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Research Article

Prevalence of Environmental Acquired Cadmium Nephropathy among smokers

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Abstract

Introduction; Cadmium had been recognized as an occupational health hazard for many decades. In the general population in the absence of specific industrial exposure, the main sources of exposure being food and tobacco smoke. During the last decade an increasing number of studies have found adverse health effects at much lower levels than in the earlier studies. For 20 cigarettes smoked, approximately 2–4 µg of Cd is inhaled by the smoker and as much as a microgram of Cd spreads into the environment. Cadmium nephropathy is characterized by low molecular weight (LMW) proteinuria, proximal tubular dysfunction persists until renal failure supervenes**. *Aim of this Study*** was to assess the risk for cadmium exposure among smokers and the risk of development of cadmium nephropathy among them. ***Patients & methods;*** This study included 60 apparently healthy men smokers and 30 non smokers volunteers as a control group matched by age and working status. Serum creatinine, urea, urine analysis, urinary protein creatinine ratio, urinary B2 microglobulin and urinary cadmium levels (U-Cd), creatinine clearance (CrCl) by Cockcroft–Gault formula were done for all participants together with smoking assessment by pack year index for smokers. ***Results***; Urinary cadmium was significantly higher among smokers and there was a statistically significant correlation between urinary cadmium and pack/year index and smoking duration. There was a significant positive correlation between urinary cadmium level and urinary beta 2 microglobulin and a highly significant negative correlation between eCrCl and urinary cadmium level among both smokers & non smokers with a highly significant correlation between U-Cd & duration of smoking & pack/year index. Those with bony aches had significantly higher urinary cadmium level as a symptom suggestive of cadmium toxicity. Also, smokers had a mean urinary beta 2 microglobulin more than 300 µg/g.cr which indicates that smoking is associated with early reversible cadmium nephropathy. ***Conclusion***; Smoking is associated with increased urinary cadmium level with significant positive correlation with urinary beta 2 microglobulin & negative correlation with creatinine clearance. The associated urinary beta 2 microglobulin level indicates early cadmium nephropathy.

Keywords: cadmium, nephropathy, urinary beta 2 microglobulin, smoking.

Introduction

Cadmium has been recognized as an occupational health hazard for many decades. In the general population in the absence of specific industrial exposure, the main sources of exposure being food and tobacco smoke. During the last decade an increasing number of studies have found adverse health effects at much lower levels than in the earlier studies[1].

Cigarette smoke contains substantial amounts of Cd. Average Cd levels in cigarettes range from 1000 to 3000 µ g/kg . One pack of cigarettes deposits 2–4 µg

into the lungs of a smoker while some of the smoke passes into the air to be inhaled by smokers and nonsmokers alike, which means, for 20 cigarettes smoked , approximately 2–4 μg of Cd is inhaled by the smoker and as much as a microgram of Cd spreads into the environment[2].

Cadmium nephropathy is characterized by low molecular weight (LMW) proteinuria due to diminished intrarenal uptake and catabolism of filtered proteins. In Cadmium nephropathy, proximal tubular dysfunction persists until renal failure supervenes [1].

Aim of the work

To assess the risk for increased cadmium exposure among smokers and to detect the prevalence of cadmium induced nephropathy among smokers.

Patients & methods

This cross sectional study was done on 90 apparently healthy men who were classified into 60 current smokers living in Cairo and working in Ain-Shams university hospital either as manual workers, clerks or medical staff and 30 apparently healthy men non smoker volunteers matched by age and working status.

Exclusion criteria

Past history of renal/urological diseases, hypertension or diabetes mellitus, family history of renal/urological diseases, intake of potentially or suspected nephrotoxic drugs, Passive smokers, occupationally exposed to cadmium e.g. workers of manufacturing nickel-cadmium batteries and also workers using paint pigments, living outside Cairo. Women were excluded, as the prevalence of smoking in women is low in Egypt (0.7%) compared to men (34%), second, due to social and cultural causes; women may deny smoking[3].

All participants were subjected to full medical history including symptoms suggestive of cadmium toxicity like bony aches, BP measurements, serum creatinine, Blood urea, urinary protein creatinine ratio, urinary $_{B2}$ microglobulin, urinary cadmium levels, estimation of creatinine clearance (CrCl) by Cockcroft–Gault formula. Renal biopsy if protein/creatinine ratio was more than 1 mg/dl to exclude the presence of primary renal disease.

Smoking Assessment

To define a participant as smoker, he must have smoked more than 100 cigarettes during his life. Smoking dose was quantified in **pack-year (PY)** and the pack contains 20 cigarettes with 1 py defined as smoking one pack per day for 1 year. All smokers used the same local brand of cigarettes.

