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Effect Of Chronic Lead And Cadmium Co-Exposure On Integrity Of The Kidney And The Role Of ß2 Microglobulin

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ABSTRACT

Background: Chronic exposure to heavy metals represents a challenging medical and environmental problem Cadmium (Cd) and lead (Pb) are both toxic metals that are extensively used in industrial fields and usually co-exist with zinc in the environment. High-level exposure to many heavy metals may increase the risk for kidney diseases.

Aim of the work: Detection of the levels of lead and cadmium in the blood of subjects with chronic co-exposure correlated with their possible toxic effects on the kidney and role ofß2 microglobulin.

Subjects and Methods: It included 70 subjects with known chronic co-exposure to lead and cadmium. In addition, another 70 healthy subjects not exposed tolead and cadmium matched for age and sex, were included as a control group. All underwent detailed assessment by history taking, clinical examination, and laboratory investigations with measurement of lead and cadmium levels and assessment of renal function in addition tourine β2 microglobulin.

Results: estimated GFR were statistically significantly decreased (76.11±9.73) in group 1 incomparable to group 2 (99.74±14.13). On the other side, creatinine, BUN, and serum uric acid, were statistically significant increases in the study than the control group. In addition, urine β2 microglobulin was statistically significantly increased (530.32±122.56) in group 1 than group 2 (171.27±56.03). Both cadmium and lead there were statistically significant negative correlations with each of hemoglobin, RBCs, hematocrit, serum albumin, and estimated GFR. In addition, there were statistically significant positive correlations, with urine β2 microglobulin, serum creatinine, and blood urea nitrogen.

Conclusion: There was a harmful effect of co-exposureto cadmium and lead on the kidney and this deterioration of kidney function was correlated with increased cadmium and lead levels. In addition, urine β2microglobulin is a good marker of renal tubular dysfunction.

Keywords: Heavy metals; Lead; Cadmium; Kidney; Nephropathy,β2 microglobulin.

INTRODUCTION

Cadmium (Cd) and lead (Pb) are both toxic metals that are broadly used in industrial fields and usually co-exist with zinc in the environment. Cd concentrations in the environment are increasing daily [(1)].The two main routes of exposure are inhalation and ingestion for human beings. Cadmium is usually accumulated in the vegetables and other foods. The food chain represented another main source of human exposure. Smoking is another rsignificant pathway to exposure humans to cadmium harmful effects[(2)].

Lead (Pb) is a bright metal, silvery in color, that becomes somewhat bluish in a dry atmosphere. When come in contact with air, it tarnishes and forming a different complex mixture of compounds, according to the given circumstances. It is a highly toxic metal, with wide spread and extensive environmental pollution. It is responsible for many health problems across the globe[(3)].

In addition, cadmium is also widely distributed with environmental contamination and potential toxicity that adversely affects the health of human. Again, the exposure is largely by inhalation and ingestion. Smoking and foods from contaminated soil or waters are the significant non-industrial sources of exposure [(4,5)].Cadmium is not biodegradable due to its chemical stable divalent nature. Thus, it persists for a long time in the environment with repeated contamination of the food chain[(6,7)].

One of the interesting features of the lead is its chemical similarity to calcium. Thus, in the human body, it handled like calcium. However, it exerts harmful effects, rather than useful effects of calcium, regardlessits route of exposure [(8,9)].

The harmful effects of Cd and Pb on the kidney had been suggested, even at a low-level of exposure. Such effects could include high urinary levels of beta-microglobulin, increased serum levels of blood urea nitrogen (BUN), serum creatinine, change in creatinine clearance or glomerular filtration rate (GFR). However, these suggestions are challenged [(10)].

Another suggested dangerous harmful effect is the development of end-stage renal disease with need for renal dialysis or transplantation. One study suggested that, end stage renal disease is increased at areas near cadmium-emitting industries[(11)]. Another study found higher levels of lead and cadmium in patients with chronic renal disease and these levels are related to the outcome of chronic renal disease[(12)].

Beta-2 microglobulin is a low molecular weight protein found in the membrane of all nucleated cells and most of body fluids such as serum, urine, and synovial fluids. It is filtrated from the glomerular membrane because of its small size, reabsorbed, and catabolized in the proximal tubules. Normally it is eliminated less than 1%, because of its proximal tubular reabsorption. Beta-2 microglobulin increases in urine in renal tubular diseases, nephrotoxicity, renal toxicity because of exposure to heavy metals. Its measurement in urine can be used to assess renal tubular injury[(13)].

