Plasma Metallothionein Antibody, Urinary Cadmium, and Renal Dysfunction in a Chinese Type 2 Diabetic Population

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OBJECTIVE — It has been reported that diabetes may increase the risk of cadmium-induced kidney damage. The presence of metallothionein antibody (MT-Ab) increased the susceptibility for tubular damage among cadmium workers. This study focused on the relationships between levels of MT-Ab, urinary cadmium, and kidney function in a Chinese type 2 diabetic population.

RESEARCH DESIGN AND METHODS — A cross-sectional study was performed on 229 type 2 diabetic patients (92 men and 137 women) who were recruited from two community centers in one district of Shanghai City in China. Information was obtained from interviews, health records, and blood and urine samples.

RESULTS — Levels of the tubular biomarker β_2-microglobulin increased significantly when the levels of MT-Ab and urinary cadmium were elevated in male and female subjects; in contrast, the levels of urinary albumin, a glomerular biomarker, did not display such a pattern. After adjusting for potential confounding covariates, logistic regression showed that the odds ratios (ORs) of tubular dysfunction increased upon *1*) increasing the MT-Ab concentration from a low to high level (OR 5.56 [95% CI 2.25–13.73]) and *2*) increasing the level of urinary cadmium from <1 to ≥ 1 μg/g creatinine (3.34 [1.17–9.53]); the OR of patients currently smoking was 3.51 (1.14–10.80) relative to that of those who had never smoked.

CONCLUSIONS — This study proves that the presence of MT-Ab can potentiate tubular dysfunction among diabetic subjects and that patients with high MT-Ab levels are more prone to development of tubular damage.

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The incidence and prevalence of diabetes are rising globally. It is predicted that the number of patients worldwide with diabetes will reach 366 million by the year 2030, with 42 million of them residing in China (1). For patients with diabetes, kidney disease is a dreaded complication. Currently, the susceptibility to toxic hazards in populations at high risk is of increasing concern. In such high-risk groups, diabetes is one condition that can be suspected of increasing the susceptibility to toxicants.

Cadmium is a well-known nephrotoxic agent with an extremely long biological half-life of 15–30 years in humans (2). From some cross-sectional population studies, it was reported that diabetes could augment the risk of cadmium-induced renal damage, especially tubular dysfunction (3,4). Several experimental studies have demonstrated an increased susceptibility toward cadmium nephrotoxicity (5,6) in spontaneously diabetic mice and hamsters, when compared with normal animals of the same strain. Streptozotocin-induced diabetic rats are more susceptible to cadmium nephrotoxicity than are normal rats when they are exposed subchronically to cadmium chloride in drinking water (7,8).

Metallothioneins (MTs) comprise a family of stress proteins that contain a high content of cysteine and divalent metals. Several physiological roles have been proposed for MTs, including detoxification of toxic heavy metals, e.g., cadmium, homeostasis of essential metals, e.g., zinc and copper (9), and scavenger of free radicals. Levels of MT are significantly increased in the liver and kidneys of diabetic animals (10–12), and in short-term experiments, the increased amounts of MT in the kidney may prevent cadmium nephrotoxicity in streptozocin-induced diabetes (12). It has been reported that metallothionein antibody (MT-Ab) is present in the circulation of healthy subjects and in patients suffering from atopic dermatitis (13). The relationship between MT-Ab and renal dysfunction has been studied among cadmium workers in China (14). Such workers having high levels of MT-Ab display cadmium-induced tubular nephrotoxicity more frequently than do those with low levels of MT-Ab, which suggests that subjects having higher MT-Ab levels more readily develop cadmium-induced renal dysfunction (14). The relationship between the levels of MT-Ab and diabetic nephropathy, however, has not yet been studied. The aim of this study was to investigate the potential effect of MT-Ab on renal dysfunction within a Chinese diabetic population.

