

Urinary Cadmium Concentration and its Risk Factors among Adults in Tanjung Karang, Selangor

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Abstract: This study is a preliminary research in Malaysia conducted to measure the urinary cadmium concentration. Cadmium is widespread toxic mineral found in the environment (air, water, soil and food) and as a pollutant coming from agricultural and industrial sources also it is a carcinogenic heavy metal. Cadmium is nephrotoxic metal and can be accumulates in the kidney for long time (half life 10-30years). It can damage the tubules of the kidney and this can lead to renal failure. This study carried out in Tanjung Karang, Selangor to detect the concentration of cadmium in the urine sample and its related factors. A total of three hundred (300) urine samples checked using primary data. Adult males and females aged 35-70 years old were the respondents. The sample size was 300 respondents, 128(42.7%) males and 172(57.3%)females. Ethnicity factor included : Malay,225(85%),Chinese, 36(12%)and Indian 9(3%). Graphite furnace atomic absorption spectrophotometer (GFAAS) used to analyze the urine samples. Study results showed that 44 urine samples were have high cadmium level out of 300(Cadmium normal level < 2 µg / litre urine). The prevalence rate was 14.7 %. This revealed that about 15 people out of 100 have urinary cadmium level above the normal limits which can be considered toxicity level. There was significant correlation between the age of study population and urinary cadmium level as the age getting higher, the urinary cadmium level gets higher ($r=0.118$)($p=0.041$).There was significant association between urine cadmium level and smoking ($p=0.0001$) (POR=5) and that explain smoking cigarettes can add a burden on the body in addition to the ingestion of foods contaminated with cadmium and inhalation air that is usually contains percentage of cadmium. This study opens the doors for many future studies in Malaysia to investigate about this important heavy metal from checking the environment (air, water and food) for cadmium and the contribution that relates to the human health exposure and risk.

Key words: Cadmium • Nephrotoxic • POR (Prevalence Odds Ratio)

INTRODUCTION

Cadmium (Cd) is a nonessential heavy metal and is known as an important industrial and environmental pollutant. It is also a contaminant of tobacco smoke. The wide environmental distribution of cadmium has led to an increased interest in its toxicity and biological effects. Environmental exposure to cadmium occurs primarily through smoking and the consumption of contaminated food and water [1,2]. Other sources of exposure include inhalation of contaminated air, particularly near specific point sources such as smelters and incinerators [3]. Cadmium accumulates in target tissues, especially in the renal cortex. The whole-body half-life for cadmium is estimated to be between 15 and 30 years [1]. This long half life is due to the fact that

cadmium is unlike organic toxicants, which can often be degraded metabolically to less toxic derivatives, cadmium remains intact in biological systems. Cadmium that enters the blood through pulmonary and internal pathways rapidly clears from the circulation, depositing mainly in the liver and kidney [4]. Cadmium resides in these organs with a very long half-life (10-30 years); excretion into urine or feces is extremely limited. As a result of this characteristic metabolic profile, cadmium accumulates in the body over time, increasing in concentration with age in a number of organs. Cadmium can be measured in blood, urine, hair or nails.

Urinary cadmium has been shown to accurately reflect the amount of cadmium in the body. The amount of cadmium in blood shows recent exposure to cadmium. The amount of cadmium in urine shows both recent and

past exposure. The average blood cadmium of Canadians aged 6 - 79 years is 0.35 micrograms/litre [5]. The average normal levels of cadmium were 0.59-0.77 microgram/litre in urine [6].

The critical target organ for cadmium toxicity as recognized for a long time is the kidney. Human studies indicate that 7% of the general population have renal dysfunction from cadmium exposure [4]. Once human reaches the age of 50 years old, kidney Cd concentrations reach approximately 12 µg/g wet weights in non-smokers and 25 µg/g in smokers reflecting the fact that tobacco leaves concentrate Cd from the soil. The renal cadmium concentration at which renal tubular dysfunction develops is estimated to be about 200 µg/g wet weights for long-term exposures. A focal point for chronic Cd nephrotoxicity is the proximal tubule (PT), particularly its S1 segment [4]. To be toxic, Cd must enter proximal tubule cells and also be present as a free inorganic ion in the cytoplasm compartment of PT cells. For this to occur, Cd must cross plasma and/or organelle membranes. Cadmium is associated with a general transport defect of the PT which minimizes the Fanconi syndrome (Fanconi syndrome is a disorder of the kidney tubes in which certain substances normally absorbed into the bloodstream by the kidneys are released into the urine instead). Renal dysfunction in the form of proteinuria, aminoaciduria, glucosuria, phosphaturia and reduction in glomerular filtration rate has been demonstrated in persons occupationally exposed to cadmium.