Creatinine clearance assessment (Cr Cl) using Cockcroft–Gault formula

(CrCl) = (140-age) X (body weight in Kg) X 0.85 if female/72 X creatinine (cr)[4].

Analytical methods

To prevent degradation of beta 2 microglobulin occurring in acidic urine (at pH <5.5) , the pH of the urine was checked and adjusted to be > 5.5 using 1 N NaOH and stored at –20°C.[5] Urine samples were examined for presence of beta 2 microglobulins using ELISA method. The lower detection limit for b2-microglobulin has been determined at 0.1 μg/ml. The level of normal β2-MG is less than 300 μg/g.cr.[6]

Urinary creatinine level was measured using BECKMAN synchron cx delta systems. Assay of urinary proteins was done using photometric test using pyrogallol red (DiaSys). Assay of serum creatinine and urea were done using BECKMAN synchron cx delta systems.

Determination of Cd in urine was performed with a flameless atomic absorption spectrophotometer equipped with a Zeeman graphite furnace (Perkin Elmer Model SIMAA 6000). Briefly, urine was added to nitric acid, diluted with diammonium hydrogen phosphate and Triton X-100, and mixed vigorously. The limit of detection was 0.1 g/L in urine.

Statistical method

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 16) as following:

Description of quantitative variables as mean, SD and range .
Description of qualitative variables as number and percentage.
Chi-square test was used to compare qualitative variables between groups.
Unpaired t-test was used to compare quantitative variables, in parametric data (SD<50% mean).
One way ANOVA test was used to compare more than two groups as regard quantitative variable.
Correlation coefficient test was used to rank variables positively or inversely.
P value: is the value of rejection of the null hypothesis, P value > 0.05 insignificant, P <0.05 significant, P<0.001 highly significant

Results

This cross sectional study was done on 60 current smokers men living in Cairo and working in Ain-Shams university hospital either as manual workers ,clerks or medical staff (group 1) and 30 apparently healthy male non smokers volunteers (group 2) matched by age and working status.

Group (1) was further subdivided into; **group (1a)**: smokers ≥ 10 years (30 participants) and **group (1b)**: smokers < 10 years (30 participants).

Table (1): Comparison between the studied groups as regard age, body weight, blood pressure & occupation,
#chi-square test

Variables	**Non smokers N=30**	**Smokers <10 years N=30**	**Smokers ≥10 yrs N=30**	**P**	**LSD**
Age (yrs)	41.8±9	38.5±6.8	41.9±9	0.13NS	
Pack/year	-	11±5.6	26±12	**0.00HS**	
Body weight (kg)	79.5±13	76.8±16	78.5±15	0.19NS	
SBP (mm Hg)	132±14	128±15.7	130±20	0.20NS	
DBP (mm Hg)	80±6.5	82.5±7	85.9±5	**0.05S**	Smoking >10 yrs vs non smokers
Occupation Manual Medical staff Clerk	 5(16.7%) 11(36.7%) 14(46.7%)	 8(46.7%) 12(40%) 10(33.3%)	 5(16.7%) 11(36.7%) 14(46.7%)	0.75 NS#	

Table (1) shows that participants in both groups were matched as regard age, occupation, body weight and systolic blood pressure (SBP). On the other hand, the group with more than 10 years smoking (group 1a) had significantly higher diastolic blood pressure (DBP) & pack year index compared to non smokers.

Table (2) Comparison between the studied groups as regard laboratory data:

Variables	Smokers <10yrs Group (1b) N=30	Smokers ≥10 yrs Group(1a) N=30	Non smokers Group(2) N=30	P value	LSD
Urinary Cd (µg/g.creatinine)	1.05±0.3	1.2±0.3	0.67±0.2	0.00HS	**-Smokers ≥10 yrs vs non smokers P (0.00 HS) -Smokers<10 vs non smokers P (0.03S)**
B_2 microglobulin (µg/g. cr)	309±155.7	330±178	286±177	0.28 NS	
S. creatinine (mg/dl)	0.95±0.2	0.96±0.4	0.89±0.5	0.19 NS	
blood urea (mg/dl)	18.3± 3.6	18.9± 3.9	17.6 ±4.3	0.21NS	
Cr. clearance (ml/min)	119±44.0	110±44.6	118.9±35.9	0.22 NS	
Urine Protein /creatinine ratio	0.17±0.4	0.15±0.2	0.18±0.3	0.30 NS	

Table (2) shows that urinary cadmium was higher among smokers ≥10 years group (1.2±0.3 µ /g. creatinine) compared to non smokers (0.67+0.2 µ /g. creatinine) with a highly significant difference (p value = 0.000) **see figure (1).** And also smokers < 10 years (1.05±0.3) had significantly higher urinary cadmium level than controls and p value = 0.03. As regard beta 2 microglobulin, controls had the lowest level (286+77 µ/g. creatinine) compared to smokers <10 years (309+155.7 µ/g.creatinine) and to smoking ≥10 years (330+178 µ /g. creatinine) with statistically no significant difference among studied groups p= 0.28 **(see figure (2))**. No statistically significant difference between the studied groups as regard serum creatinine, blood urea, protein/creatinine ratio or eCrCl.