RESEARCH DESIGN AND METHODS

— A total of 262 patients having diabetes, who had been diagnosed previously in local hospitals according to the World Health Organization diagnostic criteria protocol (15) and who were willing to participate in this study, were recruited from two nearby community centers in one district of Shanghai City in China. Among them, 229 patients had type 2 diabetes; of these patients, 92 were male and 137 were female. All participants were of the same ethnicity, Han

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Abbreviations: FCG, fasting capillary glucose; MT, metallothionein; MT-Ab, metallothionein antibody.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Characteristics of diabetic subjects*

	Total subjects	Male subjects	Female subjects	*P* value*
n	229	92	137	
Age (years)	66.1 ± 0.6	67.2 ± 0.8	65.3 ± 0.6	0.087
Durations of diabetes (years)	8.6 ± 0.6	8.6 ± 0.7	8.6 ± 0.5	0.982
Smokers (current/previous/never)	33/33/163	27/31/34	6/2/129	<0.001
Drinkers (current/previous/never)	26/30/173	21/26/45	5/4/128	<0.001
BMI (kg/m^2)	26.0 ± 0.2	25.9 ± 0.3	26.1 ± 0.3	0.670
Hypertension	152 (66.38)	63 (68.48)	89 (64.96)	0.581
Dyslipidemia	114 (49.78)	42 (45.65)	72 (52.55)	0.306
MT-Ab (units/ml)	134.58 (32.56–564.14)	119.45 (32.56–564.14)	145.80 (41.10–516.40)	0.006
Urinary albumin (mg/g Cr)	26.12 (0.97–848.89)	25.66 (0.97–848.89)	26.44 (1.14–724.08)	0.869
Urinary β_2-microglobulin (μg/g Cr)	113.20 (31.87–3,856.23)	104.13 (31.87–1,275.02)	113.20 (36.09–3,856.23)	0.273
Fasting capillary blood glucose (mmol/l)	8.02 ± 0.18	7.95 ± 0.24	8.08 ± 0.26	0.736
Blood cadmium (μg/l)	0.61 (0.03–4.54)	0.64 (0.03–3.50)	0.59 (0.03–4.54)	0.609
Urinary cadmium (μg/g Cr)	0.38 (0.05–4.17)	0.32 (0.05–4.17)	0.43 (0.05–2.14)	0.023

Data are means ± SE, *n* (%), or GM (range) unless otherwise indicated. *Compared with male subjects (*t* test or χ^2 test). Cr, creatinine.

race, with ages ranging from 44 to 87 years and no history of occupational exposure to toxic metals. The other 33 patients either had type 1 diabetes or were excluded from the study because of the lack of some data. All of the subjects were members of a community diabetes club (health promotion center), and a comprehensive health record was obtained for each patient. Trained and supervised doctors completed a questionnaire for each participant. Personal data, such as living customs, social and economic conditions, and lifestyles, including smoking habits, drinking habits, modes of diabetes management, and diabetes syndromes and complications, were collected. The presence of diabetes syndromes and complications was checked by doctors and confirmed according to the patient's health records. Dyslipidemia was diagnosed according to the Guide for Dyslipidemia in China (total cholesterol >5.72 mmol/l and/or triglycerides >1.70 mmol/l and/or HDL <0.91 mmol/l). Hypertension was defined as having an average (mean value of three readings) blood pressure of ≥140/90 mmHg or using medication for hypertension regardless of blood pressure reading. This study was conducted with the permission of both local authorities and the Ethics Committee of Fudan University and with the informed consent of each participant.

Sampling and measurements

Venous blood samples for blood chemistry analysis were obtained after an overnight fast. Whole-blood fasting capillary glucose (FCG) was measured using a Roche Glucotrend 2 glucose meter (Roche Diagnostics, East Sussex, U.K.). Morning spot urine samples were collected in acid-washed containers and stored at −70°C until required for analysis. The levels of urinary β_2-microglobulin and albumin were measured using an enzyme-linked immunosorbent assay; the levels of creatinine were measured using the Jaffe reaction method. Urinary cadmium and blood cadmium concentrations were measured by graphite furnace atomic absorption spectrometry using a standard addition method (16). All urinary parameters were adjusted for the levels of creatinine in urine. Plasma MT-Ab was measured using an enzyme-linked immunosorbent assay as described previously (14). In this study, an optical density >0.200 was considered to be a high level of MT-Ab (14). Details regarding the laboratory procedures for these tests have been published elsewhere (14,16). In this study, albuminuria was defined as a urinary albumin level of ≥30 mg/g creatinine; β_2-microglobulinuria was defined as a urinary β_2-microglobulin level of ≥200 μg/g creatinine (17).