Cadmium metal is used in the steel industry and in plastics. Cadmium compounds are widely used in batteries (nickel-cadmium batteries). Cadmium is released to the environment in wastewater and diffused pollution is caused by contamination from fertilizers and local air pollution [4]. Contamination in drinking-water may also be caused by impurities in the zinc of galvanized pipes and solders and some metal fittings. Food is the main source of daily exposure to cadmium. Vegetables can be a source of cadmium contamination as Cd pollution was observed in radish, Cress, Dill, spinach and eggplant [31] The daily oral intake is 10-35µg. Smoking is a significant additional source of cadmium exposure [7].

On the other hand, Cadmium affects negatively other biological living organism other than human being as There were hazardous effect of sub lethal concentration of cadmium chloride solution 0.8ppm on the histology of the liver of the fish *Channa striatu* for a period of 45 days. The histopathological changes induced in the liver were cytoplasmic vacuolization of the hepatocytes, blood

vessel congestion, inflammatory leucocytic infiltration and necrosis [26]. Cadmium can influence the growth of the grasshopper fed by food treated with cadmium chloride and there were significant growth retardation in both sex. [30]. Cadmium can be found in some kinds of arthropods like. *Callinectes* spp. *M. macrobrachium* and *A. trifasciata* have the highest cadmium (0.07, 0.05 and 0.03ppm) respectively and these arthropods can be used as traditional foods in Africa and Latin America [32].

Methodology: This is a cross sectional study to find out the prevalence rate of the urinary cadmium concentration among adults population in Tanjung Karang. It is part of a preliminary study about the toxicity of lead and cadmium in adult population of Tanjung Karang area (Prospective Urban and Rural Epidemiological Study PURE) and we used the primary data that were collected before from that survey(PURE). Purposive (judgmental) sampling method was used to achieve 300 urine samples from adult's population.

Tanjung Karang, Selangor (population about 16000 people and is mainly Malay ethnicity. Tanjung Karang area is a rural area located about 200 km north of Kuala Lumpur, Malaysia. The samples obtained were from adults of both genders (35-70 years old) living in Tanjung Karang, Selangor.

Urine samples collected from the participants were refrigerated then transported to the environmental laboratory for freezing until analysis. The collected frozen urine samples were analysed with Polarized Zeeman Graphite Furnace Atomic Absorption Spectrophotometer Z-5700 (GFAAS) using the direct method to measure the cadmium concentration in the urine samples under National Institute for Occupational Safety and Health protocol.

Urine Samples: A total of 300 urine samples were collected from the adults of Tanjung Karang area in the morning as spot samples. This urine samples were collected directly in disposable polypropylene containers that deionised (free from heavy metals) and previously washed with 5% nitric acid. The urine samples stored at the mobile clinic fridge then directly transferred to the deep freeze at -20°C at the environmental laboratory at Hospital of University Kebangsaan Malaysia(HUKM) and every sample had own number matched with the respondent data. After we obtained the standard (working) curve for the GFAAS, 58 urine samples were taken out from the freezer to the refrigerator for thawing.

After that each sample was acidified with 100 µl of 65% (v/v) HNO₃ then returned to the fridge. Before the dilution, each sample was shaken strongly then went to the next step of dilution with the deionised water with the all consideration of safety and cleanliness to make sure that no contamination occurred to the samples. The dilution factor was 10 as we used 0.1 ml of the urine sample mixed with 0.9 ml of the deionised water. This first batch of the samples transferred to the auto sampler on the GFAAS machine plus two samples (1 ml deionised water as blank and 1 ml cadmium stock solution) as control.

After we did the urine samples dilution then the first batch transferred to the auto sampler and the GFAAS was ready with the obtained working curve. A total of 60 samples were put in the auto sampler and the GFAAS was working as every urine sample took about 1-5 minutes for analysis. Double reading for the urine samples as re-run were used for the accuracy purpose.

