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Research Article

Lifestyle Changes and Increased Urinary Cadmium Levels in People with Type 2 Diabetes Mellitus: A Case Control Study in Tehran-Iran

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Abstract

Background: Cadmium is ranked in the top ten environmental toxicants but its impact on Type 2 Diabetes Mellitus (T2DM) through lifestyle and diet is contradictory.

Purpose: This study aimed to compare the urinary Cadmium levels (u Cd) in T2DM in an age and gender matched case control study in over 40 years volunteers and find the association of u Cd with diet, smoking, anthropometric factors and lifestyle in study participants.

Methods: Face-to-face interviews based on structured questionnaires were conducted to obtain sociodemographic and life style of 200 female and male participants (100 cases and 100 control). Considering the exclusion criteria, u Cd of 30 T2DM and 30 normal participants were determined by ICP-mass analysis in Tehran.

Results: Urine analysis indicated that individuals with type 2 diabetes have significantly higher U-Cd (0.0407 ± 0.0073 ppm vs. 0.0150 ± 0.0019 ppm, $p = 0.001$) but this difference was not contributed to their recent smoking habits, diet, life style, living and working address and anthropometric factors. The same results were observed in females and males separately. Long term history (> 20 years) of smoking as well as number of smoke buts/day affected the U-Cd levels in total volunteers ($n = 60$, $p = 0.043$).

Conclusion: Chronic Cadmium exposure could be contributed to the incidence of T2DM. Except long term smoking history, lifestyle didn't affect U-Cd levels in the residents of Tehran. Precautionary measure to reduce the exposure of people with this element is recommended to prevent the occurrence of diabetes.

***Keywords**: Cadmium; Type II Diabetes Mellitus; Lifestyle; Diet; T2DM*

Research Highlights

- Urinary Cadmium level in UT2DM patients was 4 times more than control.
- Although the U-Csd level was significantly higher in T2DM ($p < 0.001$), direct correlation between anthropometric factors (weight, height or BMI levels), dietary habits, recent smoking and life style was not found in both genders of cases and control.

- Long term (20 years) history of active smoking caused increased U-Cd level (P = 0.043) in total population of cases and control.
- This is the first study on U-Cd in Iranian population in both genders in this age range and females didn't show higher U-Cd despite similar studies in western countries.
- Higher U-Cd levels in newly diagnosed T2DM could be considered as a new etiologic biomarker without association with recent lifestyle, diet and smoking habits.

Introduction

Type 2 diabetes mellitus (T2DM) with > 450 million affected people worldwide [1] is a heterogeneous disease, which is characterized by hyperglycemia, insulin deficiency or insulin resistance over an extended period, in the liver and peripheral tissues [2]. There is a diverse array of non-modifiable risk factors for this global silent killer disease such as age (> 45 yrs.), genetics, ethnicity, family history and history of gestational diabetes but many modifiable risk factors such as hypertension, hypercholesterolemia, abnormal body mass index, lack of physical inactivity and high body fat could accelerate the progression of prediabetes conditions to T2DM [1]. Other than these non-modifiable and modifiable risk factors, multiple physical and chemical stressors have been considered as novel risk factors of T2DM like living in rural areas with air pollution [3], long term exposure to Fine particulate matter ($PM_{2.5}$) which is an air pollutant that is a concern for people's health when levels in air are high [4] and continues exposure to endocrine disrupting chemicals (EDCs which cause insulin resistance and increase the risk of T2DM in modern world human population [5].

EDCs are a wide range of synthetic or natural products which can mimic human natural hormones to interact with receptors in the endocrine system, change the hormone levels, and disrupt the functions of the endocrine system. This group of toxicants are raising the public health concerns because their long term exposure are associated with increased risk of many diseases which have dramatically increased over the last several decades including T2DM by binding to androgen receptor [6]. Although older evidence in a sub chronic rat model of Cadmium-induced hyperglycemia shows the diabetogenic effects of Cadmium in animal studies by its potentials to cause islet dysfunction, insulin release impairment and changing the fasting leptin, Glucose-dependent Insulin tropic Polypeptide (GIP) and pancreas polypeptide hormone levels [7], more recent evidence from basic science suggests that Cadmium can cause endocrine disruption through binding to the androgen receptor [8] in the adipose tissue, pancreatic islet cells, hypothalamus, skeletal muscle, liver and accounts for glucose homeostasis and maintenance or disruption in energy metabolism [9].