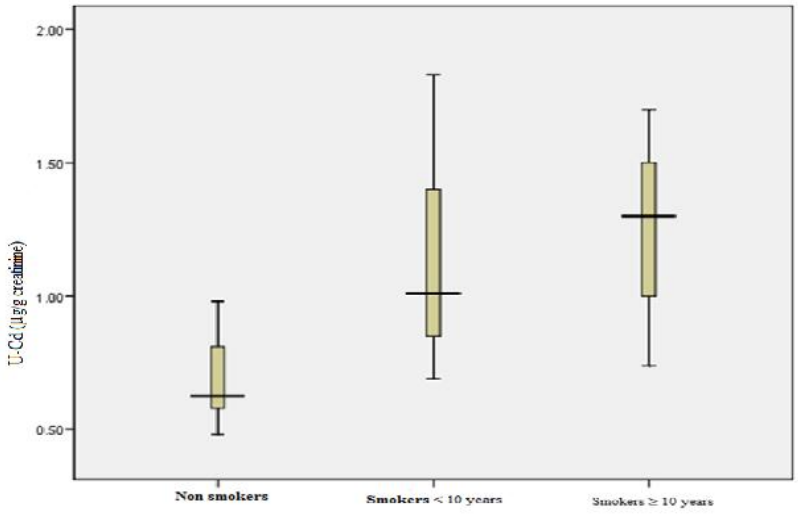

Figure (1): Box plot for comparison between studied groups as regard urinary cadmium measures in µg/g creatinine.

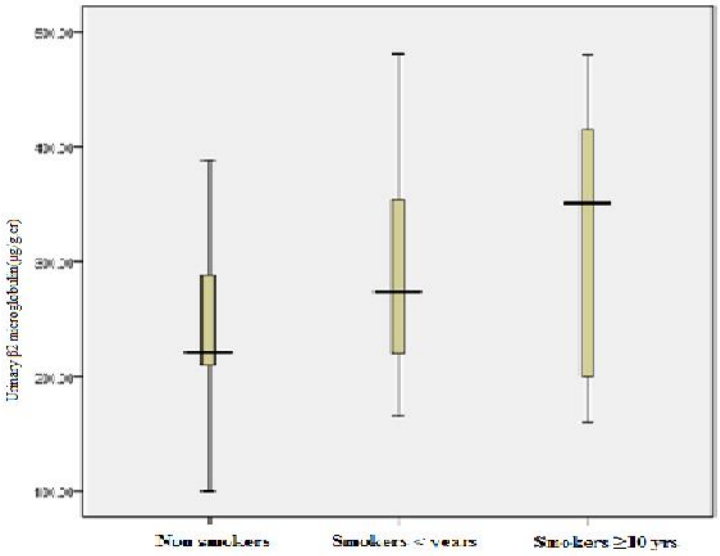

Figure (2): Box plot for comparison between the studied groups as regard urinary beta 2 microglobulin (µg/g creatinine).

Table (3): Comparison between smokers versus non smokers as regard laboratory data.

Variables	**Smokers (Group 1) N=60**	**Non smokers (Group 2) N=30**	**t**	**P**
Urinary Cd (µ/gm.cr)	1.17±0.3	0.67±0.2	**2.8**	**0.01S**
Beta 2 microglobulin (µ/gm.cr)	315.6±196	286±177	1.9#	0.17NS
Serum creatinine (mg/dl)	0.95±0.8	0.89±0.5	1.7	0.15NS
Creatinine clearance	115±35	118.9±35.9	0.4	0.82NS
U. Protein /creatinine	0.13±0.7	0.18±0.3	0.8	0.70NS

Mann Whitney Willcoxon test

Table (3) shows that urinary cadmium was significantly higher among smokers (1.19±0.3 µg/g.cr) compared to non smokers (0.67±0.2 µg/g.cr). As regard beta 2 microglobulin, smokers had a higher level (315.6±196 µg/g.cr) compared to non smokers (286±177 µg/g.cr) although with no statistically significant difference. Also, there were no significant difference between smokers & non smokers as regard serum creatinine, creatinine clearance & urinary protein/ creatinine.