THE AIM OF THE WORK

Detection of the levels of lead and cadmium in the blood of subjects with chronic co-exposure correlated with their possible toxic effects on the kidney and the role of ß2 microglobulin.

PATIENTS AND METHODS

The study was carried out on 140 subjects, divided into two groups according to the history of chronic co-exposure to Pb and Cd: Group 1: study group: included 70 subjects already exposed to Pb and Cd selected from workers of different occupational groups, at Damietta, Egypt, including; thermal power station

workers, lead battery factories, cosmetic factories, and gas station workers. Group (2): 70 healthy subjects not exposed to Pb and Cd as a control group.

Inclusion criteria: subjects already exposed to Pb and Cd toxicity of more than 3 months, age range 20-55, and both gender.

Exclusion criteria: Patients with kidney diseases, Diabetes mellitus, Hypertension, chronic kidney disease (CKD), chronic pyelonephritis, renal stone, and use of nephrotoxic drugs. in addition persons with a blood level ofPb, less than5 µg/Land Cd less than 5 µg/L were excluded from the study.

All participants were submitted to detailed history taking, clinical assessment, and laboratory investigations includingblood levels of lead and cadmium, urine β2 microglobulin,serum creatinine, blood urea nitrogen (BUN), urine analysis, complete blood picture (CBC), serum albumin level, serum uric acid, fasting and postprandial blood glucose level, estimated glomerular filtration rate (eGFR)by Cockcroft-Gault formula((male) = ([140-age] × weight in kg)/(serum creatinine × 72). (female) = (male) × 0.85)[14].

Urine β2 microglobulin: The sampling was random mid-stream urine samples were collected within 1 hour after drinking a large glass of water. once collected, we adjust the PH of all urine samples to between 6 and 8 with 1.0 M Na OH then stored at –20°C until analysis.

Methods:

β2-microglobulin levels in random urine samples were measured using a chemilumine scence-based immunometric Assay (Immulite 1000; Siemens Immulite® Beta-2 Microglobulin Kit Cat.No.: LKBM1, Test Code: BMG.The detection limit was 4 Ng/Ml, Inter- and variation coefficients were < 8.0 and 3.4% for intra and inter-observe variations. The normal level of β2 microglobulin is < 300 ng/ml.

Blood lead and cadmium levels were determined by graphite furnace atomic absorption spectrophotometry (GFAAS) using A-Analyst 600 (PerkinElmer, Turku, Finland). Detection limits for Cd and Pb were 0.1 and 1 µg/L, respectively. Metals determination by Graphite Furnace Atomic Absorption Spectrophotometer (GFAAS). The samples and matrix modifiers were introduced by an autosampler. After the steps of atomization, cadmium and lead concentrations were automatically reported in micrograms of metals/g, wet weight of the sample. There was a periodic verification of calibration each 20 readings by analyzing the standard. The analysis was stopped if the recovery was deviated than the standard limits. The device was re-calibrated after correction of the causative problem.

Ethics approval and consent to participate:

The study was accepted by the local Ethics committee of the Damietta faculty of medicine Al-Azhar University. Registration Number: IRB 00012367-21-01-017. Issuing: 17Jan. 2021, Expiration Date: valid until 16Jan 2023, Damietta faculty of medicine IRB, Al-Azhar University. Before inclusion in the research, the study aims and procedures were explained for each participant and an informed consent was signed by each participant.

Statistical analysis of data: the collected data was documented, organized, anonymized, and fed to a personal computer to be analyzed by the statistical package for social science (SPSS) version 18 (IBM®SPSS® Inc., Chicago, USA). Qualitative data were presented by their relative frequency and percentages, while quantitative, normally distributed data were presented as mean and standard deviation (SD). For comparison between groups, the independent samples (t) and Chi-square tests were used for quantitative and qualitative data respectively. Pearson's correlation coefficient (r) was calculated to test the correlation between different variables, p-value < 0.05 was set as the margin of

significance.