Other than basic sciences, a growing number of human population studies have reported the involvement of Cadmium exposure in etiology of T2DM. Literature show residents of big cities like Tehran are exposed to Cadmium by PM 2.5 contamination [10], consuming cereal and legumes, canned tuna fish, vegetables [11], dairies [12], fruit juice [13], rice [14,15] and smoking habits [16]. To the best of our knowledge only one study in 2012 [9] has been done on urine Cadmium level (U Cd) in Iran but there is still no information about urine Cadmium level (U Cd) as a biomarker of long term Cadmium exposure and total body burden [17] in Iranian T2DM patients. Based on this concept, we decided to compare the effect of diet, smoking habit, environmental exposure, and lifestyle on the incidence of Type 2 Diabetes (T2D) in a total population of 200 persons (100 cases and 100 control) at first and then compare the urine Cadmium levels in a subgroup participants who were more eligible for this case control study based on our exclusion criteria. We finally decided to answer the key question: What is the impact of diet, smoking habits, air pollution and life style as the major resources of chronic Cadmium exposure on developing type II diabetes in a pilot study in Tehran?

Patients and Methods

Study population

This research is a population-based cross sectional study initiated in one of the central zones of Tehran (zone 6, where the hospital located) with the aim of comparing the effect of diet, smoking habits and lifestyle on the incidence of Type 2 Diabetes (T2D) in a total population of 200 over 40 years persons. T2D patients were enrolled in the study when they received their first visit by endocrinologist in Mostafa Khomeini University hospital of Tehran according to diagnosis criteria. Controls were enrolled from the volunteers who lived around the same hospital and referred to the laboratories around for routine annual check-up.

Diagnosis of T2D: A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or A hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher was considered as the initial diagnostic criteria for T2DM according to the criterian of American Diabetes Association in 2018. Patients were finally selected based on their recorded diagnostic criteria and approval of collaborating endocrinologists just before receiving their first prescriptions and starting any antidiabetic medication. The control group was healthy individuals who lived in the same zone for more than 5 years and had normal Fasting Blood Sugar (FBS) in their check -up visit without any classic symptom of hyperglycemia. All of the participants in this study provided their written informed consent. This project was approved by the ethics committee of Islamic Azad University, Tehran Medical Sciences University under the number of IR.IAU.TMU.REC.1397.271.

Data collection

Face-to-face interviews based on structured and food frequency questionnaires were used to obtain demographic lifestyle and dietary information by trained staff at the time of study enrollment. General characteristics including age, weight, height, BMI, education levels, family history of diabetes, history of gestational diabetes, history of liver and kidney diseases, occupational status, second hand or active smoke (> 30 min/day), physical activity, living and working address (urban or rural areas), dietary habits, occupational exposure to Cadmium, exposure to household chemicals, using plastics dishes or plastic water bottles, using home water purifier, using Cadmium containing cosmetics (lipsticks and eye shadow) were asked from the volunteers and recorded in their structured questionnaires. The heights and weights of volunteers were measured at the time of study enrollment.

Sample preparation

Spot urine samples were collected from most of participants from March to December 2018 after face to face interviews. Some urine samples were excluded from urine analysis and 60 spot urine samples (30 cases and 30 control) were included according to exclusion criteria from both genders. we analyzed the urine samples of patients who met our inclusion criteria. Cases and control were different in some parameters including history of T2DM and hypertension (Table 1) moreover some people in control group showed transitional hyperglycemia without T2DM. We excluded them from urine analysis. The excluded urinary samples were from volunteers who had plasma proteins in the urine (proteinuria or albuminuria), history of background diseases including spontaneous abortion, infertility, osteoporosis, cardiovascular disorders, familial history of T2D and history of gestational pregnancy. Other than above factors, urine samples of participants who lived in rural areas, individuals with any history of hyperglycemia in their first degree family, individuals with thyroid disease, chronic liver and kidney disease and participants using medications at the time of sampling were excluded. The exclusion criteria for cases and control was equal except recent incidence of T2DM. Based on the above criteria 140 volunteers excluded and urine samples of 30 T2D and 30 control were finally included in ICP-mass analysis. All these persons were included in the first survey on 200 people (100 cases and 100 control) some of them lived in other zones but referred to the same hospital we excluded them from urinary analysis.