Table (4) Correlation between urinary cadmium versus other variables among non smokers.

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Variable	r	p
B_2 microglobulin (µg/g.cr)	**0.31**	**0.05 S**
Serum creatinine (mg/dl)	0.20	0.17
Blood urea(mg/dl)	0.13	0.38
Creatinine clearance (ml/min)	**-0.60**	**0.000 HS**
Urine Protein /cr	0.09	0.40
Age (year)	0.05	0.60
Body weight (Kg)	0.04	0.88
SBP (mmHg)	0.21	0.21
DBP (mmHg)	0.16	0.49

Table (4) shows that urinary cadmium had a statistically significant positive correlation with B2 microglobulin (p value 0.05) see figure (3). On the other hand there was highly significant negative correlation between urinary cadmium and creatinine clearance (r= -0.60 and p = 0.000HS) see figure (4). There was no statistically significant correlation between urinary cadmium and other variables (serum creatinine, blood urea, urine protein/cr ratio, age, body weight ,SBP and DBP) in non smokers.

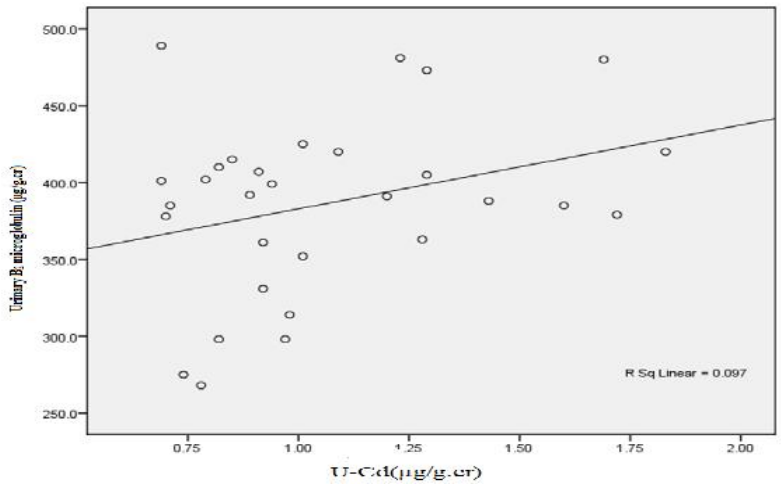

Figure (3): Correlation between urinary cadmium versus B2 microglobulin showing positive correlation among non smokers.

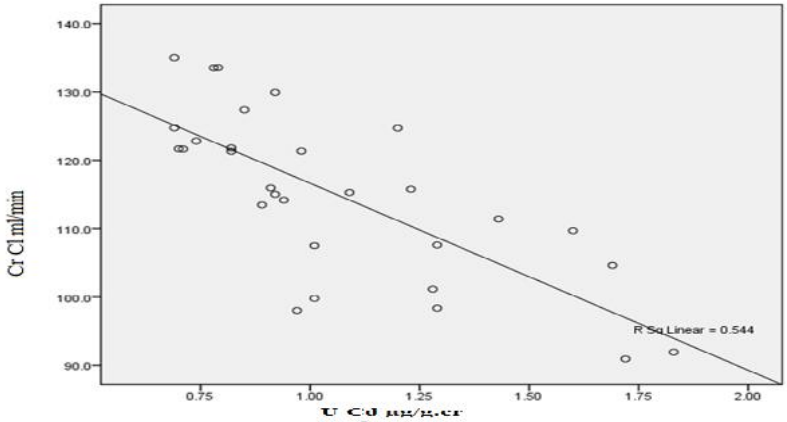

Figure (4): Correlation between urinary cadmium versus CrCL showing inverse significant correlation among non smokers.

Table (5): Correlation between urinary cadmium versus other variables among smokers.

Variable	r	p
B_2 microglobulin (µg/g.cr)	**0.38**	**0.001S**
Serum creatinine (mg/dl)	0.12	0.27
Creatinine clearance (ml/min)	**-0.77**	**0.000(HS)**
Protein /cr	0.02	0.55
Age (year)	**0.27**	**0.03(S)**
Body weight (Kg)	**0.34**	**0.04 (S)**
SBP(mm Hg)	0.11	0.41
DBP (mm Hg)	0.03	0.59
Pack/year	**0.55**	**0.0002 (HS)**
Smoking duration (year)	**0.847**	**0.000 (HS)**

Table (5) shows that urinary cadmium had a statistically significant positive correlation with B2 microglobulin (p value= 0.001) see figure (5), with age (p value= 0.03), with pack/year index with (P =0.0002), with smoking duration with (p =0.000) see figure (6). On the other hand there is inverse significant correlation between urinary cadmium and creatinine clearance p (0.000) see figure (7).