The results were showed on the computer's screen and ready to print (every sample took about 5 minutes for check). The lowest detection limit was 0.1 µg / L cadmium in the urine. Data analysis has been done using "Statistical Package for Social Sciences" (SPSS) version 17. For descriptive data the mean, median and standard deviation were detected. First the normality of data have been assessed using Kolmogorov Smirnov. Spearman's correlation test was used to test the correlation in continuous variables. Chi square test was used to determine the association between categorical variables.

RESULTS

This study includes 300 respondents aged 35-70 years old with age mean of 49. Genders were as 172 (57.3%) females and 128 (42.7%) males. Gender distribution among study population indicates that there were more females than males in this study. Ethnicity showed that most of the samples were Malay as 255 (85%) Malay, 36 (12%) Chinese and 9 (3%) were Indian.

Three hundred urine samples tested for cadmium concentration by using the graphite furnace atomic absorption spectrophotometer (GFAAS). The action threshold was 2 µg / L according to Nester *et al.* (2008) [27] the lowest detection limits for GFAAS was 0.1 µg / L urine. The results were as 44 (14.7 %) urine samples above the action threshold, 9 (3%) urine samples were non-detected (0.0 µg/L) which were under the detection limits and 247 (82.3 %) urine samples were normal.

Table 1: Descriptive statistics of urinary cadmium level

Statistics	µg/ L
Mean±SD	1.29±2.24
Median	0.53
Minimum	0.00
Maximum	14.90

Table 2: Socio-demographic and chronic diseases distribution (n=300)

Variables	Frequency (%)
Gender	
Male	128 (42.7)
Female	172 (57.3)
Ethnicity	
Malay	255 (85)
Chinese	36 (12)
Indian	9 (3)
Hypertension	
Yes	69 (23)
No	231 (77)
BMI groups	
Normal	64 (21.3)
Overweight	111 (37)
Obese	125 (41.7)
Diabetes	
Yes	39 (13)
No	261 (87)
Tobacco history	
Ever smoke	73 (24.3)
Never smoke	227 (75.7)
Job category	
Farmers	10 (3.3)
Non farmers	290 (96.7)

Table 1: Explored that the urinary cadmium level of the participants was ranged between 0.0 to 14.9 µg/L and the mean was 1.29±2.24 µg/L standard deviation and the median was 0.53. Both Kolmogorov-Smirnov and Shapiro-Wilk tests used and they were significant for the data of urinary cadmium level which is mean that the data was not normally distributed.

Table 2, showed the socio demographic characterizations and the chronic diseases of the respondents. A total of 300 respondents participated in the study. There were 128 (42.7%) males and 172 (57.3%) females. The majority of the respondents were Malay (n=255, 85%). A total of 69 (23%) of them hypertensive and 39 (13%) were diabetic. A total of 73 (24.3%) of respondents were smokers and 227 (75.7%) non- smokers. Most of the respondents were non farmers.

Bivariate Analysis

The Correlation Between Age and Urinary Cadmium Concentration: Spearman's correlation test was performed to evaluate the relationship between age and

Table 3: Correlation between age and urinary cadmium concentration(ppb)

Variable	No	Mean (SD)	Correlation Coefficient	p value
Age	300	49.95 (9.29)	0.118*	0.041

*Spearman's rho, p value of < 0.05 is considered significant.

Table 4: Urinary Cadmium level differences according to socio demographic factors

Variable	higher Cd level N (%)	Lower Cdlevel N (%)	χ^2	p value	POR (95%CI)
Gender			1.13	0.287	1.5(0.7-2.7)
Male	22 (17.2)	106 (82.8%)			
Female	22 (12.8)	150 (87.2%)			
Ethnicity			3.53	0.172	
Malay	34 (13.3)	221 (86.7%)			
Chinese	9 (25)	27 (75%)			
Indian	1 (11.1)	8 (88.9%)			
Job category			0.24	0.628	0.7(0.1-3.3)
Farmers	2 (20)	8 (80%)			
Non farmers	42 (14.5)	248 (85.5%)			

P < 0.05 is considered significant, Chi Square test

POR = prevalence odds ratio

Table 5: Urinary cadmium level differences according to chronic diseases and life style