Urinary cadmium measurement

Spot urine samples were collected in polypropylene containers at early morning and stored at −80°C for subsequent processing. The urine samples were centrifuged for 15 minutes at 3075g force at room temperature before being diluted 10 times with 2.0% (v/v) nitric acid. Cadmium levels were all measured using inductively coupled plasma mass spectrometry (ICP-MS) (Perkin Elmer ELAN 6100 DRC-e) in Kimiazi Institute, Research Center for Developing Advanced Technologies of Khaje Nasir Toosi, Tehran, Iran. All samples were measured and reported in triplicate in this Iran FDA referee laboratory.

Statistical analysis

The baseline characteristics between cases and control groups were compared using student t-test or Mann-Whitney U test for parametric and non-parametric variables respectively, which were presented as mean (± SD) values for parametrical distribution or median (interquartile range, IQR) for non-parametrical distribution, and Chi-square tests for categorical variables, which were expressed as number (percentage) unless otherwise indicated. All data were analyzed using SPSS for Windows (version 23; IBM® SPSS® Statistics, Armonk, NY, USA) and a two-sided p < 0.05 was considered statistically significant.

Results

Demographic characteristics (n = 200)

As we showed in table 1, the total number of females and males in T2DM (48 vs. 52) and control 59 vs 41) were similar (p = 0.332) and the mean age of T2DM patients and control (52.77 ± 6.804 vs. 50.57 ± 6.489, p = 0.057) was matched without meaningful difference. The results of student t- test showed no significant difference between the average weight (71.08 ± 8.354 kg vs. 68.87 ± 8.756 kg, p = 0.061) and average height (171.72 ± 7.52 cm vs. 169.73 ± 7.33, p = 0.066) of cases and control groups but the mean BMI of T2DM patients was significantly higher than healthy control [25.29 (1.6) vs. 24.51 (1.15), p < 0.001]. Among other demographic factors including education, employment and history of background disease, the prevalence of hypertension (p = 0.001) and family history of T2DM (p < 0.001) was significantly higher in T2DM compared to control (Table 1). We compared the same above parameters in subgroups of males and females and results showed the same patterns regarding the significant differences in BMI, hypertension and T2DMfamily history between cases and control in both genders (data not showed but it is accessible). Number of recent Cigarette smokes was significantly higher in T2DM patients compared to control (64 vs.49, p = 0.023).

Characteristics	T2DM (n = 100) Mean ± SD	Control (n = 100) Mean ± SD	P-Value
Age (years)	Over	50.57 ± 6.798	0.057
Weight (kg)	71.08 ± 8.354	68.80 ± 8.756	0.061
Height (cm)	171.72 ± 7.52	169.73 ± 7.679	0.066
BMI	25.29 (1.6)	24.51 (1.15)	<0.001***
Gender		41	0.322
Male	48	59	
Female	52		
Employment (years)			
Yes	49	42	
No	33	40	0.511
Retired	18	18	
Family history of T2DM (yes)	75	25	< 0.001***
History of Hypertension			
Yes	58	34	0.001**
More than 12 years study (yes)	31	28	0.062

Table 1: *Demographic characteristics of T2DM and healthy volunteers.*
Mean values with different superscript stars in the same row are significantly different at p ≤ 0.05 (p-value < 0.05, p-value < 0.01**, p-value < 0.001***).*

Air pollution, diet and lifestyle factors (n = 200)

As we showed in table 2, no practical difference was found between cases and control regarding living or working in urban areas with heavy air pollution, dietary habits and food cadmium resources in Iranian daily regimen including rice, green vegetables, recent (5 years) and past (> 20 years) smoking habits, smoking cessation, exposure to household chemicals, consuming Cadmium containing cosmetics, consuming plastic dishes and bottles and using water purification devices at home. Out of recent lifestyle factors, extent of physical activity was significantly higher in control compared to cases (p = 0.044). Control group had more than 4 hours light physical activities than cases in present study population. We compared above parameters in subgroups of males and females and our results showed following differences.

