

Informed Consent: Not required in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.E., M.K., N.B., Design - M.K., M.E; Supervision - M.E., S.M., M.I.; Data Collection and/or Processing - M.K., N.B., S.A., M.I.; Analysis and/or Interpretation - M.E., M.K., M.I., S.M., N.B., S.A; Literature Review - M.K., N.B.; Writing - M.K., M.E.; Critical Review - M.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Bezmiâlem Vakıf Üniversitesi Deney Hayvanları Yerel Etik Kurulu'ndan alınmıştır.

Hasta Onamı: Bu çalışma için gerekli değildir.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - M.E., M.K., N.B.; Tasarım - M.K., M.E.; Denetleme - M.E., S.M., M.I.; Veri Toplanması ve/veya İşlemesi - M.K., N.B., S.A., M.I.; Analiz ve/veya Yorum - M.E., M.K., M.I., S.M., N.B. , S.A.; Literatür Taraması - M.K., N.B.; Yazıyı Yazan - M.K., M.E.; Eleştirel İnceleme - M.E..

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadığını belirtmiştir.

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