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Original Article

Chronic Cadmium Intoxication and Renal Injury Among Workers of a Small-scale Silver Soldering Company

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ABSTRACT

Background: Cadmium exposure may induce chronic intoxication with renal damage. Silver soldering may be a source of cadmium exposure.
Methods: We analyzed working environment measurement data and periodic health screening data from a small-scale silver soldering company with ten workers. Concentrations of cadmium in air from working environment measurement data were obtained. Concentrations of blood and urinary cadmium, urine protein, and urine β2-microglobulin (β2M) were obtained. The generalized linear model was used to identify the association between blood and urine cadmium and urine β2M concentrations. Clinical features of chronic cadmium intoxication focused with toxicological renal effects were described.
Results: The mean duration of work was 8.5 years (standard deviation [SD] = 6.9, range = 3–20 years). Cadmium concentrations in air were ranged from 0.006 to 0.015 mg/m^3. Blood cadmium concentration was elevated in all ten workers, with a highest level of 34.6 μg/L (mean = 21.288 μg/L, SD = 11.304, range = 9.641–34.630 μg/L). Urinary cadmium concentration was elevated in nine workers, with a highest level of 62.9 μg/g Cr (mean = 22.151 μg/g creatinine, SD = 19.889, range = 3.228–62.971 μg/g creatinine). Urine β2M concentration was elevated in three workers. Urinary cadmium concentration was positively associated with urine protein concentration (beta coefficient = 10.27, 95% confidence interval = [4.36, 16.18]). Other clinical parameters were compatible with renal tubular damage.
Conclusion: Cadmium intoxication may occur at quite low air concentrations. Exposure limit may be needed to be lowered.
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1. Introduction

Cadmium has been known to be hazardous to humans [1]. Cadmium is one of the most common carcinogens to which workers are occupationally exposed in Korea [2]. For noncarcinogenic effect, the kidney is the main target organ of cadmium toxicity. Nephrotoxicity of cadmium has been well established [3–5]. Cadmium may induce oxidative stress even at a low level of exposure. Chronic exposure to cadmium may induce renal tubular injury, especially in the proximal tubule, including cell detachment as well as autophagic and apoptotic cell death [6]. Consequently, cadmium causes a dysfunction of the proximal tubule that is characterized by increase of urinary excretion of low-molecular-weight proteins such as β2-microglobulin [1]. Eventually, irreversible renal dysfunction may occur.

It has been known that occupational exposure to cadmium may be high in casting of battery recycling industry, melting and casting of silver alloy manufacturing industry, and casting process of refining industry [7]. Soldering is one of the sources of occupational exposure to cadmium. Soldering is a method of joining two or more pieces of metals and selected other materials [8]. By definition, soldering is carried out using fillers, or solders, that melt at

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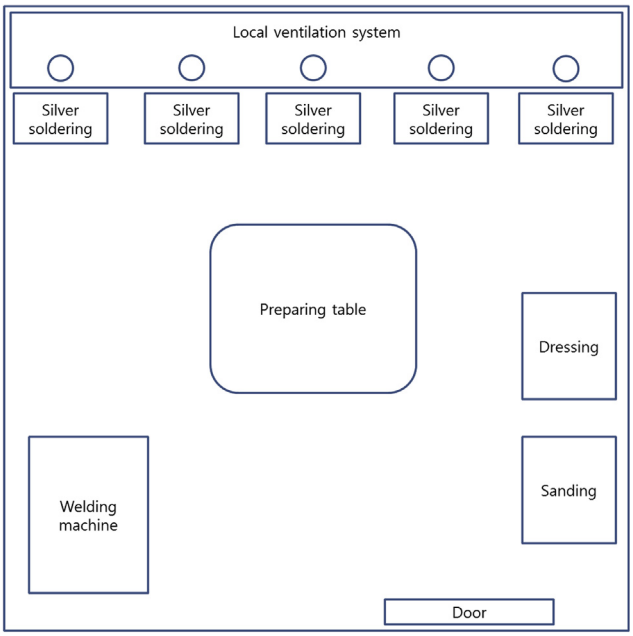

Fig. 1. Arrangement of the workplace.

