Inverse Association of Plasma Vanadium Levels With Newly Diagnosed Type 2 Diabetes in a Chinese Population

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Vanadium compounds have been proposed to have beneficial effects on the pathogenesis and complications of type 2 diabetes. Our objective was to evaluate the association between plasma vanadium levels and type 2 diabetes. We performed a case-control study involving 1,598 Chinese subjects with or without newly diagnosed type 2 diabetes (December 2004–December 2007). Cases and controls were frequency-matched by age and sex. Plasma vanadium concentrations were measured and compared between groups. Analyses showed that plasma vanadium concentrations were significantly lower in cases with newly diagnosed type 2 diabetes than in controls \( (P = 0.001) \). Mean plasma vanadium levels in participants with and without diabetes were 1.0 \( \mu \)g/L and 1.2 \( \mu \)g/L, respectively. Participants in the highest quartile of plasma vanadium concentration had a notably lower risk of newly diagnosed type 2 diabetes (odds ratio = 0.26, 95% confidence interval: 0.19, 0.35; \( P < 0.001 \)), compared with persons in the lowest quartile. The trend remained significant after adjustment for known risk factors and in further stratification analyses. Our results suggested that plasma vanadium concentrations were inversely associated with newly diagnosed type 2 diabetes in this Chinese population.

diabetes mellitus, type 2; trace elements; vanadium

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

The rapid worldwide increase in the prevalence of type 2 diabetes has become a serious public health problem (1). On the one hand, diabetes may result in abnormal metabolism and altered levels of trace elements (2). On the other hand, early imbalances in levels of specific trace elements may disrupt insulin metabolism and normal glucose homeostasis (3).

Vanadium represents the 21st most abundant transition metal in the earth’s crust and is ubiquitously distributed (4, 5). The total body pool of vanadium in humans ranges from 100 \( \mu \)g to 200 \( \mu \)g as determined by the analysis of body fluids, organs, and tissues (6). Research has shown that vanadium is a transition metal that helps regulate glucose homeostasis and insulin sensitivity (7, 8). Vanadium compounds have been proposed to have a beneficial effect on the pathogenesis and complications of type 2 diabetes. Therefore, it is of great significance to determine the concentrations of this essential element in biological samples. However, little data exist about the association between vanadium levels and type 2 diabetes, and the role of this element in overall health and in this disease specifically is still unclear. The objective of the present study was to assess the association between plasma levels of vanadium and newly diagnosed type 2 diabetes cases in a Chinese population and to quantify this association in the context of important confounding factors.

METHODS

Study population

The study protocols were approved by the Ethics Committee of Tongji Medical College (Huazhong University of Science and Technology, Wuhan, China). All participants
provided written informed consent. The present study included 802 patients with cases of newly diagnosed type 2 diabetes and 796 comparison controls. From December 2004 to December 2007, we recruited 819 case subjects in consecutive order from the outpatient clinics in the Department of Endocrinology at Tongji Hospital, which is affiliated with Tongji Medical College. During the same period, we identified and recruited 809 control subjects from an unselected population undergoing routine health examinations at the same hospital. Controls were frequency-matched with cases on age (in 5-year age groups) and sex. All subjects enrolled were of Chinese Han ethnicity.

All diabetes cases and controls met the respective diagnostic criteria recommended by the World Health Organization in 2006 (9). To avoid possible confounding effects caused by use of antidiabetic medications, we included only persons with newly diagnosed type 2 diabetes. Thus, most type 2 diabetes cases in the present study were at an early stage of type 2 diabetes progression. We restricted all study subjects to participants with no acute or chronic inflammatory diseases, acute respiratory infection, cancer, or known history of diabetes. For the present study, we excluded 19 participants with missing plasma vanadium data and 11 participants with missing values on other variables of interest, thus leaving a total of 1,598 subjects for the final analysis.

