Urinary Cadmium, Impaired Fasting Glucose, and Diabetes in the NHANES III

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OBJECTIVE — Increasing rates of type 2 diabetes worldwide suggest that diabetes may be caused by environmental toxins. Cadmium is a widespread environmental pollutant that accumulates in the pancreas and exerts diabetogenic effects in animals. To test the hypothesis that exposure to cadmium is associated with impaired fasting glucose and type 2 diabetes, we examined the associations between urinary cadmium and the prevalence of impaired fasting glucose (prediabetes) and diabetes in the Third National Health and Nutrition Examination Survey (NHANES III).

RESEARCH DESIGN AND METHODS — We analyzed data on 8,722 adults ≥40 years of age from the NHANES III (1988–1994), a cross-sectional health survey of a nationally representative sample of the noninstitutionalized civilian U.S. population. We studied urinary levels of cadmium (adjusted for urine creatinine) in relation to the prevalence of impaired fasting glucose and diabetes, using the criteria of the American Diabetes Association.

RESULTS — After adjustment for age, ethnicity, sex, and BMI, the odds of impaired fasting glucose and diabetes increased dose-dependently with elevations in urinary cadmium from 0–0.99 to 1.00–1.99 and ≥2 μg/g creatinine (impaired fasting glucose, odds ratio [OR] 1.48, 95% CI 1.21–1.82 and OR 2.05, 95% CI 1.42–2.95; diabetes, OR 1.24, 95% CI 1.06–1.45 and OR 1.45, 95% CI 1.07–1.97).

CONCLUSIONS — In this large cross-sectional study, urinary cadmium levels are significantly and dose-dependently associated with both impaired fasting glucose and diabetes. These findings, which require confirmation in prospective studies, suggest that cadmium may cause prediabetes and diabetes in humans.

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Increasing rates of type 2 diabetes in the U.S. and worldwide suggest that diabetes may be caused by environmental factors (1). For example, epidemiologic studies have implicated arsenic as a possible cause of type 2 diabetes, and a role for other environmental toxins is strongly suspected (2). Recently, we reviewed evidence indicating that exposure to the heavy metal cadmium is a cause of pancreatic cancer (3). Because pancreatic cancer and type 2 diabetes are known to be associated (4), we wondered if type 2 diabetes is also associated with cadmium.

Cadmium is an environmental pollutant with a biological half-life in the whole body exceeding 10 years. Cadmium levels in the body accumulate with age, as only a minute part of the body burden (0.01–0.02%) is excreted per day. The urinary excretion of cadmium is proportional to the body burden and is widely used as a dosimeter of lifetime exposure (5,6). We used the publicly available data collected in the Third National Health and Nutrition Examination Survey (NHANES III) to examine the associations between urinary cadmium and impaired fasting glucose and diabetes.

RESEARCH DESIGN AND METHODS

— The National Center for Health Statistics of the Centers for Disease Control and Prevention conducted the NHANES III in 1988–1994 in a nationwide probability sample of ~39,000 noninstitutionalized U.S. civilians aged 2 months and older (7,8). Information on demographic characteristics, ethnicity, and medical history of diabetes was obtained in a household interview. Information on history of diabetes included questions about prior diagnoses of diabetes by a physician and current use of insulin and oral hypoglycemic agents. In addition, women were asked whether the diagnosis had been made during pregnancy and whether they had been diagnosed with diabetes at some time other than pregnancy. Blood and urine specimens were obtained during physical examination. Urine was collected as a "spot" or untimed sample. Studies of timed urine specimens indicate that urinary cadmium levels do not show significant diurnal variation (9) and that urinary cadmium in spot specimens is well correlated with urinary cadmium detected in 12-h and 24-h specimens (10).