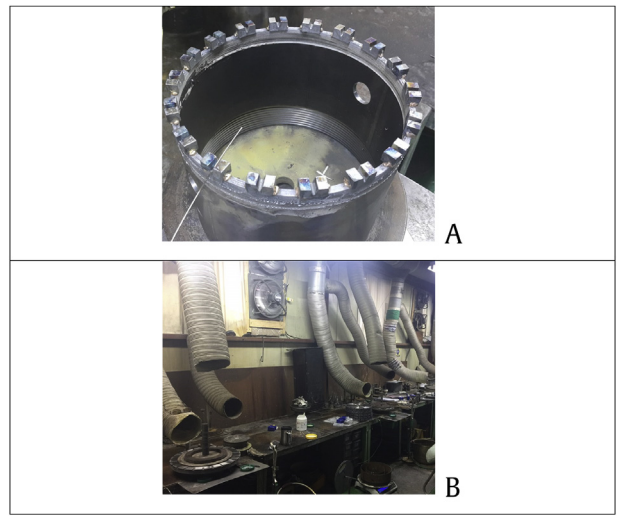

Fig. 2. Silver soldering workplace and cadmium-containing silver alloy. (A) Cadmium-containing silver alloy (Ag: 35%, Cu: 26%, Zn: 21%, Cd: 18%). (B) Local ventilators on the soldering desk.

temperatures lower than 450 °C. It is similar to welding, but usually welding uses high temperature to melt and join metals with similar characteristics. Although the bond by soldering is not as strong as the welded one, dissimilar metals including gold, silver, copper, and iron can be joined together. Because of these characteristics, soldering is widely used in jewelry industry and electrical device assembly. Main components of silver solder are silver, copper, and cadmium or lead. Although the use of lead and cadmium has been decreased owing to their toxicities, cadmium-containing silver solder is still used in small-scale companies.

There are a few studies about cadmium exposure in solderers [9,10]. Smith et al. [9] reported occupational exposure to cadmium in a group of 53 cadmium solderers in 1986. The authors reported that 27 participants among 53 workers had urine cadmium concentrations in excess of 10 nmol/mmol creatinine (approximately, 10 μg/g creatinine). However, cadmium exposure or kidney function of solderers has not been reported in Korea.

In this study, we report chronic cadmium intoxication and related renal injuries occurred among workers in a small-scale silver soldering company. Clinical features of chronic cadmium intoxication and the effect of cadmium on kidney are discussed with relevant issues.

2. Materials and methods

2.1. Data collection for the working environment and workers' health

Data on the working environment and workers' health for a silver-soldering company with 10 employees were reviewed. The main task of workers was soldering tips to make industrial cutters. In the workplace, there were a preparing table, a dressing unit, a sanding unit, one welding machine, and five units for silver soldering (Fig. 1, Fig. 2). There were local ventilators for each soldering unit. Personal protection equipment such as a mask was not given for workers.

In Korea, there is a regulation for the measurement of workplace environments. According to the Occupational Safety and Health Act, employers have a duty to measure workplace environments semiannually. Employers usually request the measurement of workplace environments to specialized institutions that certify the quality assessment conducted by a governmental agency. The institutions participate in the external quality assessment program [11]. When measuring airborne concentrations of hazardous substances, two or more personal air samples should be collected for at least six hours and analyzed for each similar exposure group.

We obtained and reviewed four assessments of airborne cadmium concentrations in the workplace conducted by other institution from 2014 to 2015. In 2016, we directly measured airborne cadmium concentration in the workplace. From 2014 to 2016, the collection of workplace air was carried out in the following way: Air samples were collected in the breathing zone of four workers including solderers for at least six hours of working time with a pump flow rate of 2 L/min. Airborne cadmium particles were sampled using mixed cellulose ester filters (SKC Inc., PA, USA) in a closed-faced three-piece cassette for atomic absorption spectrum analysis. Filters were pre-equilibrated and postequilibrated before analysis in an environmentally controlled room that was maintained at a temperature of 20°C ± 1°C and a relative humidity of 50% ± 5%. After sampling, the cassettes were tightly sealed with silicon tapes and transported in a clean box.

Special health examination data including blood cadmium and urine cadmium concentration were reviewed. Other clinical parameters such as serum blood urea nitrogen, serum creatinine, and urine creatinine concentration were also reviewed. Urinary β2-microglobulin concentrations were measured for workers with elevated blood or urine cadmium concentration.