Characteristics	T2DM (n = 100)	Control (n = 100)	P-Value
Living /working in urban areas near highways			
Yes	60	61	0.886
No	40	40	
Prevalence of Physical Activity (any type of sports e.g. walking, swimming etc.)			
No	45	21	
Monthly	17	36	0.044*
Once a week	22	24	
3 - 4 times a week	12	13	
Daily	4	6	
Recent Smokers	64	49	0.023*
Smoking habits (butts/day)			
No	39	42	0.656
1 - 5	10	8	
6 - 10	14	12	
11 - 15	25	25	
> 15	12	12	
> 20 years history of continuous smoking	7	7	0.405
Smoking cessation (yes)	9	13	0.432
Routine exposure to household solvents (yes)	87	81	0.249
Cosmetics			
No	48	41	0.456
Once a month	12	12	
1 - 2 times/week	22	28	
3- 4 times a week	10	12	
Daily use of	8	7	
Plastic dishes			
No	2	3	0.358
Once/month	59	53	
1 or 2 times a week	24	23	
3 or 4 times a week	15	21	

Water purifier at home (yes)	9	12	0.491
Plastic bottles (yes)	14	18	0.443
Rice as main food			
Persian rice	73	77	0.515
Indian -Thai	27	23	
Green leafy vegetables			
Once/week	7	4	
> 1 - 2 times/week	59	51	
3 - 4 times/week	24	32	
Daily	10	13	0.1
Fish			
No	2	4	
Once / week	72	78	0.108
1 or 2 times / week	14	12	
3 or 4 times / week	11	6	
Daily	1		

Table 2: *Comparison of dietary and lifestyle factors between T2DM and healthy volunteers (n = 200). Mean values with different superscript stars in the same row are significantly different at $p \leq 0.05$ (p-value < 0.05*, p-value < 0.01**, p-value < 0.001***).*

T2DM women: The pattern of physical activity was similar in cases and control (p = 0.122) that means healthy and T2DM women with the same age ranges showed equal levels of body exercise. Daily recent exposure to household chemicals (disinfectants, solvents, pesticides) was more prevalent in T2DM females than healthy women (p = 0.011). Number of smoker women was similar in cases and control (19 vs. 15, p = 0.572).

T2DM men: The pattern of physical activity was higher in healthy volunteers than T2DM patients (p = 0.021). Daily exposure to household chemicals was more prevalent in T2DM males than healthy men (p = 0.032). Number of smoker men was similar in cases and control (45 vs. 37, p = 0.411).

Urine cadmium levels (U-Cd)

Figure 1 shows the mean of U-Cd levels in T2DM patients and those in the control group. The mean concentration of Cadmium in the urine of T2DM patients was significantly higher than the control group (0.0407 ± 0.0073 mg/L vs. 0.0150 ± 0.0019 mg/L, p = 0.001). We described the association between U-Cd and anthropometric factors, diet, air pollution, and lifestyle factors in table 3.

Characteristics	N	Mean	SE	P-value
T2DM and Control				
T2DM	30	0.0407	0.04017	0.001***
Control	30	0.0150	0.01075	
Gender				
Males	31	0.0303	0.00673	0.537
Females	29	0.0252	0.00496	
Cadmium Dietary resources				
Yes	32	0.0300	0.0490	0.578
No	28	0.0254	0.0068	
Using Water Purifier				
Yes	5	0.0380	0.0135	0.461
No	55	0.0269	0.0321	
Plastic dishes and bottles				
Yes	15	0.0200	0.0050	0.276
No	45	0.0304	0.0051	

Recent Cigarette Smoke				
Yes	22	0.0305	0.0066	0.632
No	38	0.0263	0.0053	
Smoke cessation				
Yes	7	0.0457	0.0245	0.082
No	31	0.0219	0.0034	
Household Chemicals				
Yes	11	0.0304	0.0084	0.189
No	49	0.0164	0.0047	
Type of Rice				
Persian	41	0.0285	0.0050	0.804
Indian-Thai	19	0.0263	0.0072	

Table 3: *Association between urinary cadmium levels in total urine samples and background factors (n = 60).*

