## Letter to the Editor

# Nail Selenium Level and Diabetes in Older People in Rural China*

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**This cross-sectional study aimed to examine the association between selenium levels and diabetes in an older population with life-long natural exposure to selenium in rural China. A total of 1856 subjects aged 65 years or older from four Chinese rural counties with different environmental selenium levels were evaluated. Analysis of covariance models and logistic regression models were used to examine the relationship between nail selenium levels and serum glucose, serum insulin, insulin resistance [using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)], and the risk of diabetes. The mean nail selenium level was 0.461 μg/g and the prevalence rate of diabetes was 8.3% in this population. The mean nail selenium level was significantly higher in the group with diabetes than in the group without diabetes (*P*<0.0001). The adjusted odds ratios for diabetes were 2.65 (95% *CI*: 1.48 to 4.73), 2.47 (95% *CI*: 1.37 to 4.45), and 3.30 (95% *CI*: 1.85 to 5.88) from the second selenium quartile to the fourth quartile, respectively, compared with the first quartile group. The mean serum glucose and HOMA-IR in the higher selenium quartile groups were significantly higher than those of the lowest quartile group. However, no significant differences in insulin were observed among the four quartile groups. A long-term, higher level of exposure to selenium may be associated with a higher risk of diabetes. Future studies are needed to elucidate the association between selenium and insulin resistance.**

Diabetes is a major contributor to the global burden of disease, with an expected prevalence of 552 million by 2030[1]. Although the mechanisms underlying diabetes are not fully understood, growing evidence has shown that oxidative stress plays an important role in the development of diabetes[2]. As an essential micronutrient with antioxidant properties, selenium (Se) had been hypothesized to have the potential to prevent diabetes[3], according to evidence from animal studies and human studies. In the prospective observational Epidemiology of Vascular Ageing (EVA) study, higher baseline plasma Se levels were correlated with a lower risk of dysglycemia in older French men during a 9 year follow-up period[4].

However, this hypothesis has been challenged by findings from a few recent studies. The results of a randomized clinical trial[5], the Nutritional Prevention of Cancer Trial, have indicated that Se supplementation could increase the risk of type-2 diabetes mellitus (T2DM). More evidence of the positive association between blood Se and the risk of diabetes can be found in several cross-sectional and longitudinal studies[6-8]. Moreover, recent animal studies support the results of human studies, indicating that Se supplementation could induce hyperinsulinemia, insulin resistance, and glucose intolerance in mice, rats, and pigs[9-10].

In view of the inconsistency in the findings on the relationship between Se and diabetes, more evidence from observational studies are needed, especially in populations with lower Se levels. Older populations in rural China represent a unique opportunity for studying the relationship between long-term exposure to Se and the risk of diabetes because they are unusually stable, most residents live in the same village throughout their entire life, consume food that is locally grown, and rarely take dietary supplements. In the 2003-2005 baseline

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evaluation of the Selenium and Cognitive Decline Study Cohort study[11], the risk of self-reported diabetes increased with the increase in the nail Se level, and nail Se concentrations were significantly correlated with blood Se levels. In this cross-sectional study, with findings from a second follow-up, we evaluate the association between long-term Se levels and diabetes with more accurate measures of diabetes.

Participants were recruited from the Selenium and Cognitive Decline Study, a longitudinal epidemiologic project funded by the National Institutes of Health that examined the long-term impact of Se on cognitive decline in an older population in rural China[11]. During the third phase of cognitive evaluation (2010-2012), 1856 permanent residents aged 65 years or older who provided blood and nail samples were enrolled in this study, including 1067 participants from the original cohort and 789 new participants following the same principle. The participants lived in four counties, two in Sichuan Province and two in Shandong Province. These sites were selected because of the different environmental Se levels and similar levels of other trace elements according to the results of a previous study in China. None of the four study sites were located in regions with endemic diseases, including Keshan disease, Kaschin-Beck disease, goiter, cretinism, and fluorosis. The study was approved by the Indiana University Institutional Review Board and the Institute for Environmental Health and Related Safety, Chinese Center for Disease Control and Prevention. A written informed consent was signed by all participants.