Results

The demographic characteristics of studied populations; age ranged from 25 to 52years, 75% of studied populations were males and 25% were females. Furthermore, there was no statistically significant difference between study and control groups as regards weight, height, and body mass index (BMI), or smoking(Table 1).

The estimated glomerular filtration rate was a statistically significant decrease (76.11±9.73) in group 1 than group 2 (99.74±14.13), and hemoglobin, RBCs, hematocrit were a statistically significant decrease in the study than the control group. On the other side, creatinine, blood urea nitrogen (BUN), and serum uric acid, were statistically significant increases in the study than in the control group. Urine β2 microglobulin wasa statistically significant increase (530.32±122.56) in group 1 than group 2 (171.27±56.03).However, there is no statistically significant difference as regard platelets, white blood cells fasting, and post-prandial blood sugar between both groups(Table 2).

The presence of proteins in urine by dipstick test (2 plus or more proteins) was 25.7% in group 1 and 17.9% in group 2 and wasa statistically significant increase.the specific gravity of the urine was statistically significantly increased in the study group (22.9%) than the control group (15.0%). However, casts and crystals were not statistically significant differences between both groups (Table 3).

Both cadmium and lead were statistically significant negative correlations with each of hemoglobin, RBCs, hematocrit, serum albumin, and estimated glomerular filtration rate. In addition, there were statistically significant positive correlations, with urine β2 microglobulin, serum creatinine, and blood urea nitrogen. In addition, cadmium was statistically significant positive correlations with serum uric acid. (Table 4).

Table (1): Demographic characteristics of studied populations

Variable		Study group	Control group	Test	P value
Age (mean±SD)		36.75±3.64	36.12±4.18	0.94	0.34
Sex (n,%)	Male	53(75.7%)	52(74.3%)	0.04	0.84
	Female	17(24.3%)	18(25.7%)		
Weight		74.81±5.29	75.57±4.54	0.91	0.36
Height		171.11±2.98	172.20±4.19	1.76	0.08
BMI		25.53±1.36	25.49±1.37	0.17	0.86
Smoking (n,%)		25(35.7%)	17(24.3%)	2.17	0.14

Table (2): Results of laboratory investigations in studied populations

Variable	Study group	Control group	Test	P-value
Hemoglobin	9.88±0.58	12.31±0.65	**23.22**	**<0.001***
RBCs	3.14±0.25	4.07±0.39	**16.38**	**<0.001***
HCT	31.07±2.49	40.25±3.94	**16.46**	**<0.001***
WBCs	4.75±0.86	4.89±0.91	0.97	0.33
Platelets	331.85±48.70	328.30±44.45	0.45	0.65
Creatinine	1.25±0.50	0.52±0.14	**11.72**	**<0.001***
BUN	35.54±3.89	12.78±2.11	**42.96**	**<0.001***
Estimated GFR (N:>90ml/min/1.73m^2)	76.11±9.73	99.74±14.13	**11.51**	**<0.001***

Cadmium (µg/L) (N< 5µg/L)	5.17±1.58	1.69±0.53	**17.39**	**<0.001***
Lead (µg/dl) (N< 10µg/dl)	36.07±8.25	8.52±2.32	**26.94**	**<0.001***
Serum albumin	3.95±0.45	4.24±0.23	**4.61**	**<0.001***
Serum uric acid	5.15±0.83	4.75±0.82	**2.8**	**0.006***
Fasting blood sugar	107.34±5.26	107.10±5.41	0.26	0.78
Postprandial BS	168.20±11.55	172.32±14.33	1.87	0.06
Urine ß2 microglobulin (N: < 300 ng/ml)	530.32±122.56	171.27±56.03	22.29	**<0.001***

Table (3): Comparison between study and control group as regards urine analysis

	Study		Control		Total		t	p
	n	%	n	%	n	%		
Proteins (2 plus or more proteins)	18	25.7%	7	10.0%	25	17.9%	**5.89**	**0.015***
Casts	6	8.6%	2	2.9%	2.12	0.14	1.26	0.26(ns)
Crystals	30	42.9%	23	32.9%	53	37.9%	1.96	0.16(ns)
Increased specific gravity	16	22.9%	5	7.1%	21	15.0%	**6.77**	**0.009***