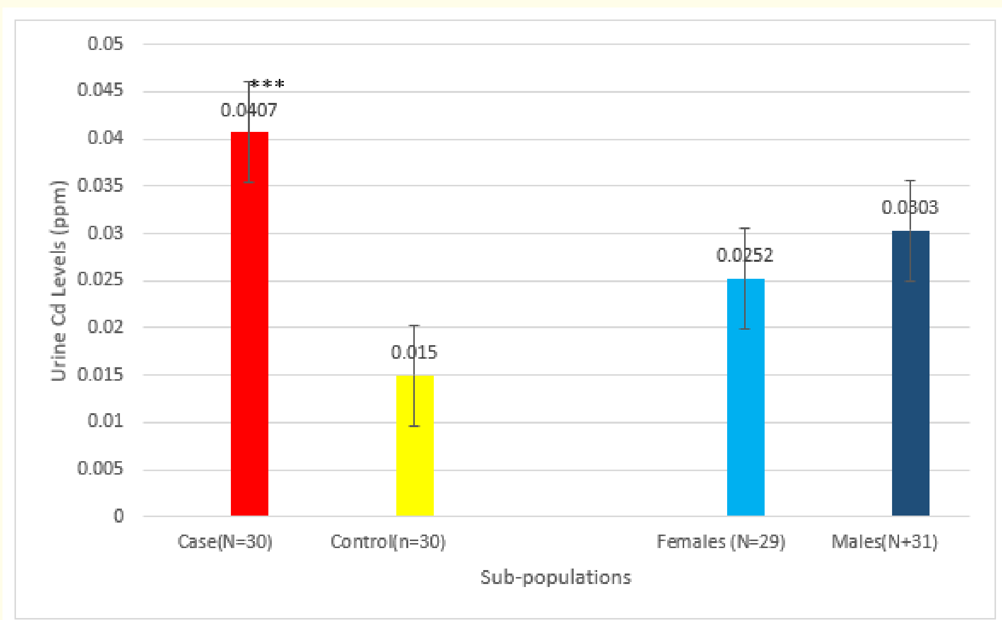

Figure 1: *Urinary cadmium levels in T2DM and control males and females: U-Cd was significantly higher in T2DM (p = 0.001) than control but the levels seems equal in males and females in the whole population (p = 0.537). The mean concentration of cadmium in the urine of T2DM patients was significantly higher than the control group (0.0407 ± 0.0073 mg/L vs. 0.0150 ± 0.0019 mg/L, p = 0.001).*

Urine cadmium levels in smokers subpopulation: As shown in table 3, we didn't find any significant difference between the mean U-Cd levels in recent active or passive smokers (0.0305 mg/L ± 0.0301, n = 22) and non-smoker [(0.0263 ± 0.0326, n = 36), p = 0.632] but independent samples Kruskal Wallis Test demonstrated the role of long term history (> 20 years) as well as increased smoke buts/day on U-Cd levels in total volunteers (n = 60, p = 0.043).

Discussion

Past studies emphasized the association between chronic Cadmium exposure (> 25 µg/day) and renal diseases, osteoporosis, cardiovascular outcomes, cancer, reproductive disorders etc [17]. Other than mentioned health risks of Cadmium exposure, many epidemiological studies have been conducted to determine the association between chronic exposure to Cadmium and diabetes, but the impact of Cadmium exposure on diabetes is still contradictory [11]. Following lifetime Cadmium exposure, this element accumulates in the kidney with an estimated half-life of 10 - 30 years and a small portion of Cadmium continuously and slowly excretes in urine. For this reason, urinary Cadmium (U-Cd) level is often considered to be a trustable biomarker of long-term Cadmium exposure and urine levels have been shown to be proportional to the kidney Cadmium level while blood Cadmium levels reflects a combination of both long-term and more recent exposures (Nordberg GF., 2009). Given the high prevalence of T2DM among 14.4% of older people (over 40 years) in Iran and the significant association between background factors and T2DM [18], more population based research is needed to understand the contribution of Cadmium on the incidence of T2DM, and to detect the association between Cadmium chronic exposure and T2DM incidence in older people in Iran, we conducted this study in Tehran to answer this critical question in a pilot study in this age group.