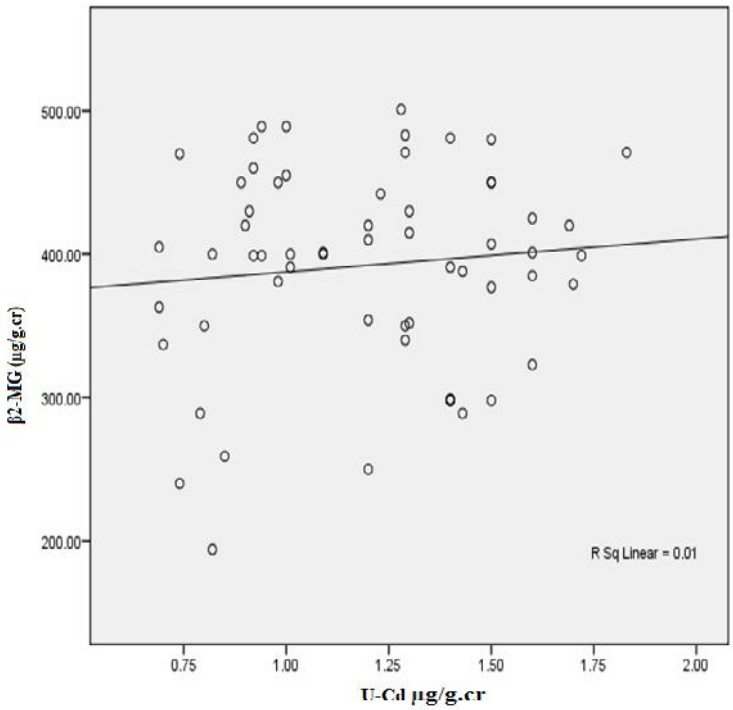

Figure (5): Correlation between urinary cadmium versus β2-MG showing significant positive correlation among smokers.

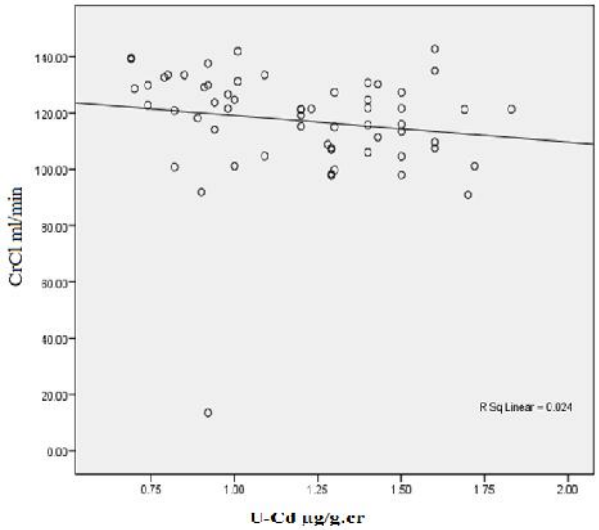

Figure (6): Correlation between urinary cadmium versus CrCl showing significant negative correlation among smokers.

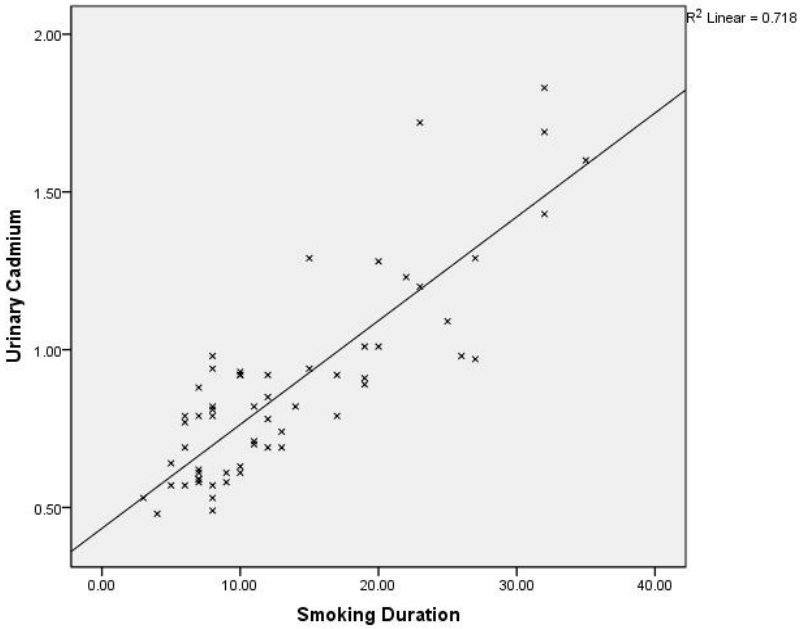

Figure (7): Correlation between urinary cadmium versus smoking duration showing significant positive correlation.