Cadmium concentrations in air samples were analyzed by atomic absorption spectrometry (AAnalyst 400; Perkin Elmer Co., Waltham, MA, USA). The limit of detection was 0.00139 mg/L. Three spiked samples were analyzed to evaluate the recovery of cadmium. Each of the three concentrations was tested three times. Six standards were prepared, and a standard curve was obtained. Standards and spiked samples were analyzed using blanks. For quality control, all air samples were analyzed by a laboratory analyst certified by the Korean Occupational Safety and Health Agency's metal analysis quality control program. Cadmium concentrations in blood and urine were also analyzed by graphite furnace atomic absorption spectrometry (AAnalyst 600; Perkin

Table 1
Concentrations of cadmium in air (mg/m^3)

Date of measurement	Sample 1	Sample 2	Sample 3	Sample 4	Mean	SD
2014.03.13	0.0061	0.0048	N/A	N/A	0.0055	0.00092
2015.01.07	0.0005	0.0003	N/A	N/A	0.0004	0.00014
2015.07.10	N.D.	Trace	N/A	N/A	—	—
2015.12.29	0.0059	0.0058	N/A	N/A	0.0059	0.00007
2016.12.27	**0.0151**	0.0097	0.0072	0.0061	0.0095	0.00401

*Permissible limit has been set lower than 0.01 mg/m^3 since 2013.
**According to the relevant act, the employer has a duty for measuring the work environment semiannually. In this company, some measurements were delayed or omitted.
***Work environment measurements were performed by other institution from 2014 to 2015. In 2016, we directly measured cadmium concentrations in air.
SD, standard deviation.
The concentration of sample exceeded the permissible limit was expressed in bold.

Elmer Co., Waltham, MA, USA). Quality control of the laboratory has been accredited by the Korean Occupational Safety and Health Agency. An enzyme-linked immunosorbent assay kit was used to analyze urinary β2-microglobulin concentration. Urine creatinine and protein concentrations were measured using an automatic biochemical analyzer (Sysmex UN-2000; Sysmex Co, Japan). Blood and urine samples were analyzed in the qualified laboratory.

This study was approved by the Institutional Review Board of Gachon University Gil Medical Center after reviewing ethical issues (IRB no. GBIRB2019-291).

2.2. Statistical analysis

The generalized linear regression model was used to identify the association between biological indices such as blood and urine cadmium concentration and renal function indices such as urine protein and urine β2-microglobuin concentration. All models were adjusted for age, gender, systolic blood pressure, and diastolic blood pressure. The *P*-values of less than 0.05 were considered statistically significant.

3. Results

3.1. Airborne cadmium concentration in the workplace

The most recently measured cadmium concentration in air ranged from 0.0061 to 0.0151 mg/m^3 (Table 1). The cadmium concentration of only one sample exceeded the permissible limit of 0.01 mg/m^3. The last four measurements of cadmium concentration in air did not exceed the permissible limit.

3.2. Cadmium concentrations in the blood and urine and indicators of renal function

No previous health examination record existed despite exposure to hazardous substances such as cadmium. Table 2 shows job history, blood and urinary cadmium levels, and indicators of kidney function for the participants. There were four male and six female workers aged from 51 to 65 years including the employer. Two solderers had been working for 20 years. Blood cadmium concentrations of all ten workers exceeded the reference level of 5 μg/L (mean = 21.288 μg/L, standard deviation [SD] = 11.304, range = 9.641–34.630 μg/L). Urine cadmium levels also exceeded the reference level of 5 μg/g creatinine, except for one worker (mean = 22.151 μg/g creatinine, SD = 19.889, range = 3.228–62.971 μg/g creatinine).

Although the serum creatinine concentrations were in the normal range for all ten workers, two workers showed proteinuria with severely increased urinary β2-microglobulin concentration. In addition, there was one worker who showed slightly increased urinary β2-microglobulin concentration. Serum uric acid levels were decreased in two workers who showed increased urinary protein and β2-microglobulin concentration.