Nail samples were collected and stored in clean plastic bags at the time of the interview. Nail samples were cleaned by ultrasound, soaked in nitric acid and perchloric acid, digested on an electric hot plate, and reduced in hydrochloric acid. The pretreated samples were restored to room temperature, immersed in potassium ferricyanide and hydrochloric acid solutions, and diluted with deionized water to a volume of 10 mL. The concentration of Se was determined by atomic fluorescence spectrometry at a wavelength of 196.0 nm.

In the 2010-2012 survey, fasting peripheral blood samples were collected, and the plasma fraction was isolated within four hours. All samples were stored at -80 °C before analysis. Plasma glucose was measured using the Roche Diagnostic Kits (F. Hoffmann-La Roche Ltd) in a Hitachi Automatic Biochemistry Analyzer 9700, and insulin was measured using DRG ELISA kits (DRG-international, Inc.) made in German.

Diabetes was defined as the self-reported use of antidiabetic medications or fasting plasma glucose (FBG) equal to or greater than 7.0 mmol/L[12]. Insulin resistance (HOMA-IR) was calculated using the equation: HOMA-IR=(glucose×insulin)/22.5, and glucose was measured in mmol/L.

Information on age, gender, education, ethnicity, alcohol consumption, smoking, use of antidiabetic medications and physical activity were collected using a questionnaire. The ethnicity of all study participants was Han Chinese. Physical activity was classified into three categories as low, moderate, or high according to the Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire. Height and weight were measured during the interviews. Body mass index (BMI) was calculated as weight in kilogram divided by height in square meters.

Comparisons of demogr- aphic characteristics and medical history between the diabetic group and the non-diabetic group were conducted using chi-square tests for categorical variables and *t*-tests for continuous variables. The participants were divided into four groups (Q1, Q2, Q3, and Q4) according to the quartiles of nail Se concentration. The cutoff values for Se were 0.320, 0.467, and 0.568 μg/g. In addition to Se levels, the following variables were considered potential confounding factors related to diabetes: age, gender, BMI, education, smoking, alcohol consumption, and physical activity. A logistic regression model was used to estimate odds ratios and 95% confidence intervals for diabetes between the four Se quartile groups for all participants. The cutoff value for the BMI group was 18.5 and 25.0, and the cutoff value for the age group was >75. Analysis of covariance (ANCOVA) models were used to calculate the adjusted differences in glucose, insulin, and HOMA-IR, and compare these differences between the four Se quartile groups. All analyses were performed using SAS software version 9.1 for Windows (SAS Institute Inc., Cary, North Carolina, USA). *P* values smaller than 0.05 were considered statistically significant.

For the total sample of 1856 participants, the mean nail Se level was 0.461±0.190 μg/g and the mean age was 73.8±5.9 years. The overall prevalence of diabetes was 8.3%, and 163 participants met the criteria for diabetes. The mean nail Se level in the group with diabetes was

0.523±0.185 μg/g, which was significantly higher than that in the group without diabetes (0.455±0.189 μg/g). Significant differences in BMI, glucose, insulin, and HOMA-IR were also observed between the sexes and between the groups with and without diabetes (Table 1).

The characteristics of the study participants by nail Se quartile groups are shown in Table 2. Nail Se concentrations were positively associated with BMI, glucose, insulin, and HOMA-IR. The higher Se quartile groups had fewer men and lower rates of alcohol consumption, smoking, and moderate and high physical activity. No difference in age was observed between the four Se quartile groups.