Table (4): Correlation between cadmium and lead with other variables

	Cadmium		Lead	
	r	p	r	p
Hemoglobin	**-0.72**	**<0.001***	**-0.69**	**<0.001***
RBCs count	**-0.65**	**<0.001***	**-0.58**	**<0.001***
HCT	**-0.65**	**<0.001***	**-0.58**	**<0.001***
WBC	-0.09	0.30	-0.028	0.74
Platelets	0.04	0.63	0.09	0.26
Creatinine	**0.56**	**<0.001***	**0.69**	**<0.001***
BUN	**0.78**	**<0.001***	**0.84**	**<0.001***
Estimated glomerular filtration rate	**- 0.59**	**<0.001***	**-0.63**	**<0.001***
Serum albumin	**-0.31**	**<0.001***	**-0.238**	**0.005***
Serum uric acid	**0.25**	**0.004***	0.074	0.39
Fasting blood glucose	0.007	0.93	0.104	0.22
Postprandialglucose	-0.12	0.14	-0.133	0.117
Urine ß2 microglobulin	**0.69**	**<0.001***	**0.98**	**<0.001***

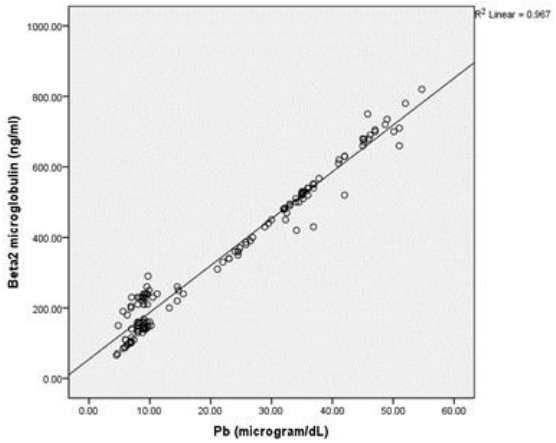

Figure (1):Correlation of Pb withβ_2 microglobulin

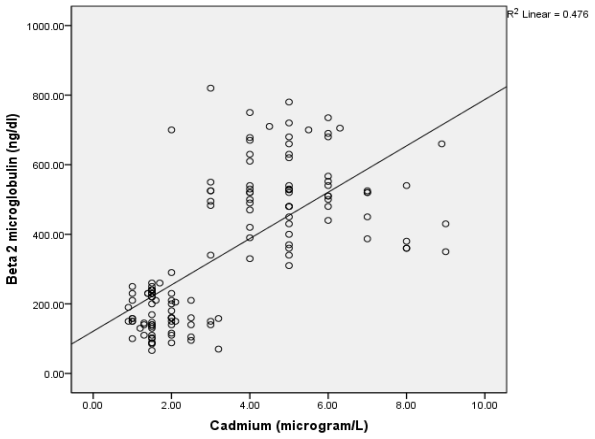

Figure (2): Correlation of Cd withβ_2 microglobulin

DISCUSSION

Because of their central role in the elimination of cadmium and other heavy metals from the body, the kidneys represent a critical target of cadmium toxicity [(4)]. Thus, the present study was designed to study the possible toxic effects of lead and cadmium co-exposure on the kidney. It included 70 patients with known exposure to lead and cadmium and another 70 healthy controls.

Regarding the estimated glomerular filtration rate, it was statistically significantly decreased (76.11±9.73) in group 1 than group 2 (99.74±14.13). On the other side, creatinine, blood urea nitrogen (BUN), and serum uric acid, were statistically significant increases in the study than control group this signifying the toxic effect ofCd and Pb. These results have coincided with Chenet al. [(15)].who demonstrate that The eGFR of subjects in the polluted area with lead and cadmium was decreased compared with that in the control group and concluded that Cd and Pb exposure, alone or in combination, are associated with renal impairment. In addition, co-exposure to Pb and Cd propagates the renal tubular dysfunction compared with Cd or Pb exposure alone.

Chronic exposure to lead predominantly results in proximal tubular damage with mitochondrial dysfunction[(16)]. The main mechanism of lead-induced renal injury was believed to be oxidative stress. Metals, including lead and cadmium, generate excessive amounts of oxygen radicals as the reactive oxygen species (ROS) that, deplete endogenous radical ROS scavengers, deteriorate a variety of transport proteins, leading to injury. Lead exposure causes tubular injury[(17)].