Statistical analysis

Analyses were undertaken using SPSS software (version 11.5; SPSS, Chicago, IL). For non-normally distributed values, the biological measurements were normalized by logarithmic transformation and were expressed in terms of their geometric mean (GM) and range. For comparisons among groups of more than two, one-way ANOVA was used. Statistical significance was considered to be a value of $P < 0.05$. Final estimates of the relationships between the levels of MT-Ab, urinary cadmium, and renal dysfunction were computed and adjusted for all potential covariates by logistic regression.

RESULTS

Characteristics of diabetic subjects

Table 1 presents the main characteristics of this diabetic population. In this study, the percentages of male smokers (27 of 92 vs. 6 of 137, $\chi^2 = 27.82$; $P < 0.001$) and alcohol drinkers (21 of 92 vs. 5 of 137, $\chi^2 = 20.11$; $P < 0.001$) were higher than those of the female smokers, but between the sexes there were no statistical differences with respect to age, duration of diabetes, BMI, FCG levels, or blood cadmium. Nevertheless, the levels of urinary cadmium (GM 0.43 vs. 0.32 μg/g creatinine; $P = 0.023$), as well as the titer of MT-Ab (145.80 vs. 119.45 units/ml; $P = 0.006$), in female subjects were statistically higher than those in the male subjects.

In this study, diabetes management models including diet therapy, exercise, oral hypoglycemic drugs, insulin, and traditional Chinese medicine were recorded. The χ^2 results indicated that none of these diabetes management models significantly affected the MT-Ab levels (data not shown; $P > 0.05$) for either men or women. The relationships between smoking habits, drinking habits, and MT-Ab levels were also studied using a χ^2 test. There was no statistical difference in the MT-Ab levels of the subjects who had different smoking and drinking habits, for both male and female diabetic subjects (data not shown; $P > 0.05$). The relationship between the levels of MT-Ab and age

Table 2—*Characteristics of subjects with different renal function*

	Albuminuria (−) and β_2-microglobulinuria (−)	Albuminuria (+) and β_2-microglobulinuria (−)	Albuminuria (+) and β_2-microglobulinuria (+)	Albuminuria (−) and β_2-microglobulinuria (+)
n	129	55	29	16
Sex (male/female)	56/73	16/39	13/16	7/9
Age (years)	66.2 ± 0.8	65.9 ± 1.2	65.2 ± 1.4	66.7 ± 2.2
Duration (years)	8.3 ± 0.5	8.3 ± 0.9	10.6 ± 1.7	8.1 ± 1.5
Smokers (current/previous/never)	16/22/91	7/6/42	6/3/20	4/2/10
Drinkers (current/previous/never)	18/14/97	3/7/45	4/5/20	1/4/11
BMI (kg/m^2)	25.7 ± 0.3‡	26.9 ± 0.5*	26.4 ± 0.7*	25.4 ± 1.0
FCG (mmol/l)	7.60 ± 0.22	8.05 ± 0.35	9.79 ± 0.54†§	7.56 ± 0.53
MT-Ab (units/ml)	125.55 (32.56–516.40)	130.14 (41.40–400.14)	151.30 (58.93–429.11)	213.79 (69.29–564.14)†§
Urinary albumin (mg/g Cr)	11.13 (0.97–29.74)‡	97.88 (31.00–848.89)†	139.09 (31.99–724.08)†‡	13.04 (3.18–29.78)§
Urinary β_2-microglobulin (μg/g Cr)	69.37 (31.87–192.04)‡	98.52 (34.47–192.04)†	598.97 (208.46–2076.98)†‡§	461.81 (215.09–3856.23)†‡§
Blood cadmium (μg/l)	0.56 (0.03–3.16)	0.66 (0.06–2.58)	0.63 (0.06–4.54)	0.91 (0.31–3.50)
Urinary cadmium (μg/g Cr)	0.34 (0.05–1.91)	0.39 (0.07–4.17)	0.45 (0.14–2.14)	0.64 (0.19–2.00)†‡

Data are means ± SE or GM (range). Compared with the albuminuria (−) + β_2-microglobulinuria (−) group: *$P < 0.05$, †$P < 0.01$. Compared with the albuminuria (+) + β_2-microglobulinuria (−) group: ‡$P < 0.05$, §$P < 0.01$, Cr, creatinine.

were studied using Pearson's correlations; the correlation coefficients were 0.16 ($P > 0.10$) and 0.14 ($P > 0.10$) in male and female patients, respectively.