Table (5): Comparison between smokers versus non smokers as regard cut off value for β2-MG of 300 µ/g.cr .

β2-MG	**Non Smokers N=30**	**smokers N=60**	**P**
β2-MG between 300-1000 µg/g.cr	4 (13.33%)	14 (23.33%)	0.20(NS)
β2-MG <300 µg/g.cr	26 (86.66%)	46 (76.66%)	

Table (5) shows that the prevalence of high β2-MG > 300 µg/g.cr was higher in smokers (23.33%) compared to non smokers (13.33%). However, there was no statistical significant difference between both groups.

Table (6): Comparison between total smokers versus non smokers as regard presence of bony aches as a symptom related to cadmium exposure.

Bony aches	Non smokers N=30	Smokers N=60	P
Absent	16(53.3%)	24(40%)	0.14 NS
Present	14(46.7%)	36(60%)	

Table (6) shows that there is no significant difference between both groups as regard the presence of bony aches.

Table (7): Comparison between mean urinary cadmium level in participant with and without bony aches.

Bony aches	Mean urine cadmium (µg/g.cr)	±SD	t	P
Absent (N:40)	0.8	0.2	**2**	**0.04 S**
Present (N:50)	1.2	0.3		

Table (8) shows that those with bony aches had significantly higher urinary cadmium level.

Table (9): Comparison between participants with and without bony aches as regard urinary beta 2 microglobulin:

Bony aches	Mean β2-MG(µg/g.cr)	±SD	T	P
Absent	378	210	1.8	0.08 NS
Present	412	176.8		

Table (9) shows that urinary beta 2 microglobulin was higher in those with bony aches (412 µg/g.cr) compared to those without bony aches (378 µg/g.cr) although of non significant difference between both groups (P=0.08).

Discussion

Cadmium has been recognized as an occupational health hazard for many decades. The risks to environmentally exposed populations were emphasized later, when it was concluded that the infamous Itai-itai disease was caused by intake of cadmium-polluted rice. Since then, numerous studies have reported health effects of cadmium exposure in the general population also in the absence of specific industrial exposure, the main sources of exposure being food and tobacco smoke. An increasing number of studies have found adverse health effects at much lower levels than in the earlier studies.The average cadmium intake from food generally varies between 8 and 25 µg per day. [7]

The tobacco leaves accumulate cadmium in a manner similar to certain food from plants. One cigarette may roughly contain 1–2µg cadmium (varies depending on the type and brand). Roughly 10% of the cadmium content is inhaled with an approximate 50% absorption in the lung. It is estimated that a person smoking 20 cigarettes per day will absorb about 1 µg cadmium daily[3].

After pulmonary and/or gastrointestinal absorption, Cd binds to serum albumin and accumulates in the liver, where it is complexed to a metal binding protein, metallothionein-1. The Cd-metallothionein-1 complex reaches the kidney where it is filtered and accumulates in the proximal tubule, whose cells possess transporters for free and bound forms of Cd and interferes with the tubular function.[1]

Cadmium nephropathy is characterized by low molecular weight (LMW) proteinuria due to diminished intrarenal uptake and catabolism of filtered proteins. In Cadmium nephropathy, proximal tubular dysfunction persists until renal failure supervenes.[1]

β2-microglobulin is a typical marker of proximal tubular dysfunction, which is considered as one of the best indicators of Cd-induced nephropathy, so it was chosen to be a marker of the expected cadmium induced nephropathy.[8]

The aim of this study was to determine the risk of cadmium exposure among smokers by measuring urinary cadmium level and to detect any renal injury associated with this possible exposure to cadmium by measuring urinary beta 2 microglobulin and estimation of creatinine clearance in smokers and non- smoker.

This study was done on 90 male subjects who were classified into 60 current male smokers working in Ain Shams university hospitals either manual workers, clerks or medical staff and 30 apparently healthy male non smokers volunteers matched by age and working status.

Urinary cadmium (U-Cd) is commonly interpreted in epidemiological studies to measure cadmium accumulated in the kidney, and is thus used as a marker of long-term exposure.[3] Blood cadmium also reflects long term exposure but it is more influenced by recent exposure.[9]

In this study, the urinary cadmium level was significantly higher in the smoker group (1.17±0.3µg/g.cr) when compared to non smokers (0.67±0.2 µg/g.cr) with P value of (0.01). Also the urinary cadmium in group 1a (1.2±0.3 µg/g.cr) and group 1b (1.05±0.3 µg/g.cr) separately was higher than that of nonsmokers (0.67±0.2 µg/g.cr) with a significant P value of (0.00) and (0.03) respectively. Also, there was statistically positive correlation between urinary cadmium in smokers and py index (p=0.0002).