Exposure to cadmium and its consequent renal dysfunction seems to be clear. The Cd-induced nephrotoxic manifestations comprise proteinuria, calciuria, aminoaciduria, glycosuria, and change in estimated glomerular filtration rate (eGFR) as reported previously[(18)].Similar results were reported by Navas-Acien et al. [(19)].They demonstrated the health hazards of long-term cadmium environmental exposure on subjects resides near a Cd-contaminated area. In addition to the significant increase of tubular damage indicators, research investigated the effects of Cd-exposure on eGFR revealed that the CKD prevalence is 1.32 times higher in the highest thanthe lowest quartile of blood cadmium levels[(19)].

Detailed pathophysiologic mechanisms that initiate renal injury due toCd-exposure have been investigated by several previous experimental studies. Cd is mainly deposited in the renal cortex proximal tubules. Theanimal kidneys after Cd-exposure became enlarged with degeneration of the proximal tubules, apoptosis, atrophy, interstitial inflammation, and swelling of glomeruli[(17)].

In the present work, the presence of proteins in urine by dipstick test (2 plus or more proteins) was 25.7% in group 1 and 17.9% in group 2 and it was a statistically significant increase in group 1 than group 2. These results are similar to the study by **Tsai et al.[20],**who concluded that High blood Pb may be associated with proteinuria and an eGFR of <60 mL/min/1.73 m^2. High urine Cd was significantly associated with proteinuria. Co-exposure to Cd and Pb may have synergistic effects on proteinuria also these results are comparable to a study by **Garcon et al.[21]**who reported that one of the earliest signs of renal damage is increased proteinuria with the predominance of low-molecular-weight proteins derived from plasma due to the failure of proximal tubule to reabsorb proteins filtered through the glomeruli. In addition, the study done by **Cabral et al. [22]**revealed a positive relation between proteinuria and Cd, also between proteinuria and Pb levels in studied populations.

In the present work urine, β2 microglobulin was statistically significant increased (530.32±122.56) in group 1 than group 2 (171.27±56.03) in additionthere were statistically significant positive correlations, with urine β2 microglobulin. These results concise with astudy by **Mahmoud et al.[23]**who showed that β2 microglobulin has the highest correlation among the studied parameters so, β2 microglobulin is the best predictive biomarker in the evaluation of renal dysfunction in lead-exposed workers. The advice to the regular periodic measurement of β2 microglobulin was recommended for all workers exposed to leadso**Lin et al.[24]**demonstrated that β2 microglobulin measurement in urine can be used to assess the renal tubular injury and toxic elements such as lead, cadmium, and mercury, which cause renal tubular injury, increase the excretion of β-2 microglobulin

In the present work, each cadmium and lead were statistically significant positive correlations with creatinine and blood urea nitrogen. In addition, cadmium was a statistically significant positive correlation with serum uric acid. On the other hand, each cadmium and lead werea statistically significant negative correlation with each of hemoglobin, RBCs, hematocrit, and eGFR. In addition, cadmium was inversely correlated with serum albumin. These results are comparable to a study by **Spector et al. [25]** who showed the results of 3941 US participants with average blood lead level of 1.7μg/dL.

In an experimental study, the rising blood Pb-concentrations were inversely correlated with the eGFR. Animals with blood lead levels from 2.4 to 4.7μg/dL developed glomerular hypertrophy as a result of increased mesangium and capillary volumes **[26],**eventually resulting in hyperfiltration of the glomeruli. This is a consistent effectand an epidemiological study showed that increasing GFR and reduced levels of creatinine, cystatin C and β_2-microglobulin were observed at low lead levels(< 5.5 μg/dL), without recognition of a threshold point[27]. However, blood lead levels>7 μg/dL were associated with an increase of urinary protein secretion and hyperuricemia, indicating impaired tubular function **[28].**

Conclusion: There was a harmful effect of co-exposure to cadmium and lead on the kidney and this deterioration of kidney function was correlated with increased cadmium and lead levels. In addition, urine β2 microglobulin is a good marker of renal tubular dysfunction in such patients.

Conflict of interest

None

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Authors contributions:

All authors shared equally in the research, and the final manuscript was revised and accepted by all

authors. All are responsible for the scientific content.

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