As noted above, diagnosis of type 2 diabetes was based on the 2006 World Health Organization criteria (9). Persons with a fasting plasma glucose concentration of ≥7.0 mmol/L (≥126 mg/dL) or a 2-hour plasma glucose concentration of ≥11.1 mmol/L (≥200 mg/dL) were diagnosed as having type 2 diabetes. Participants with a fasting plasma glucose concentration less than 6.1 mmol/L (<110 mg/dL) and a 2-hour plasma glucose concentration less than 7.8 mmol/L (<140 mg/dL) were designated controls. None of the control participants reported taking any antidiabetic medications.

Information collected by questionnaire included age, sex, family history of diabetes in first-degree relatives, histories of diabetes, hyperlipidemia, and hypertension, cigarette smoking (yes/no), alcohol consumption (yes/no), and physical activity (low, moderate, or high). Height (m), weight (kg), and blood pressure (mm Hg) were measured using standardized techniques. Body mass index (BMI) was calculated by dividing measured weight in kilograms by measured height in meters squared. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, self-reported current use of antihypertensive medication, or self-reported physician’s diagnosis. All participants underwent a complete physical examination in the morning after an overnight fast; venous blood samples drawn from the participant’s antecubital vein were collected in heparinized tubes for plasma separation.

**Laboratory measurements**

Plasma concentrations of biochemical parameters, including fasting plasma glucose, 2-hour postglucose load, total cholesterol, and triglycerides, were measured using previously described methods (10).

Plasma vanadium levels were measured in the Ministry of Education Key Lab of Environment and Health at Tongji Medical College by means of inductively coupled plasma mass spectrometry (7700 series; Agilent Technologies, Tokyo, Japan). Inductively coupled plasma mass spectrometry can detect most elements in the periodic table at concentrations as low as 1 part per trillion. The sample is ionized by the inductively coupled plasma. Subsequently, a mass spectrometer separates and quantifies those ions (11, 12). The detection limit was 0.0001 μg/L, and 0.2% of study participants had plasma vanadium levels below the detection limit. Intra- and interassay coefficients of variation were 4% for plasma levels of biochemical parameters and 3% for plasma vanadium levels.

**Statistical analysis**

Statistical analyses were performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, Illinois). Comparisons between diabetes cases and controls were performed by t test (continuous variables, normal distribution) or χ² test (categorical variables).

For risk analyses, multivariate logistic regression analysis was used to estimate the independent association of plasma vanadium concentration with the likelihood of newly diagnosed type 2 diabetes. Hosmer-Lemeshow tests were used to evaluate whether the model provided a good fit. Adjustments were made for age and sex (model 2), for BMI and family history of diabetes (model 3), for smoking, alcohol drinking, and hypertension (model 4), and for fasting glucose level (model 5). For calculation of the odds ratios for newly diagnosed type 2 diabetes, plasma vanadium concentrations were categorized in the following quartiles according to the control group: quartile 1, 0.87–1.09 μg/L; quartile 2, 1.10–1.43 μg/L; quartile 3, 1.44–2.0 μg/L; and quartile 4, >2.0 μg/L. To further explore the shape of the relationship between plasma vanadium concentration and type 2 diabetes, we used restricted cubic splines with 5 knots at the 5th, 25th, 50th, 75th, and 95th percentiles of the plasma vanadium distribution (13).

To estimate the consistency of the findings according to participant characteristics, we performed analyses stratified by age (<50 years/≥50 years), sex, BMI (<24/≥24), family history of diabetes, smoking, alcohol drinking, and hypertension. Interaction tests were also used to measure whether risks differed between the strata analyzed. A P value less than or equal to 0.05 was considered statistically significant. All P values were 2-sided.

**RESULTS**

Table 1 shows demographic and clinical characteristics of the study subjects. Plasma vanadium levels were significantly decreased in patients with newly diagnosed type 2 diabetes compared with controls. The mean plasma vanadium levels were 1.0 (standard deviation, 0.6) μg/L in participants with newly diagnosed type 2 diabetes and 1.2 (standard deviation, 0.6) μg/L in those without diabetes (P = 0.001). Compared with controls, participants with newly diagnosed type 2 diabetes had higher BMIs and higher prevalences of family histories of diabetes and hypertension. As expected, when evaluating fasting plasma glucose, we observed higher fasting plasma
glucose levels in newly diagnosed type 2 diabetes cases than in the controls (Table 1).