3.3. Pathologic findings

Among ten patients, three underwent renal biopsy. The morphologic findings in the kidney were dominated by tubulointerstitial injury (Fig. 3). Tubular epithelial cells showed degeneration and regeneration in the cortex. The degree of interstitial inflammation and fibrosis were variable. No significant changes were noted in glomeruli of all three cases. The immunofluorescence results showed no specific findings.

3.4. Association between urine protein, β2-microglobulin, and urine cadmium concentration

The scatter plot suggested a linear association between urine cadmium and urine protein concentration (Fig. 4). The urine protein level was significantly associated with urine cadmium concentration even after adjusting for gender, age, and systolic and diastolic blood pressure. The beta coefficient of urine cadmium was 10.27 (95% CI = [4.36, 16.18], $p = 0.001$) for urine protein concentration (Table 3). However, blood cadmium concentration was not significantly associated with urine protein concentration (beta coefficient = -1.37, 95% CI = [-10.00, 7.28], $p = 0.757$). Similarly, there was a linear association between urine cadmium and urinary β2-microglobulin concentration (Fig. 5). Urine cadmium concentration was significantly associated with urinary β2-microglobulin concentration (beta coefficient = 6.72, 95% CI = [1.52, 11.92], $p = 0.011$), whereas blood cadmium concentration was not statistically significantly associated with urinary β2-microglobulin concentration (beta coefficient = 9.07, 95% CI = [-1.13, 19.26], $p = 0.081$) (Table 4).

4. Discussion

In this study, we reported cadmium-induced renal injury among workers in a small-scale silver soldering company. These workers have been chronically exposed to cadmium, up to 20 years. All ten workers were diagnosed as having chronic cadmium intoxication based on the blood and urinary cadmium level. Three workers were diagnosed as having renal tubular dysfunction.

Cadmium exposure in silver soldering has been known to be relatively low. In this study, cadmium concentrations in air samples were also moderate to low. It is known that internal exposure levels (i.e., blood or urine cadmium) are compatible with external exposure levels (i.e., cadmium concentration in air) [12]. It is also known that cadmium burden in the kidney is correlated well with the intensity of tubular damage [13]. However, in this study, cadmium-induced renal injuries were identified in some workers who had a long tenure. This is consistent with the findings of an earlier report that cadmium body burden and risk of tubular dysfunction in end users of cadmium may be as high as those found in smelters or production workers [9].

There may be several possibilities in those inconsistencies between internal exposure levels and external cadmium concentrations. First, internal exposure levels might be higher due to extended working hours. When setting up most of the exposure limits, it is assumed that workers work eight hours per day, forty hours per week [14]. If an employee works for more than the regular working hours, cumulative exposure may be higher than expected. Korea has longer working hours than any other developed

Table 2
Blood and urine cadmium levels, indicators of renal function, and urine β_2-microglobulin concentration

Case no.	Gender	Age (years)	Job title	Job duration (years)	Blood cadmium (μg/L)*	Urine cadmium (μg/g Cr)†	BUN (mg/dL)‡	Serum creatinine (mg/dL)§	Proteinuria (dip stick)	Urine protein (mg/g Cr)‖	Urine β_2-microglobulin (μg/L)¶	Uric acid (mg/dL)**
1	F	53	Assist	3	**9.985**	**9.636**	12.1	0.6	—	77.9	17	
2	F	62	Dressing	8	**28.590**	**26.836**	17.1	0.8	—	104.2	**429**	4.3
3	F	49	Soldering	5	**9.641**	**5.929**	16.4	0.6	+-	83.2	37	
4	M	63	Assist	4	**34.630**	**14.190**	21.6	1.1	—	122.1	238	
5	M	65	Employer		**11.080**	**9.169**	16.9	0.8	—	76.7	286	
6	F	58	Soldering	20	**34.510**	**62.971**	13.3	0.7	**1+**	**535.1**	**12,642**	**2.1**
7	M	50	Soldering	20	**28.920**	**32.638**	20.7	1.2	**1+**	**381.1**	**>20,000**	**2.4**
8	F	51	Soldering	10	**32.500**	**46.796**	11.8	0.6	—	77.6	115	
9	M	62	Dressing	4	**12.220**	**10.119**	22.8	0.7	—	50.4	172	
10	F	59	Assist	3	**10.800**	3.228	13.7	0.6	—	73.4	49	