MT-Ab, urinary cadmium, and diabetic renal dysfunction

In this study, the prevalence of hypertension, dyslipidemia, and albuminuria were as high as 66.4, 49.8, and 36.7%, respectively, in all subjects, and the prevalence of β_2-microglobulinuria reached 19.7% in all subjects (Tables 1 and 2). The results indicated that the percentage of high levels of MT-Ab was significantly higher in those subjects with β_2-microglobulinuria than those without in both males (9 of 20 vs. 13 of 72, $\chi^2 = 4.85$; $P = 0.028$) and females (16 of 25 vs. 33 of 112, $\chi^2 = 10.61$; $P = 0.001$). In contrast, the prevalence of albuminuria and other diabetes complications did not vary significantly at different MT-Ab levels (data not shown).

Pearson's correlations were analyzed among MT-Ab, FCG, urinary β_2-microglobulin, albumin, and cadmium. The results indicate that positive associations existed between FCG and both urinary albumin and β_2-microglobulin ($r = 0.18$ and 0.14, $P < 0.05$). The correlation coefficient between the levels of urinary albumin and β_2-microglobulin was 0.42 ($P < 0.01$). Significant positive correlations exist between the levels of MT-Ab and urinary β_2-microglobulin ($r = 0.21$ in men and 0.20 in women; $P < 0.05$) and between urinary β_2-microglobulin and urinary cadmium ($r = 0.25$ in men and 0.24 in women; $P < 0.05$). Nevertheless, urinary cadmium does not show significant correlation with MT-Ab, either in male or in female subjects ($r = -0.17$ and -0.06, respectively; $P > 0.10$).

To further differentiate the possible effects of MT-Ab on renal dysfunction in the diabetic population, the subjects were divided into four subgroups according to their tubular and glomerular function: groups of albuminuria (–) + β_2-microglobulinuria (–), albuminuria (+) + β_2-microglobulinuria (–), albuminuria (+) + β_2-microglobulinuria (+), and albuminuria (–) + β_2-microglobulinuria (+). Some basic information, such as age, sex, duration of diabetes, smoking habits, and drinking habits, was matched among these four groups ($P > 0.05$). Table 2 indicates that in the albuminuria (–) + β_2-microglobulinuria (+) group, the levels of urinary β_2-microglobulin, MT-Ab, and urinary cadmium were significantly higher than those in the albuminuria (–)

Table 3—*Logistic regression between diabetic renal dysfunction and potential variables*

Variables		Regression coefficient	SEM	Wald value	*P* value	OR (95% CI)
Dependent	Covariates					
Albuminuria						
	Constant	1.39	0.42	10.76	0.001	0.25
	FCG levels (mmol/l)					
	<6.1	—	—	—	—	1.00
	≥6.1	1.01	0.46	4.89	0.027	2.75 (1.12–6.74)
β^2-Microglobulinuria						
	Constant	−4.39	0.80	29.88	0.000	0.12
	Smoking habits					
	Never smoked	—	—	—	—	1.00
	Previously smoked	0.18	0.63	0.08	0.772	1.20 (0.35–4.16)
	Currently smoking	1.26	0.57	4.81	0.028	3.51 (1.14–10.80)
	Urinary cadmium levels (μg/g Cr)					
	<1.0	—	—	—	—	1.00
	≥1.0	1.21	0.54	5.08	0.024	3.34 (1.17–9.53)
	MT-Ab levels					
	Low	—	—	—	—	1.00
	High	1.72	0.46	13.80	0.000	5.56 (2.25–13.73)

*Definition of covariates in logistic analysis: sex: male/female; hypertension, no/yes; dyslipidemia, no/yes; age grades: <60, 60–66, 66–72, or ≥72 years old; duration of diabetes: <10, 10–20, or ≥20 years; BMI: <24, 24–28, or ≥28 kg/m^2; blood cadmium levels: <1 or ≥1 μg/l.