Variables	higher Cd level N (%)	Lower Cd level N (%)	χ^2	p value	POR(95%CI)
Hypertension			0.68	0.411	0.7(0.3-1.6)
Yes	8 (11.6%)	61 (88.4%)			
No	36 (15.6%)	195 (84.4%)			
BMI groups			2.66	0.264	
Normal	7 (10.9%)	57 (89.1%)			
Overweight	21 (18.9%)	90 (81.1%)			
Obese	16 (12.8%)	109 (87.2%)			
Diabetes			1.22	0.269	1.6(0.7-3.8)
Yes	8 (20.5%)	31 (79.5%)			
No	36 (13.8%)	225 (86.2%)			
Tobacco history			18.83	0.0001*	4.9(2.3-10.7)
Ever smoke	35 (23.6%)	113(76.4%)			
Never smoke	9 (5.9)	143(94.1%)			

* p< 0.05 is considered significant, Chi Square test

Table 6: Logistic regression for factors associated with urinary cadmium level

	B	S.E.	Wald	p value	POR(95%CI)
Age	-0.006	0.02	0.1	0.753	0.99(0.96-1.0)
Smoking status					
Ever smoke	1.6	0.4	16.4	0.0001**	5.0(2.3-10.8)
Never smoke*					
Constant	-2.5	0.9	6.8	0.009**	0.1

* Referent group

** Significant at p<0.05

urinary cadmium level. There was weak significant correlation ($r = 0.118$, p value 0.041) between them (Table 3).

The Association Between Sociodemographic Factors and Urinary Cadmium Level: Table 4 showed that there was no significant association between higher urinary cadmium level and gender, ethnicity and job category (farmers and non farmers). Among 36 Chinese in

this study there were 9 (25%) persons had higher urinary cadmium level comparing to 34 (13.3%) of Malay and 1 (11%) of Indian ($p = 0.172$).

The Association Between Chronic Diseases and Life Style with Urinary Cadmium Level: We conducted Chi square test to determine the relationship between urinary cadmium level and chronic diseases and life style of participants. There was no significant association

between urine cadmium level and hypertension, diabetes and BMI group of participants. The proportion of diabetic persons with higher cadmium level was higher (20.5%) than the non diabetic persons (13.8%) (p value 0.269). Among 73 smokers, 35 of them (23.6%) were had positive urinary cadmium level comparing to 9 (5.9%) of non smokers. This difference was significant with a p value of 0.0001.

Multivariate Analysis: In order to determine which of the study risk factors best explained the association between the risk factors and the urinary cadmium level, multiple logistic regressions was done (enter technique). Logistic regression analysis revealed that smoking (OR= 5 ; confidence interval (CI): 2.3-10.8; $p < 0.0001$) was independent factor related to the urine cadmium level.

Table 6 showed that smokers had 5 times higher risk having higher urinary cadmium level compared to the non smoker. The age of participants was not significant in the logistic regression. Age is not a significant risk factor to the urinary cadmium level. The smoking status was appearing to be confounder for age.

The total model was significant ($p < 0.0001$) and accounted for 11.4% of the variance in the urine cadmium level (Nagelkerke R Square=0.114). The Hosmer and Lemeshow Test indicated a good fit ($p = 0.051$). From this model we can calculated probability of positive urine cadmium level by this formula $\text{probability} = 1 / (1 + e^{-Z})$, $Z = -2.5 + (1.6 * \text{smoker})$.

DISCUSSION

This study includes 172 (57.3%) females and 128 (42.7%) males. Gender distribution among study population indicates that there were more females than males in this study. However, the percentage of subjects with higher cadmium level in the urine in both genders was the same and equal to 22 respondent. Some studies stated that the urinary cadmium level can be higher in females comparing to the males especially in women with iron deficiency as Akesson *et al.* [8], they found that it seems clear that low iron status leads to increased body burden of cadmium via increased intestinal absorption of dietary cadmium. This is probably the main reason why the body burden of cadmium is generally higher among women, whose prevalence of iron depletion is higher than that of men.