Table 2 presents logistic analysis results (odds ratios) for the association of newly diagnosed type 2 diabetes with plasma vanadium concentration, by quartile of its distribution in controls. In unadjusted analysis, a significant inverse association was found between plasma vanadium concentration and newly diagnosed type 2 diabetes when comparing the highest quartile of plasma vanadium with the lowest (crude odds ratio (OR) = 0.26, 95% confidence interval (CI): 0.19, 0.35; \( P < 0.001 \)). After adjustment for age, sex, BMI, and family history of diabetes, newly diagnosed type 2 diabetes retained a statistically significant association with plasma vanadium when comparing the highest and lowest quartiles of plasma vanadium concentration (adjusted OR = 0.31, 95% CI: 0.21, 0.47; \( P < 0.001 \)). Additional adjustment for smoking, alcohol drinking, hypertension, and fasting glucose level did not materially alter the association (adjusted OR = 0.23, 95% CI: 0.14, 0.38; \( P < 0.001 \)). In spline regression models, the odds of type 2 diabetes decreased significantly with increasing vanadium concentrations at less than 1.7 \( \mu \text{g/L} \) plasma vanadium, and then a slight decline was observed (Figure 1). The nonlinear spline terms were not statistically significant (\( P > 0.05 \)), indicating that the relationship between plasma vanadium concentrations and type 2 diabetes was nonlinear. Furthermore, Spearman correlation analysis showed a negative correlation between vanadium concentrations and fasting glucose in the control group (\( P = 0.218 \)).

Table 1. Characteristics of the Study Population by Diabetes Status, Wuhan, People’s Republic of China, 2004–2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetes Cases (( n = 802 ))</th>
<th>Controls (( n = 796 ))</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) No. %</td>
<td>Mean (SD) No. %</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>50.8 (10.9) 49.5 (11.7)</td>
<td>49.5 (11.7)</td>
<td>0.638</td>
</tr>
<tr>
<td>Female sex</td>
<td>340 42.6 312 39.2</td>
<td>312 39.2</td>
<td>0.179</td>
</tr>
<tr>
<td>Body mass index(^a)</td>
<td>23.0 (3.9) 22.9 (4.0)</td>
<td>22.9 (4.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>287 35.8 244 30.6</td>
<td>244 30.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>282 35.2 230 28.9</td>
<td>230 28.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>121 20.5 60 12.5</td>
<td>60 12.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension(^b)</td>
<td>255 42.9 141 18.9</td>
<td>141 18.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Vanadium level, ( \mu \text{g/L} )</td>
<td>1.0 (0.6) 1.2 (0.6)</td>
<td>1.2 (0.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose level, mmol/L</td>
<td>9.8 (3.1) 4.6 (0.6)</td>
<td>4.6 (0.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
\(^a\) Weight (kg)/height (m)\(^2\).
\(^b\) Hypertension was defined as systolic blood pressure \( \geq 140 \) mm Hg, diastolic blood pressure \( \geq 90 \) mm Hg, self-reported current use of antihypertensive medication, or self-reported physician’s diagnosis.