In this study, although there is increased urinary cadmium level in non-occupationally exposed smokers , this increase is still too much lower than that in occupationally exposed people which may reach levels more than 10 µg/g.cr as revealed by the study done by **Bernard (2004).** [10]

In agreement with our study Huang et al. found that in Korean males, concentrations of urinary Cd were significantly higher in current smokers with mean urinary cadmium of 0.88 µg/g.cr when compared to non smokers with mean urinary cadmium of 0.67 µg/g.cr and P value less <0.05.[11] Analysis of data from NHANES 1999-2006 also revealed that male smokers in (USA) has significantly higher urinary cadmium level with mean of 0.39 µg /g.cr than non smoker with mean of 0.23 µg /g.cr with a P value of 0.001.[8]

The difference in the mean urinary cadmium level among smokers in these studies may be due to difference in the cadmium content of cigarette brands used in the different countries, difference in the pack/year index which was not mentioned in both studies or due to difference in food habits and cadmium content in different food between different countries.

The analysis of data from NHANES 1999–2010 revealed a positive co-relation between urinary cadmium and pack/year index of smoking which agrees with the present study[12]. Moreover, the current study showed statistically significant positive correlation between urinary cadmium and smoking duration.

In the current study, there was a statistically significant positive correlation between urinary cadmium and age among smokers (p value =0.03) which agrees with the study done by Adams and Newcomb who analyzed the National Health and Nutrition Examination Survey data (1999–2010) (NHANES) in which U-Cd was

200% higher at age group more than 70 years than those with age 20-29 years[12]. The

explanation for this finding may be due to increased body burden of cadmium as a result of longer duration of exposure with the increase in age.

In the present study urinary B2 microglobulin had the highest level in smokers ≥10 years (330±178 µg/g.cr) when compared to smokers <10 years duration (309±155.7 µg/g.cr) while that of non smokers had the lowest level (286±77 µg/g.cr), although statistically of no significant difference. Meanwhile, there was a statistically significant correlation between urinary cadmium and urinary beta 2 microglobulin (p value 0.05).

In agreement with this finding, Mortada et al. found that smokers had significantly higher urinary cadmium level than non smokers. However, this higher level is not enough to produce nephrotoxicity (there was no significant increase in urinary beta 2 microglobulin in smokers when compared to non smokers) and they concluded that in the presence of other risk factors for kidney disease or other sources for heavy metal exposure, this exposure from smoking may motivate signs of nephrotoxicity[5].

According to OSHA, 2013**,** the normal level of urinary beta 2 microglobulin is less than 300 µg/g.cr and people who are exposed to cadmium and had urinary beta 2 microglobulin more than 300 µg/g.cr had elevated risk of renal tubular proteinuria. Any risk for increased cadmium exposure in this group should be removed if possible and they must be followed annually with biological monitoring and annual medical examination until measurement returns back to normal **(OSHA, 2013)**.[6]

In the current study ,the mean urinary beta 2 microglobulin in the non smokers was 286±177 µg/g.cr i.e. towards the safe level (less than 300 µg/g.cr) while that of the smoker groups was 315.6±196 µg/g.cr i.e more than 300 µg/g.cr and according to recommendation from OSHA 2013,this group must avoid cadmium exposure if possible so, it is recommended to give up smoking and to follow urinary beta 2 microglobulin annually.[6]

According to **Bernard, (2008)**, urinary beta 2 microglobulin between 300-1000 µg/g.cr indicates the presence of early cadmium nephropathy which is reversible after removal of source of cadmium exposure while urinary beta 2 microglobulin more than 1000 µg/g.cr indicates evident irreversible cadmium nephropathy. In the current study, 23.33% of smokers and 13.33% of non smokers had urinary β2-MG between 300-1000 µg/g.cr but with no statistically significant difference between them.[13]

From these results we can conclude that in smokers the prevalence of cadmium induced nephropathy (early and reversible) is 23.33% which needs to be confirmed by other studied including males and females with a large sample size and using 2 or more biomarkers for cadmium induced nephropathy.