+ β_2-microglobulinuria (–) ($P < 0.01$) and albuminuria (+) + β_2-microglobulinuria (–) ($P < 0.01$) groups. The prevalence of high levels of MT-Ab in the groups was also studied with respect to their different levels of renal dysfunction (data not shown). Compared with the albuminuria (–) + β_2-microglobulinuria (–) group (26.38%), the prevalence of high levels of MT-Ab in the albuminuria (+) + β_2-microglobulinuria (+) and albuminuria (–) + β_2-microglobulinuria (+) groups (44.83 and 75.00%, respectively) was significantly higher: odds ratios (ORs) were 2.27 (95% CI 0.99–5.21; $P = 0.049$) and 8.38 (2.53–27.76; $P < 0.001$), respectively. These results indicate that an increased level of MT-Ab was related to an increase in the excretion of β_2-microglobulin, which is a typical indicator of tubular dysfunction, but not to increased levels of urinary albumin, the glomerular biomarker.

Logistic regression analysis was used to compute the association between diabetic renal dysfunction (albuminuria or β_2-microglobulinuria) and MT-Ab and to adjust for all potential influencing covariates (including sex, age, duration of diabetes, FCG, BMI levels, smoking habits, hypertension, dyslipidemia, and blood and urinary cadmium levels). Multivariate analysis revealed a statistically significant relationship between albuminuria and the quality of the diabetic subjects' glucose control (FCG levels); subjects having FCG ≥6.1 mmol/l had a 2.75-fold (95% CI 1.12–6.74) increased OR for albuminuria relative to those having FCG <6.1 mmol/l (Table 3). Table 3 indicates that significant relationships existed between β_2-microglobulinuria and smoking habits, urinary cadmium, and MT-Ab levels. After multivariable adjustment, the OR for β_2-microglobulinuria in subjects with high levels of MT-Ab was 5.56 (2.25–13.73) compared with that for subjects with a low titer of MT-Ab. Those subjects having a urinary cadmium level ≥1.0 μg/g creatinine had a 3.34-fold (1.17–9.53) increased OR of β_2-microglobulinuria compared with those having urinary cadmium levels <1.0 μg/g creatinine. Current smokers exhibited a 3.51-fold (1.14–10.80) increased risk of β_2-microglobulinuria compared with that of the subjects who had never smoked. To further elucidate the effects of smoking on tubular dysfunction, a smoking index was calculated as the number of cigarettes smoked per day divided by 20 and multiplied by smoking days for current and previous smokers. Smoking index levels were defined as 0, <11,000, and ≥11,000 (equal to one package per day for 30 years). Using smoking index levels instead of smoking habits, logistic regression was performed as described above. However, the results showed no statistically significant ($P > 0.05$) effect related to the smoking index (data not shown).

CONCLUSIONS — Some previous cross-sectional studies demonstrated that cadmium-induced renal tubular dysfunction was potentiated by diabetes in groups of the general population (3,4). Because of its relatively low prevalence and possible confounding factors in a study of the general population, research within a diabetic population may provide more valuable information concerning the relationship among cadmium exposure, diabetes, and renal dysfunction. Several recent studies have demonstrated the presence of various autoantibodies in patients with both type 1 and type 2 diabetes (18–20). In the present study, we too found that MT-Ab was present in the circulation of diabetic patients. Interestingly, we found the first example of a sex difference in distribution of MT-Ab in this study: the levels of MT-Ab in female subjects were statistically higher than they were in male subjects; however, we are not aware of the exact reason for this phenomenon. In the current study, we also explored the possible factors affecting the levels of MT-Ab. According to our results, no statistically significant relationship existed between the MT-Ab levels and smoking habits, drinking habits, diabetes management, age, FCG, urinary cadmium, or blood cadmium. These results are in accordance with those we obtained from a study of an occupational population exposed to cadmium (14). We believe that the level of MT-Ab might

manifest some inherent trait that is not easily mediated by extrinsic factors, such as plasma glucose levels, the use of diabetes medications, and cadmium exposure.