Table 2. Odds Ratios for Newly Diagnosed Type 2 Diabetes by Quartile of Plasma Vanadium Level, Wuhan, People’s Republic of China, 2004–2007\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>1 (&lt;0.87)</th>
<th>2 (0.87–1.09)</th>
<th>3 (1.10–1.43)</th>
<th>4 (≥1.44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. OR 95% CI</td>
<td>No. OR 95% CI</td>
<td>No. OR 95% CI</td>
<td>No. OR 95% CI</td>
</tr>
<tr>
<td>No. of cases</td>
<td>307 216</td>
<td>199 80</td>
<td>198</td>
<td>198</td>
</tr>
<tr>
<td>No. of controls</td>
<td>198 201</td>
<td>199</td>
<td>198</td>
<td>198</td>
</tr>
<tr>
<td>Model</td>
<td>1 (crude)</td>
<td>2(^b)</td>
<td>3(^c)</td>
<td>4(^d)</td>
</tr>
<tr>
<td>1.00 Referent</td>
<td>0.69 0.53, 0.90</td>
<td>0.65 0.50, 0.85</td>
<td>0.64 0.44, 0.93</td>
<td>0.62 0.42, 0.92</td>
</tr>
<tr>
<td>1.00 Referent</td>
<td>0.73 0.55, 0.96</td>
<td>0.74 0.56, 0.98</td>
<td>0.72 0.47, 0.99</td>
<td>0.71 0.48, 0.99</td>
</tr>
<tr>
<td>1.00 Referent</td>
<td>0.65 0.44, 0.95</td>
<td>0.64 0.44, 0.93</td>
<td>0.63 0.43, 0.92</td>
<td>0.62 0.42, 0.92</td>
</tr>
<tr>
<td>1.00 Referent</td>
<td>0.58 0.38, 0.88</td>
<td>0.58 0.38, 0.88</td>
<td>0.57 0.37, 0.88</td>
<td>0.56 0.37, 0.88</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
\(^a\) \( P < 0.001 \) for all models.
\(^b\) Results were adjusted for age and sex.
\(^c\) Results were adjusted for model 2 variables, body mass index (weight (kg)/height (m))\(^2\), and family history of diabetes.
\(^d\) Results were adjusted for model 3 variables, smoking, alcohol drinking, and hypertension.
\(^e\) Results were adjusted for model 4 variables and fasting glucose level.
The current study indicated that decreased plasma vanadium levels were associated with increased odds of newly diagnosed type 2 diabetes. The inverse association between plasma vanadium concentrations and type 2 diabetes could not be explained by possible confounding effects caused by adjustment factors such as age, sex, BMI, and family history of diabetes. These observations held in the analyses with additional adjustment for smoking, alcohol drinking, hypertension, and fasting glucose level.

Daily intake of vanadium, which is derived mainly from black pepper, mushrooms, parsley, dill seeds, shellfish, and spinach, is estimated to range from 10 μg to 160 μg (6, 14). Perhaps because of differences between the foods themselves and between the analytical methods used, the few data on

Figure 2 shows the association between plasma vanadium concentration and diabetes risk by age, sex, BMI, family history of diabetes, smoking, alcohol drinking, and hypertension. The inverse association between plasma vanadium levels and newly diagnosed type 2 diabetes was consistent for all subgroups examined.

**DISCUSSION**

The current study indicated that decreased plasma vanadium levels were associated with increased odds of newly diagnosed type 2 diabetes. The inverse association between plasma vanadium concentrations and type 2 diabetes could not be explained by possible confounding effects caused by adjustment factors such as age, sex, BMI, and family history of diabetes. These observations held in the analyses with additional adjustment for smoking, alcohol drinking, hypertension, and fasting glucose level.

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Vanadium concentrations in food vary considerably. Concentrations of vanadium in the human diet range from 19 μg/kg to 50 μg/kg (mean = 32 μg/kg) (15). The concentration of vanadium in human milk has been reported to be 0.1–0.2 ng/g (16). If drinking 1 L of human milk per day, an infant would have a daily vanadium intake of 0.1–0.2 μg (17). The concentration of vanadium in drinking water depends significantly on geographical location and ranges from about 0.2 μg/L to more than 100 μg/L (18).

Vanadium levels in the blood or tissue of persons with diabetes have been poorly evaluated in the literature. Vanadium status in diabetic patients is still unclear. A previous study (19) indicated that higher vanadium levels were found in the erythrocytes of diabetic persons than in controls. However, that study involved a small number of cases (n = 53). In contrast, in an animal study, results showed that the tissue vanadium content of the liver was significantly lower in diabetic Wistar rats than in normal rats (20). This finding is in accordance with our results. In the present study, we found that plasma vanadium levels were significantly lower in patients with type 2 diabetes than in control subjects. Our findings also suggested a significant association between plasma vanadium level and type 2 diabetes. An explanation for these findings cannot be definitively given. It may be necessary for plasma vanadium levels to be maintained within the scope of homeostatic regulation. Owing to reduced plasma vanadium levels, the bodies of patients with type 2 diabetes are unable to benefit from the insulin-mimetic properties of this metal (21).