The explanation of the non significant difference in urinary β2-MG level between non smokers and smokers in spite of positive correlation between urinary cadmium and urinary β2-MG in the current study may be attributed to:

First, relatively **small sample size**. Second, the participants were **only males** so, the **adjustment of urinary β2-MG to urine creatinine** gave a lower urinary β2-MG value due to theoretical increase in urine creatinine as a result of increased muscle mass in males. Also, Women have higher cadmium body burden than men, reflected as higher concentrations of cadmium in blood, urine and kidney cortex[14]**.** The main reason for the higher body burden in women is increased intestinal absorption of dietary cadmium at low iron stores[15]. Third, the present study included smokers with **low pack/year index** especially in group 1b (smokers less than 10 years) which might cause lower U-Cd. Fourth, this may be due to instability of β2-MG in acidic urine with pH less than 5.5 leading to its destruction (although NaOH have been added to urine sample with pH less than 5.5, there is possibility that **β2-MG might be destructed in acidic urine in bladder** before voiding).

Another explanation for the non significant association between group (1) and group (2) as regard urinary beta 2 microglobulin level inspite of the positive correlation between urinary

cadmium and urinary beta β2-MG in this study, is that the relationship between urinary cadmium and urinary β2-MG is not a linear but a **J shaped** with the point of flexion at urinary cadmium of 10-11 ug /g.cr at which urinary β2-MG level will markedly increase with the increase in urinary cadmium level.[16] So, below this level there will be no significant increase in urinary β2-MG level.

Tubular proteinuria may not give rise to any subjective symptoms or disease, but it may progress to glomerular damage with a decreased GFR, as demonstrated in studies of occupationally exposed workers**[17].** Recent studies in environmentally exposed populations suggest that decreased GFR and creatinine clearance may occur at similar cadmium levels as that causing tubular damage**[18].**

In this study, there was no significant correlation between U-Cd and serum creatinine and urea among smokers which agrees with the finding of Prozialeck et al. which revealed that changes in serum or urinary creatinine are generally not seen during the early or mild stages of cadmium-induced kidney injury.[19]

In the present study, there was a statistically significant negative correlation between urinary cadmium and creatinine clearance (P value of **0.000).**The study done by Wallin et al. showed a statistically significant negative correlation between urinary cadmium and estimated creatinine clearance in both smokers and non smokers**[20]**. Also, Suwazono et al. found a statistically significant lower CrCl at U-Cd 0.75–1.0 µg/g cr than at U-Cd < 0.5 µg/g.cr **[21]**.

In the study done by Akesson et al., there was a paradoxical positive correlation between urinary cadmium and estimated creatinine clearance and this positive correlation became significant at urinary cadmium level of 1.0 µg/g.cr. Akesson et al. concluded that the increased creatinine clearance was secondary to increased glomerular filtration of creatinine (indicating glomerular lesion) and also increased tubular secretion of creatinine indicating early tubular lesion at low levels of cadmium exposure. In this study, the estimated creatinine clearance in group 1b (smokers less than 10 years) was 119.4±40 ml/min slightly higher than that in group b (non smokers) 118.9±35.9 ml/min which agrees with the findings in **(Akesson et al.,** study.[22]

In the current study, participants with bony aches had mean urinary cadmium of 1.2 µg/g.cr while those without bony aches had a mean urinary cadmium level of 0.8 µg/g.cr with a statistically significant difference between both of them indicating that higher urinary cadmium level among smokers may be associated with bone effects like osteomalacia and osteoporosis.

This is in agreement with Swedish and Belgian data that confirmed the negative effects of low-level cadmium exposure on bone mineral density. The threshold for cadmium effect on bone mineral density was U-Cd=0.31–1.6 µg/g.cr[23]**.** Another US study using NHANES data, reported among almost 3000 women also showed an increased risk of bone mineral density-defined osteoporosis of the hip at U-Cd concentrations between 0.50 and 1.00 µg/g creatinine which agrees with findings in this study [24]**.**

On the other hand, in this study there was no significant difference between the presence of bony aches and the urinary β2-MG indicating that the bony effects (like osteomalacia and osteoporosis) in cadmium exposed people among smokers may occur before renal affection which is in agreement with Cheong et al. who found high prevalence of osteoprosis in the population who environmentally exposed to cadmium with a mean urinary cadmium of (2.1 µg/g.cr). **[25]**

In the present study, there was a statistically significant difference between diastolic blood pressure in non smokers and group smokers ≥10 years with p value of 0.05, although there was no significant correlation between U-Cd & blood pressure. The study done by **Caciari et al.(2012)**[26] revealed that there was a significant positive correlation between urinary cadmium level and blood pressure especially diastolic blood pressure among female smokers, it partly disagrees with the present study, may be due to relatively small sample size in the current study,

including only men participants, with lower cadmium body burden.

Conclusion

Smoking is associated with increased urinary cadmium level which had a significant positive correlation with urinary beta 2 microglobulin & negative correlation with creatinine clearance. The associated urinary beta 2 microglobulin level indicates early cadmium nephropathy.

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