Cadmium is a toxic metal ranked in the top ten environmental toxicants of concern by environmental health agencies [19] which is involved in oxidative stress [20], oncogenesis [21] and cardiac inflammation [22] with different major sources of exposure, including air pollution, diet (e.g. rice, fish, and green leafy vegetables), cigarette smoking, occupational or household exposures, as well as living near an industrial area that increased the risk of human population to be polluted or poisoned [23]. Present work aimed to understand the impact of life style, diet and air pollution on U-Cd levels to detect its potential as an etiologic factor of diabetes in people who lived in Tehran for more than 20 years. To the best of our knowledge, this is the first cross sectional study in Iran to demonstrate an association between the urinary concentrations of Cadmium in early T2DM diagnosis and their existing etiologic factors. In this study we found 4 times higher urinary Cadmium levels in T2DM patients (p < 0.001) and found the association of this metal with the incidence of T2DM in Tehran and long term (> 20 years) history of active smoking and heavy smoking. Although these finding significantly strengthen the hypothesis on the involvement of long term history of Cadmium exposure through smoking or other undetermined resources in the incidence of T2DM, but its levels was not associated with gender, recent anthropometric factors, diet, smoking habits or lifestyle factors. It is possible that our structured questionnaire does not reflect their historic exposure or the urine Cadmium levels were not enough as a biomarker for finding exposure backgrounds in T2DM patients. Despite the gender dependent differences in the incidence, and etiology of T2DM according to a recent survey in Iran [24], we didn't find any differential etiologic role for U-Cd levels in men and women. Our statistical analysis showed predictable differences e.g. history of hypertension, family history of T2DM and higher BMI levels (p < 0.001) between T2DM patients and control. Although the U-Cd level was 4 time higher T2DM patients compared to control (p < 0.001), we didn't find any direct correlation between anthropometric factors (weight, height or BMI levels) and U-Cd in separate groups of T2DM males, T2DM females, healthy males, healthy females and total population in additional analysis.

In the general population, in absence of occupational exposure or excessive environmental contamination, industrial emissions and exposure to Cadmium-containing fertilizer, the main sources of Cadmium exposure may include food and tobacco and among nonsmoker's subgroups, the primary source of Cadmium exposure is through the diet but it seems in regions with specific environmental of geological contamination, significant correlations could be expected between estimated levels of Cadmium exposure, urinary Cadmium levels and incidence of T2DM in highly exposed populations. Although from reports in western populations, in the absence of unusually high environmental or occupational sources, a situation similar to present work, the urinary Cadmium creatinine concentration was usually < 2 µg Cadmium/g creatinine [17] and was most strongly correlated with smoking, age, and female sex therefore the same study should be repeated in larger scales and analyzing more analytic parameters as well as the contribution of other etiological factors especially other heavy metals like Arsenic and lead in this regard. Moreover, it seems necessary to look for the contribution of most consumed domestic and imported black tea brands in Iran with unsafe levels of Cadmium in the incidence of T2DM according to high consumption of tea in Iranian people [16]. It is suggested to focus on the correlation between dietary Cadmium, Urinary Cadmium and incidence of T2DM in a large scale prospective study if getting multiple urine samples in prediabetes conditions years before T2DM diagnosis would be possible. In this new setting the impact of Cadmium and its urinary changes would be determined with more interpretable data and the alterations in different samples would be more reasonable for risk assessment analysis.

Current smokers showed higher urinary concentrations than former and never smokers which is expectable. Studies have been widely reported that former smokers have significantly higher urinary Cadmium than never smokers, which one would expect if U-Cadmium is a biomarker of long-term exposure. We faced the same pattern in our work but in this study we had few with > 20 years history of smoking which could not be meaningful for assessment as an etiological factor for T2DM incidence in Iranian population however, at least two reports suggested there might be no such difference between former and never smokers in normal population [25].

Conclusion

According to our presented data, urinary Cadmium level of T2DM patients was significantly higher than their normal counterparts and this exposure biomarker suggests U-Cd as a practical tools for the assessment of long-term exposure to Cadmium. This elevated levels in a small sample of Iranian population without any clear history of occupational or environmental exposures could emphasize the contribution of smoking in this phenomena. Changes in U-Cd following years of smoking, second hand smoking, and smoking cessation should be considered in next prospective studies, however present data suggests the importance of smoking pattern for the next investigators. We recommend prospective longitudinal studies to clarify the risks from relatively low levels U-Cd that have been suggested through present cross-sectional investigation and identify Cadmium -induced changes in glucose levels, damage to pancreatic beta cells, and subsequent changes in insulin release and organ damages.

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Conflict of Interest

Authors declare no conflict of interest in present work.

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