Plasma glucose, measured using a modified hexokinase enzymatic method (8), was used to classify participants under the headings "normal," "impaired fasting glucose," and "diabetes." Subjects with serum cotinine ≤10 ng/ml and who reported smoking fewer than 100 cigarettes in their lifetimes were classified as nonsmokers; otherwise, subjects were classified as ever-smokers. Serum cotinine was measured using high-performance liquid chromatography coupled with an atmospheric pressure chemical ionization tandem mass spectrometer (11). Urine cadmium was measured by Zeeman effect graphite furnace atomic absorption (12), and urine microalbumin

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Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; NHANES III, Third National Health and Nutrition Examination Survey.

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

Table 1—*Association of urinary cadmium with the prevalence of impaired fasting glucose and diabetes among subjects 40 years of age and older in the NHANES III*

Exposure level	Urinary cadmium (μg/g creatinine)	Normal (*n*)	IFG		Diabetes		IFG + diabetes	
			OR (95% CI)	*n*	OR (95% CI)	*n*	OR (95% CI)	*n*
Reference	0–0.99	5,176	1	422	1	879	1	1,301
I	1.00–1.99	1,426	1.48 (1.21–1.82)	150	1.24 (1.06–1.45)	269	1.32 (1.16–1.51)	419
II	≥2	303	2.05 (1.42–2.95)	38	1.45 (1.07–1.97)	59	1.65 (1.28–2.12)	97
	P value for trend			<0.0001		<0.0001		<0.0001

Exposure levels I and II were modeled as two indicator variables. Odds ratios were adjusted for age (continuous), sex, ethnicity (non-Hispanic blacks, Mexican Americans, and others vs. non-Hispanic white), and BMI (continuous). Normal fasting glucose, IFG, and diabetes were defined according to the criteria of the American Diabetes Association: FPG < 110 mg/dl, 110 ≤ FPG < 126 mg/dl, and FPG ≥ 126 mg/dl or current use of insulin or oral hypoglycemic agents, respectively. The *P* value for trend was obtained from logistic model with ordinal variable for the levels of urinary cadmium: reference level, exposure level I, and exposure level II.

was measured using a solid-phase fluorescence immunoassay (13). To adjust for variation in the diluteness of urine, urinary cadmium levels were expressed as urine cadmium/urine creatinine (μg/g). Details regarding the laboratory procedures for these tests are published elsewhere (8).

Subjects were categorized as having impaired fasting glucose (IFG) and diabetes based on fasting (8- to 24-h) plasma glucose (FPG) levels in accordance with the criteria of the American Diabetes Association (14). IFG was defined as 110 ≤ FPG < 126 mg/dl; diabetes was defined as FPG ≥126 mg/dl and/or current use of insulin or oral hypoglycemic agents.

We restricted the analysis to adults 40 years of age and older to exclude cases of type 1 diabetes, which is etiologically distinct from type 2 diabetes. After excluding those with missing values, we analyzed data for the 8,722 subjects for whom there were complete records. We quantified the associations between urinary cadmium and IFG, diabetes, and the combined outcomes (IFG + diabetes) by estimating odds ratios (ORs) and calculating 95% CIs by logistic regression. The cadmium concentration in urine was categorized in three levels: 0–0.99 (reference), 1–1.99 (exposure level I), and ≥2 μg/g creatinine (exposure level II). Exposure levels I and II were modeled as two indicator variables. The ORs were adjusted for age, race, sex, and BMI. The relationship between urinary cadmium (μg/g creatinine) and smoking (ever-smokers versus nonsmokers) was examined using the Wilcoxon-Mann-Whitney test.

RESULTS — The prevalence of IFG, diabetes, and the combined outcomes (IFG + diabetes) were positively associated with urinary cadmium in a dose-dependent manner (Table 1). The odds of the combined outcomes increased by ~30% at each level of urinary cadmium. The magnitudes of these associations were slightly higher for IFG than for diabetes. Similar effects were observed when urinary cadmium was modeled as a continuous variable; the ORs associated with an increase of 1 μg/g creatinine were 1.19 (95% CI 1.08–1.31) and 1.11 (95% CI 1.03–1.20) for IFG and diabetes, respectively.