**Table 1.** Characteristics of the Study Population According to the Diabetes Status

| Characteristics* | Overall (*n*=1856) | Non-diabetes (*n*=1693) | Diabetes (*n*=163) | *P*-value |
|---|---|---|---|---|
| Age (y) | 73.8±5.9 | 73.8±5.9 | 73.7±6.1 | 0.7855 |
| Female (%) | 53.50 | 52.33 | 65.64 | 0.0011 |
| Ever attended school (%)# | 49.41 | 49.68 | 46.63 | 0.4573 |
| BMI (kg/m$^2$) | 23.08±3.77 | 22.98±3.72 | 24.20±4.11 | <0.0001 |
| Alcohol consumption (%) | 38.63 | 39.28 | 31.90 | 0.0647 |
| Smoking (%) | 39.66 | 40.22 | 33.74 | 0.1061 |
| Physical activity | | | | 0.7718 |
| Low (%) | 4.75 | 4.84 | 3.73 | |
| Moderate (%) | 16.29 | 16.18 | 17.39 | |
| High (%) | 78.88 | 78.97 | 78.88 | |
| Glucose (mmol/L) | 4.77±1.69 | 4.41±0.89 | 8.48±3.02 | <0.0001 |
| Insulin (μU/mL) | 8.11±7.69 | 7.62±6.77 | 13.27±13.06 | <0.0001 |
| HOMA-IR | 1.88±2.69 | 1.56±1.58 | 5.29±6.72 | <0.0001 |
| Selenium (μg/g) | 0.461±0.190 | 0.455±0.189 | 0.523±0.185 | <0.0001 |

***Note.*** *Described as mean±SD or percentages. #Received school education, including elementary education and higher education.

**Table 2.** Characteristics of the Study Population by Nail Selenium Quartile Groups

| Characteristics* | Quartile Groups of Nail Selenium | | | | *P*-trend |
|---|---|---|---|---|---|
| | Q1 (<0.320 μg/g) | Q2 (0.320-0.466 μg/g) | Q3 (0.467-0.567 μg/g) | Q4 (≥0.568 μg/g) | |
| *N* | 465 | 468 | 462 | 461 | |
| Age (y) | 73.26±6.01 | 73.57±5.99 | 74.08±5.96 | 74.20±5.67 | 0.0545 |
| Female (%) | 43.87 | 47.86 | 57.36 | 65.08 | <0.0001 |
| BMI (kg/m$^2$) | 21.75±3.04 | 22.55±3.74 | 23.53±3.74 | 24.52±3.94 | <0.0001 |
| Alcohol consumption (%) | 48.17 | 41.45 | 33.12 | 31.67 | <0.0001 |
| Smoking (%) | 39.14 | 47.65 | 39.39 | 32.32 | <0.0001 |
| Physical activity | | | | | 0.0228 |
| Low (%) | 2.59 | 4.91 | 5.21 | 6.29 | |
| Moderate (%) | 14.01 | 14.74 | 19.52 | 16.92 | |
| High (%) | 83.41 | 80.34 | 75.27 | 76.79 | |
| Glucose (mmol/L) | 4.07±1.20 | 4.95±2.02 | 4.94±1.41 | 5.11±1.79 | <0.0001 |
| Insulin (μU/ml) | 6.99±6.32 | 7.89±8.03 | 8.75±9.01 | 8.80±6.98 | 0.0007 |
| HOMA-IR | 1.34±1.48 | 1.91±3.41 | 2.08±2.81 | 2.19±2.64 | <0.0001 |
| Selenium (μg/g) | 0.232±0.054 | 0.408±0.040 | 0.516±0.029 | 0.691±0.166 | <0.0001 |

***Note.*** *Described as mean±SD or percentages.

The association between the Se quartiles and diabetes after adjusting for age, gender, BMI, smoking, alcohol consumption, and physical activity is shown in Table 3. The adjusted odds ratios for diabetes were 2.65 (95% *CI*: 1.48 to 4.73), 2.47 (95% *CI*: 1.37 to 4.45), and 3.30 (95% *CI*: 1.85 to 5.88) from the second Se quartile to the fourth quartile, respectively, compared with the first quartile group. The prevalence of diabetes was not significantly different between the top three quartile groups.