The majority of study population were Malay, constituting about 85% of the study population ($n=255$). Of them about 13.3 % ($n=34$) have higher cadmium level in

urine. There were 12% ($n=36$) Chinese in this study, 25% of them ($n=9$) have higher cadmium level. The remaining 3% ($n=9$) of the study population were Indian and 1 (11.1%) had positive urine cadmium level. This finding regarding the high percent of Malay as compared to other race groups was expected as the study sample was withdrawn from Tanjung Karang area, where the majority of residents of this area were Malay. The age included in this study was between 35-70 years. This study was chosen adults of 35 years old and above to highlights the accumulation of cadmium level with age.

Participants were also classified according to their jobs to farmers and not farmers. This classification was done because it is well known that farmers or workers usually have higher Cadmium level as compared to non occupationally exposure group, this is due to the higher environmental exposure of workers as compared to non workers for various types of metals including Cadmium. In case of farmers, the higher environmental exposure belongs to phosphate fertilizers that contain cadmium and they were using it.

Association Between Urinary Cadmium Level and Age:

Generally there was no significant association with all the socio-demographic factors that were tested in this study except for age. Spearman's correlation test result of this study indicated the presence of significant association between age and increased urinary cadmium level ($p=0.041$). However, this correlation was weak (correlation coefficient=0.12). This significant association could be explained by the tendency of cadmium to accumulate in the human body (bioaccumulation of heavy metals) with time and cadmium has long half life. The concentration of cadmium in urine increases with age because of cadmium's long half life in human (10-30years). Also the Agency for Toxic Substances and Drug Registry [9] stated that because of cadmium long half-life in humans, the concentrations of cadmium in blood and urine increases with age. However, in logistic regression age became not significant and it was confounded by the smoking status variable.

Olsson *et al.* [10] found that blood cadmium and urinary cadmium increased with age in both men and women as there were significant correlation between them ($r = 0.41, p < 0.0001$).

Association Between Urinary Cadmium Level and Smoking Status:

Smoking habit was among the risk factors that were tested in this study. There was significant association between smoking and urinary

cadmium level. The logistic regression revealed that the smokers had 5 times more risk to have higher urinary cadmium level comparing to the non smoker. The current findings support the prior evidence suggesting that cigarette smoking as a risk factor associates with the high urinary cadmium level as Mortensen *et al.* [11] in their study on adults from USA analyzed data from the National health and Nutrition Examination Survey 1999-2006 found that the relative risk for getting higher urinary cadmium for the current smokers was 3-13 times and 2-3 times for the former smokers.

Mannino *et al.* [12] in their study on 16 024 adults from the Third National Health and Nutrition Examination Survey data were analysed and showed that smokers had higher urinary cadmium (OR= 2) and the study showed that current and former smokers had higher body burdens of cadmium than non-smokers and that within smokers, the body burden of cadmium was related to lung injury related to smoking. The authors conclude that cadmium might be important in the development of tobacco related lung disease.

Ikeda M *et al.*[13] stated on their study smoking-induced in urinary cadmium levels among Japanese women, the urinary cadmium level for current smokers was significantly higher than that for non smokers and urinary cadmium for current smokers increased dependently to the number of cigarettes (about 0.09 microgram/ cigarette/day) and levelling off at 15 or more cigarettes.

The study findings was also supported by the study done by Galazyn-Sidorczuk *et al.* [14] that showed that blood and urinary Cd concentrations in the smokers have 2-4 times higher than in the non-smokers. The results give clear evidence that in the case of inhabitants of areas unpolluted with Cd, habitual cigarette smoking, due to tobacco contamination, creates a serious source of chronic exposure to the cadmium. A total of 91% of Cd present in a cigarette originated from the tobacco seems to indicate that cigarettes contamination with this metal may be estimated based on their content in tobacco. Lampe *et al.* [15] found in his sub cohort study that chronic cadmium exposure is associated with reduced pulmonary function and cigarette smoking modifies this association. There was statistically significant reduction in FVC(forced vital capacity) ratio across smoking status in association with urinary cadmium.

Association Between Life Styles and Chronic Diseases with Urinary Cadmium Level: The association of life style with increase cadmium level in urine have been tested.

One of the risk factors that were tested was high BMI. There was no significant association between high BMI level and increase urine cadmium level according to the chi-square results of this study. Teeyakasema *et al.* [16] also showed no significant differences between high urinary cadmium (Nephropathy or osteopathy) and the BMI except little tendency in diabetic group. However, Akesson *et al.* (2008) [28] shown that such association is significant.