F, female, M, male.
The concentrations or values of each test exceeded the reference level were expressed in bold.
* Reference level, blood cadmium <5 μg/L.
† Reference level, urine cadmium <5 μg/g Cr.
‡ Reference level, BUN (blood urea nitrogen) = 8~22 mg/dL.
§ Reference level, serum creatinine = 0.5~1.2 mg/dL.
‖ Reference level, urine protein <150 mg/g Cr.
¶ Reference level, urinary β2-microglobulin <370 μg/L.
** Reference level, uric acid = 2.5~8.3 mg/dL.[17]

country [15]. In this study, it is possible that internal exposure levels were higher than expected because of long working hours. Second, workplace hygiene might be worse in the past. The company moved into a new space several years ago. According to the employer and employees, the previous workplace was smaller and poorly ventilated. Third, inadequate air conditioning may result in higher concentration of cadmium in air. Operating the air conditioner in a confined space with closed doors and windows may increases the cadmium concentration in air.

Cadmium is efficiently absorbed when exposed via the respiratory route. Up to 50% of inhaled cadmium reaches the systemic circulation, whereas less than 10% of cadmium absorbed into the gastrointestinal tract [16,17]. When absorbed into the bloodstream, cadmium is transported to the liver and taken up by hepatocytes. In hepatocytes, cadmium induces the synthesis of metallothionein which binds to cadmium and buffers toxicity of cadmium in the cell [18,19]. The cadmium–metallothionein complex is released into the bloodstream when the hepatocyte dies [20]. The cadmium–metallothionein complex can be filtered at the glomerulus. In the proximal tubule, cadmium can enter into the tubular cell through a variety of mechanisms [21]. Various studies have shown multiple mechanisms on how to uptake cadmium in the proximal tubule cell including megalin-mediated transport at the brush border [20], a variety of channels and transporters for ions such as calcium and zinc [21], and uptake of low-molecular-weight cadmium–thiol conjugates [22].

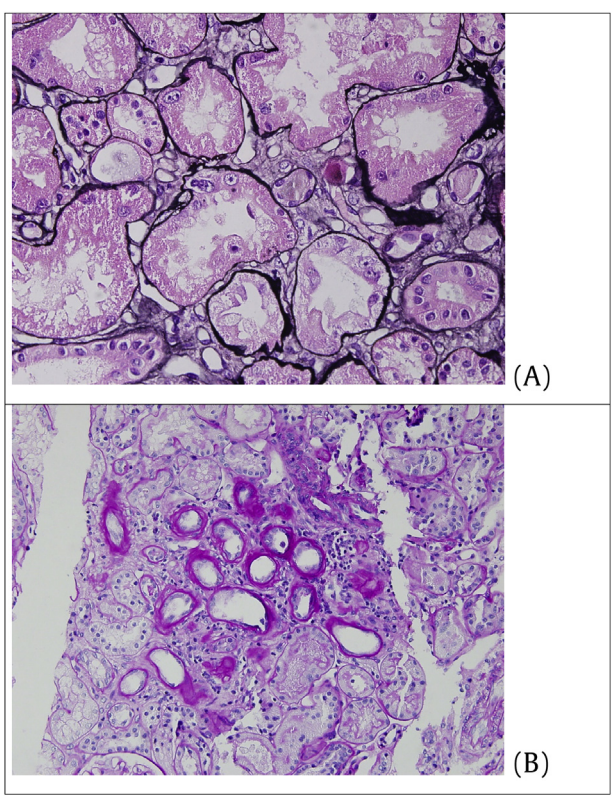

Fig. 3. Findings of renal biopsy. (A) Note the swollen and detached tubular epithelial cells in dilated tubules (periodic acid–methenamine silver, ×400), (B) Atropic tubules with interstitial lymphoplasmocytic infiltration (periodic acid-Schiff, ×400).