Vanadium compounds can inhibit gluconeogenesis and the activities of the gluconeogenic enzymes (22). These compounds can stimulate glucose uptake, glycogen synthesis, and lipid synthesis in adipose, muscle, and hepatic tissues (23, 24). The insulin-like potential of vanadium has been indicated in both in vitro and in vivo systems (7, 25, 26). In animal models of type 2 diabetes, the antidiabetic role of various vanadium compounds has been examined. These reports have suggested that vanadium may improve glucose homeostasis and insulin resistance (27–29). In addition, in a limited number of patients with type 2 diabetes, several studies have indicated that vanadium decreases plasma glucose levels (8, 30, 31).

In a study of rats, vanadium complexes showed insulin-like effects by activating the mitogen-activated protein kinase pathway (32). Vanadium-induced phosphatidylinositol 3-kinase activation has been found to play a critical role in mediating vanadyl sulfate- and sodium orthovanadate-induced stimulation of glucose uptake (33), glycogen synthesis (34), and glucose transporter translocation (35) in several types of cells. Considering that protein kinase B has been implicated in mediating the physiological response of insulin in glycogen synthesis (36) and glucose uptake (37), it is more likely that the phosphatidylinositol 3-kinase/protein kinase B signaling system is one of the mechanisms that leads to the insulin-like effects of vanadium compounds. Moreover, vanadium salts can cause an increase in the phosphotyrosine content of insulin receptor substrate 1 by inhibiting protein tyrosine phosphatase activity and thus stimulating the insulin-signaling pathway (38, 39). Taken together and based on available data, vanadium activates several key signaling events of the insulin-signaling pathways and thus contributes to their insulin-like effects.

Conversely, if there is a lower concentration of vanadium, these effects may be severely affected.

Despite the impressive antidiabetic effects of vanadium compounds, vanadium compounds have also been associated with toxic effects (40). The most common are gastrointestinal distress (such as diarrhea), dehydration, and decreased fluid and food uptake (40). Organic vanadium compounds may be much safer than inorganic vanadium salts. In one rat study, diarrhea was observed in half of the rats receiving vanadyl sulfate, but not in those treated with the organic compounds (41). Some studies have also found other kinds of toxicity of vanadium salts, including teratogenicity, hepatotoxicity, nephrotoxicity, and developmental/reproductive toxicity (40, 42). Furthermore, there is no consensus on the efficacy of vanadium in the oral treatment of diabetes mellitus. A systematic review of oral vanadium supplementation showed no high-quality evidence that it improves glycemic control in type 2 diabetes (43). Therefore, the toxicity of various vanadium compounds, as well as their efficacy as potential treatments for human diabetes, needs to be further evaluated before undertaking long-term clinical trials in humans.

Although our study was relatively large, with a total of 1,598 participants, it had several limitations. First, despite adjusting the results of our analyses to reduce the potential for confounding, our findings may have been subject to residual confounding or the influence of unmeasured factors. The associations of vanadium levels with type 2 diabetes could relate to dietary or other lifestyle factors, rather than the effects of lower vanadium levels. Second, all participants were of Chinese Han ethnicity, which minimized the effects of confounding by ethnic background. In future studies carried out in ethnically diverse populations, researchers should attempt to generalize these findings to other populations. Additionally, the case-control study design did not allow us to establish a temporal relationship, and it was very difficult to avoid recall and selection biases. Thus, these findings should be verified in further prospective cohort studies.

In conclusion, our results suggested that plasma vanadium levels are significantly lower in newly diagnosed type 2 diabetes cases than in healthy control subjects in a Chinese population. Such findings contribute to knowledge regarding the prevention and treatment of type 2 diabetes. Whether vanadium supplementation is beneficial for preventing type 2 diabetes needs to be determined in long-term clinical trials.

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