It is interesting to note in the present study that the prevalence of tubular dysfunction only (with β_2-microglobulinuria but without albuminuria) reached 7% (Table 2). This finding indicates that both glomerular and tubular dysfunctions were involved in diabetic nephropathy, which is in accordance with the results of a previous study conducted in Singapore (21). The results suggest that greater emphasis should be placed on tubular dysfunction within the diabetic population, although diabetic renal damage is manifested primarily as glomerular dysfunction. In fact, far from being bystanders in diabetic nephropathy, changes in the proximal tubule are important for the development of progressive diabetic kidney disease (22). The proximal tubule is uniquely susceptible to a variety of internal and external factors associated with diabetes (22). There is growing evidence that tubular injury is a major feature in the development of renal dysfunction in type 2 diabetes (23–26). Thus, identification of risk factors for diabetic tubular dysfunction is essential for prevention of renal damage in diabetic patients.

Many studies have confirmed the increased renal risk in smokers having type 1 and type 2 diabetes (27). In this study we did not find such an effect on urinary albumin, but we did find that current smoking could increase the risk of development of β_2-microglobulinuria (Table 3). Cigarette smoking does contribute to cadmium exposure in the general population. In this study, blood cadmium levels (GM 1.00 μg/l [range 0.13–3.51]) in smokers were notably higher than those in previous smokers (0.50 μg/l [0.03–1.41]) and in subjects who had never smoked (0.51 μg/l [0.06–1.91]). Although increased cadmium body burden related to cigarette smoking may play a role in the pathological process of diabetic tubular dysfunction, the present study may be not large enough (only 33 current smokers) to demonstrate a relationship between accumulative smoking index and renal dysfunction. The possibility exists that other effects of smoking, such as smoking-related oxidative stress and inflammation, may play a more important role in smoking-related kidney damage (27,28). When compared with the results obtained from the subjects who had never smoked, results from previous smokers did not show an increased risk of β_2-microglobulinuria (Table 3), indicating that cessation of smoking reduces the risks of tubular damage among diabetic subjects.

Apart from smoking, a major source of cadmium exposure in the general population is the consumption of cereals, particularly rice, in southeast China, vegetables, and shellfish. Because the level of urinary cadmium is proportional to the body burden, it is used widely as a biomarker of lifetime exposure (2). In this diabetic population, we found that the levels of urinary cadmium correlated positively with urinary β_2-microglobulin, a tubular biomarker. We did not find, however, any significant relationship between the levels of the cadmium biomarkers and urinary albumin, although it has been reported that cadmium can also exacerbate glomerular damage in diabetic patients (4). It might be that in our present study the urinary cadmium level (GM 0.38 μg/g creatinine) was not sufficiently high to potentiate glomerular dysfunction. Although this urinary cadmium level is relatively low, it still had an obvious effect on tubular dysfunction (Table 3).

In the present study, MT-Ab displayed a positive correlation exclusively with urinary β_2-microglobulin and not with albumin. Therefore, this result indicates that MT-Ab interacted mainly with the tubular function in this diabetic population, in accordance with the results of our previous study on a cadmium-exposed population (14). The discrepancy of effects of MT-Ab on renal tubular and glomerular functions implies that renal tubules, the main storage tissues for MT in the body, are the more important target tissues of MT-Ab. Even now, the precise mechanism through which MT-Ab influences renal tubular dysfunction remains unclear. From a previous study of an occupational population, we hypothesized that MT-Ab may interfere with the detoxification of cadmium mediated by MT in renal tubular cells exposed to cadmium (14). Inhibition of MT synthesis within tubular cells might be one reason for MT-Ab affecting renal dysfunction in this diabetic population. On the other hand, MT is a kind of multifunctional stress protein that also exhibits potent antioxidant and immunoregulation effects (29,30). It is reasonable to speculate that MT-Ab may interfere with these other functions of MT to provide alternative mechanisms for the effect of MT-Ab on diabetic renal damage. Nevertheless, the exact mechanisms through which MT-Ab affects tubular function remain to be elucidated. Further studies with the aim of untangling the mechanism behind the intriguing effect of MT-Ab may provide additional clues to the relationship between the levels of MT-Ab and diabetes and may have broader implications for our understanding of the pathogenesis of damage caused by diabetes.

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