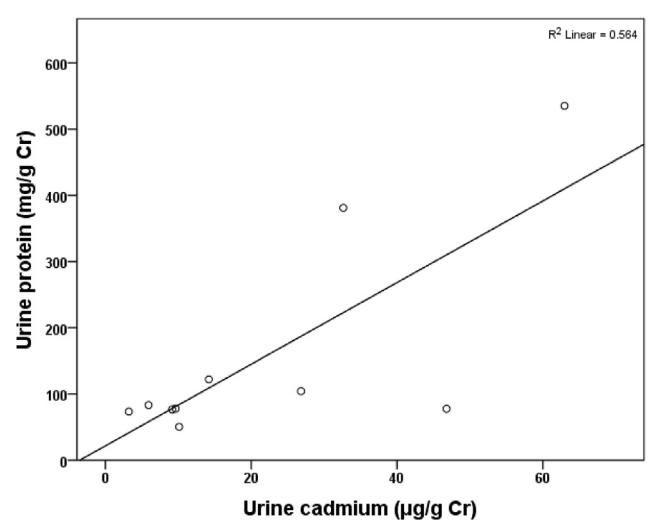

Fig. 4. Scatter plot of urine cadmium and urine protein concentration.

Table 3
Beta coefficients of blood cadmium and urine cadmium for urine protein using the generalized linear model

Variables	Beta coefficient	95% confidence interval	*p*-value
Blood cadmium (μg/L)	-1.37	-10.00, 7.28	0.757
Urine cadmium (μg/g Cr)	**10.27**	**4.36, 16.18**	**0.001**

Adjusted for gender, age, systolic blood pressure, and diastolic blood pressure. Statistically significant values (i.e., $p<0.05$) were expressed in bold.

Table 4
Beta coefficients of blood cadmium and urine cadmium for urinary β2-microglobulin using the generalized linear model

Variables	Beta coefficient	95% confidence interval	*p*-value
Blood cadmium (μg/L)	9.07	-1.13, 19.26	0.081
Urine cadmium (μg/g Cr)	**6.72**	**1.52, 11.92**	**0.011**

Adjusted for gender, age, systolic blood pressure, and diastolic blood pressure. Statistically significant values (i.e., $p<0.05$) were expressed in bold.

There has been emerging evidence that specific changes in the proximal tubular cell such as cell–cell adhesion, cellular signaling cascades, and autophagic responses occur before cadmium-induced proximal tubular cell death begins [6]. The primary toxic effect of cadmium on epithelial cells has been revealed to be disruption of cadherin-dependent cell–cell junctions [23]. It has been shown that alteration of various cellular signaling pathways in epithelial cells by cadmium may be one of the mechanisms of cadmium-induced renal proximal tubular damage [24]. In addition, oxidative stress has long been thought to be an important mechanism in cadmium-induced renal injury [25]. Cadmium seems to indirectly induce oxidative stress by binding to intracellular thiols or by interfering with the protective enzymes against oxidative stress. It has been shown that oxidative stress may trigger the activation of specific oxidative signaling pathways [26]. Taken together, an emerging model of cadmium-induced proximal tubular injury has been proposed [6]. In early stage, the low level of cadmium exposure may result in oxidative stress, alteration of signaling cascades, and alteration in cell adhesion. Mild to moderate injuries may be repaired by autophagic response. Severe injuries that cannot be repaired by the proliferative process result in necrosis of the proximal tubule cells. Consequently, increase in the urinary excretion of glucose, amino acids, electrolytes, and low-molecular-weight proteins such as β2-microglobuin and N-acetyl-β-D-glucosaminidase may be observed.

In Korea, there were two nationwide investigations for occupational exposure to cadmium in 1992 and 1999 [27,28]. Investigators tried to access as many workplaces as possible where workers were exposed to cadmium. The major cadmium-using processes were cadmium alloy refinery, cadmium alloy production, nickel–cadmium battery recycling, disposal smelting, electroplating, and battery production. Solderers using cadmium-containing alloy were not included at that time. Workers involved in nickel–cadmium battery recycling and cadmium alloy production were exposed to relatively high concentrations of cadmium (0.066 mg/m^3 and 0.017 mg/m^3, respectively), whereas workers in the refinery and those involved in electroplating were exposed to a medium to low level of cadmium (0.007 mg/m^3 and 0.0005 mg/m^3, respectively) [7]. For workers, cadmium exposure levels were evaluated using various biomarkers including blood and urine cadmium, urinary β2-microglobulin, and urinary N-acetyl- β-D-glucosaminidase. Although blood and urine cadmium levels of several workers exceeded the biological monitoring standards, which were 10 μg/L of blood cadmium and 7 μg/g creatinine of urine cadmium concentration, there was no cadmium-induced renal dysfunction. At that time, estimated cumulative cadmium exposure did not exceed 500 μg/m^3•year, the suggested level at which kidney injury could occur [29].