Because cadmium is known to exacerbate renal damage in diabetes (15), renal damage could cause cadmium to leak into urine, leading to a (noncausal) association between cadmium and diabetes. We therefore restricted the analysis to persons without laboratory evidence of renal damage, using a standard cut-point of urine albumin, ≤30 μg/ml, as described by Paschal et al. (6). This restriction did not appreciably affect our findings (Table 2). Thus, the higher levels of cadmium in the urine of persons with IFG and diabetes do not appear to be the result of renal impairment.

Apart from occupational exposure to cadmium (which should be rare in this cohort), the major source of cadmium exposure among nonsmokers is the diet (16). Among smokers, the major source of cadmium exposure is cigarettes. As has been observed repeatedly (6,16), urinary cadmium levels were significantly higher among ever-smokers: the mean levels of urinary cadmium were 0.92 and 0.63 μg/g creatinine (ever-smokers versus nonsmokers; $P < 0.0001$). We examined the prevalence of the combined outcomes (IFG + diabetes) in ever-smokers and nonsmokers. Despite small variations in effect size at the different levels of exposure, the associations were apparent in both groups (Table 3). Thus, regardless of the source of exposure, diet or cigarettes, higher levels of cadmium in urine were associated with increases in the odds of IFG and diabetes. Finally, we tested the association between smoking and the combined outcomes: the OR adjusted for age, race, sex, and BMI was 1.12 (95% CI 1.00–1.25).

CONCLUSIONS — To our knowledge, this is the first report of an association between cadmium exposure and both IFG and type 2 diabetes. Because this

Table 2—*Association of urinary cadmium with the prevalence of impaired fasting glucose and diabetes among adults 40 years of age and older with normal albumin excretion in the NHANES III*

Exposure level	Urinary cadmium (μg/g creatinine)	Normal (*n*)	IFG + diabetes	
			OR (95% CI)	*n*
Reference	0–0.99	4,577	1	913
I	1.00–1.99	1,208	1.29 (1.10–1.51)	276
II	≥2	233	1.61 (1.18–2.21)	57

Exposure levels I and II were modeled as two indicator variables. Normal fasting glucose, IFG, and diabetes defined as in Table 1. Odds ratios were adjusted as indicated in Table 1. Urinary albumin ≤30 μg/ml.

Table 3—*Association of urinary cadmium with the prevalence of impaired fasting glucose and diabetes among non- and ever-smokers 40 years of age and older in the NHANES III*

Exposure level	Urinary cadmium (μg/g creatinine)	IGT + diabetes vs. normal			
		Non-smokers		Ever-smokers	
		OR (95% CI)	*n*	OR (95% CI)	*n*
Reference	0–0.99	1	632/2,589	1	669/2,587
I	1.00–1.99	1.47 (1.18–1.86)	134/365	1.26 (1.06–1.49)	285/1,061
II	≥2	1.40 (0.83–2.35)	22/64	1.74 (1.29–2.34)	75/239

Exposure levels I and II were modeled as two indicator variables. Normal fasting glucose, IFG, and diabetes defined as in Table 1. Odds ratios were adjusted as indicated in Table 1. *n*, number of case/control subjects.

association is observed among persons without evidence of renal damage and among persons with IFG (i.e., prediabetes), these data suggest that exposure to cadmium precedes the development of diabetes. In addition, we observed a small association between smoking, as measured by serum cotinine, and the combined outcomes (IFG + diabetes). This finding is consistent with several (but not all) prospective studies of smoking and type 2 diabetes (17) and with the results of a large cross-sectional study that found a significant association between smoking and glycosylated hemoglobin (18).

In rats and mice, cadmium damages pancreatic β-cells, reduces glucose tolerance, and is diabetogenic (19–22). Our analyses suggest that cadmium may have similar effects in humans. However, it is important to emphasize that these results were obtained in a cross-sectional study in which exposure and disease were measured at the same time. A prospective study, in which cadmium levels are determined before the development of disease, will be required to establish a causal basis for these associations.

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