Another risk factor that was tested in this study was hypertension. Despite the fact that there was no association between high blood pressure and increase urinary cadmium level according to the results of this study, the same result found by Sorahan and Waterhouse [17]. They examined mortality rates in a cohort of 3,205 nickel cadmium battery workers (2,559 males and 466 females). Cadmium levels in air ranged from 0.05 to 2.8 mg/m³, primarily as cadmium oxide. Duration of exposure ranged from 1 year to more than 6 years. No increase in mortality from diseases of the circulatory system (e.g. hypertension) was seen in cadmium-exposed workers.

Staessen and Lowerys [18] found in a study known as the cadmium study evaluated 2,327 people from a random sample of the population of four Belgian districts chosen to provide a wide range of environmental exposure to cadmium. Participants completed a questionnaire regarding their medical history, current and past occupations, smoking habits, alcohol consumption and intake of medications. Urine and blood samples were taken and pulse rate, blood pressure, height and weight were recorded. Exposure to cadmium was considered to be by both the oral and inhalation routes. Cadmium levels in blood and urine were significantly increased in the high-exposure areas compared to the low-exposure areas ($p < 0.001$). Blood pressure was not correlated with the urine or blood cadmium levels. The prevalence of hypertension or other cardiovascular diseases was similar in all four districts and was not correlated with urine or blood cadmium levels. These results do not support a hypothesis that higher urinary cadmium increases blood pressure, prevalence of hypertension or other cardiovascular diseases.

On the other hand, hypertension was found to be one of the risk factor can be caused by higher urinary cadmium and there was a dose response relationship between hypertension and urinary cadmium Eum *et al.* [19]. The significant association between hypertension and urinary cadmium level was also documented in other studies like Statarug *et al.* [20] and Tellez-Plaza *et al.* [21].

Diabetes is also among the risk factors that has a significant relationship with urinary and even blood cadmium level according to the results of other studies (Haswell-Elkins *et al.* [22], Schwartz *et al.* [23] and Chen *et al.* [24]). This study found no significant association between diabetes mellitus and higher urinary cadmium.

CONCLUSION

This study found prevalence rate of 14.7 % of respondents having higher urinary cadmium concentration. This study also attempts to assess the association between the higher and lower of urinary cadmium level with the socio demographic factors like age, gender and ethnicity also with the smoking status and with the chronic diseases like hypertension and diabetes mellitus and also with the body mass index. From the socio demographic factors, age showed that there was weak association with the high urine cadmium level. There was no association between the gender and the urine cadmium level. Ethnicity showed no association also but there is a prediction of relation for the Chinese participants and the urine cadmium level as there were 36 Chinese participants, 9 of them were have high urine cadmium level(25%) from the total respondents.

There were no association between chronic diseases like hypertension and diabetes mellitus and the urine cadmium concentration. BMI showed no association also with the urine cadmium level. There was strong significant association between smoking habit and the urine cadmium concentration(OR=5).

Recommendation: The information from this research shows that the prevalence rate for the higher urine cadmium concentration in Tanjung Karang area is 14.7 %. This issue can be considered as the first step for providing real information about the nephrotoxic substances like cadmium. This study also provides optimism and caution regarding the level of urine cadmium. Few data currently available on most of the cadmium profile in Malaysia. Respondents who had high urinary cadmium levels and might have cadmium-induced toxic effects should be screened for early detection of chronic cadmium toxicity. Today, the principal determinants of human cadmium exposure are smoking habits, diet, also table salt can be contaminated with cadmium[29] and, to a certain extent, occupational exposure. In general population like in Tanjung Karang ingestion of food contaminated by cadmium is might be a source of cadmium for non-smokers. Rice, sunflower

seeds, soy beans, seafood like shellfish that grown in contaminated soil with cadmium that can originated from industrial discharges and mining activities. Also drinking water can be a source for cadmium exposure to the community. More studies recommended in this aspect for the soil and the crops that grow in that area.

Cigarette smoking is a habit which cans more than double the average person's daily cadmium intake [25]. Smoking cessation programs should be one component of the preventive action beneficial for the study population.

Further research based on random sampling needs to calculate the exposure risk and then can quantify the carcinogenic risk.

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