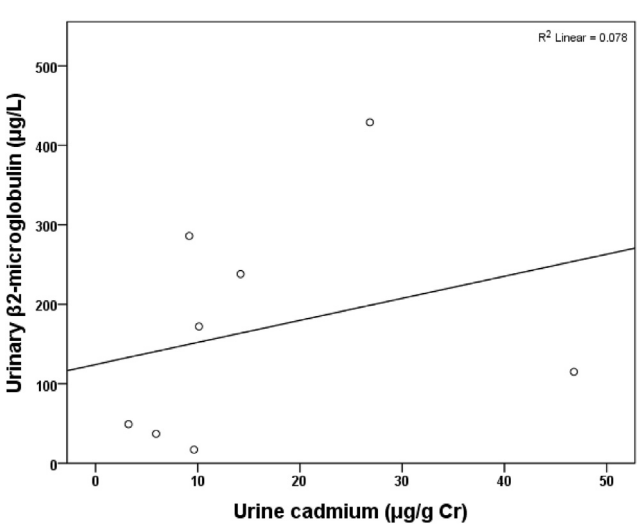

Fig. 5. Scatter plot of urine cadmium and urinary β_2-microglobulin concentration (two observations are omitted).

However, in this study, there were at least two workers who were diagnosed as having renal tubular dysfunction although the estimated cumulative cadmium exposure did not seem to exceed the suggested level. Because they worked for up to 20 years, it is possible that they may be exposed to cadmium at a higher level in the past. Occupational exposure limit of airborne cadmium in Korea, which was 50 μg/m^3, has been lowered to 10 μg/m^3 in 2013. A previous study suggested that clear scientific evidence did not exist for recommending air concentration of cadmium lower than 10 μg/m^3 in the workplace [30]. Although this value is compatible with the threshold limit value of the American Conference of Governmental Industrial Hygienists for cadmium, it seems necessary that occupational exposure limit of cadmium in the workplace should be lower to prevent cadmium-induced renal injury. The Occupational Health and Safety Administration has set up the permissible exposure limit as 5 μg/m^3, considering lung cancer and renal dysfunction [14,29]. Although the occupational exposure limit of airborne cadmium of 10 μg/m^3 is widely used, it may not be enough to prevent kidney damage owing to the possibilities discussed previously.

Cadmium-induced renal tubular dysfunction has been suggested to be irreversible. Roels et al. [31] showed that cessation of cadmium exposure could not prevent the progression of cadmium-induced renal dysfunction if there were severe tubular injury (e.g., urinary β2-microglobulin >1,500 μg/g creatinine) and high body burden of cadmium (e.g., urine cadmium >20 μg/g creatinine). Prevention and early detection of renal dysfunction should be emphasized.

In this study, urine β2-microglobulin concentrations were significantly associated with urine cadmium levels, but not with blood cadmium levels. In special health examination of workers of Korea, blood cadmium concentration is set as a primary screening item to identify cadmium exposure. Urine cadmium concentration may be measured when the blood cadmium level is elevated or cadmium-induced health effects are suspected. To detect cadmium-induced renal injury early, urine cadmium and urinary β2-microglobulin concentration should be screened primarily for workers exposed to cadmium. It is also noteworthy that serum uric acid levels were decreased for those who had renal tubular damage.

Uric acid is a low-molecular-weight substance of 168 daltons, which is filtered from glomeruli, and up to 90% of filtered uric acid is reabsorbed into the proximal tubule [32]. Serum uric acid concentration can be more easily assessed than urinary β2-microglobulin concentration in the clinical setting. Persons with low levels of serum uric acid should not be ignored especially in cases of suspected renal tubular damage.

Although at low levels, chronic cadmium exposure may induce renal dysfunction. Studies about the relationship between cumulative exposure to cadmium and health effects should be encouraged. Efforts to reduce both occupational and nonoccupational exposure to cadmium are needed to prevent cadmium-induced renal injury.

Conflicts of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.shaw.2020.03.005.

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