Significant differences in the mean fasting plasma glucose and HOMA-IR were observed (Table 3), and the fasting plasma glucose and HOMA-IR in the quartile groups 2, 3, and 4 were significantly higher than those in the first quartile group. However, no significant difference in insulin was observed between the four quartile groups.

In this cross-sectional study involving older people aged 65 years or older in China, we examined the association between nail Se levels and the prevalence of diabetes. Our results suggest that higher nail Se levels are associated with higher fasting plasma glucose, HOMA-IR, and a higher prevalence of diabetes. The results of this study were consistent with those of the 2003-2005 baseline evaluation in the same cohort[11], which indicated a trend of increase in the prevalence of self-reported diabetes from the lowest to the highest Se quintile groups.

Our findings are consistent with those of several other studies. The third National Health and Nutrition Examination Survey (NHNES III) 1988-1994[6] and NHANES 2003-2004[7], which had the same cross-sectional design used in our study, consistently indicated a significant positive association between serum Se levels and the risk of diabetes. A prospective study conducted in Northern Italy found that increased dietary Se intake was associated with an increased risk of T2DM[8]. The results from the Nutritional Prevention of Cancer Trial[5] indicated that Se supplementation (200 μg/d) increased the incidence of T2DM compared with the placebo group [hazard ratio (*HR*), 1.55; 95% *CI*: 1.03 to 2.33]. Further evidence for this positive association is found in a recent case-control study involving Chinese populations and indicated that higher plasma levels of Se might increase the risk of metabolic syndrome and increase fasting plasma glucose[13].

However, an inverse association was observed in some studies. Results from cross-sectional and nested case-control analyses in the Health Professionals Follow-up Study (HPFS) in the United States suggested that the toenail Se levels were lower among diabetic men with or without cardiovascular disease (CVD) than among healthy controls[14]. A pooled longitudinal analysis that used data from the Health Professionals Follow-up Study and Nurses' Health Study[15] confirmed that at dietary intake levels, individuals with higher toenail Se levels are at lower risk of T2DM. Moreover, the Epidemiology of Vascular Ageing (EVA) longitudinal study[4] conducted in France indicated that the risk of dysglycemia was significantly lower in men with plasma Se levels in the highest tertile (T3: 1.19-1.97) than in those in the lowest tertile (T1: 0.18-1.00) [*HR*=0.48 (0.25-0.92)]; however, a significant relationship was not observed in women.

Other longitudinal studies and randomized controlled trials found no association between Se levels and the risk of incident diabetes[16-17]. It is of

**Table 3.** Adjusted Odds Ratios (95% *CI*) for Diabetes and Adjusted Differences in Fasting Plasma Glucose, Insulin, and HOMA-IR

| Characteristics* | Quartile Groups of Nail Selenium | | | | *P*-trend |
|---|---|---|---|---|---|
| | Q1 (<0.320 μg/g) | Q2 (0.320-0.466 μg/g) | Q3 (0.467-0.567 μg/g) | Q4 (≥0.568 μg/g) | |
| Diabetes* | 1.00 (reference) | 2.65 (1.48, 4.73) | 2.47 (1.37, 4.45) | 3.30 (1.85, 5.88) | 0.0008 |
| Glucose** | 0.00 (reference) | 0.72 (0.54, 0.91) | 0.72 (0.53, 0.91) | 0.73 (0.54, 0.93) | <0.0001 |
| Insulin** | 0.00 (reference) | 0.52 (-0.52, 1.57) | 0.68 (-0.39, 1.74) | 0.35 (-0.74, 01.43) | 0.6266 |
| HOMA-IR** | 0.00 (reference) | 0.41 (0.07, 0.76) | 0.47 (0.07, 0.76) | 0.34 (0.08, 0.80) | 0.0329 |

***Note.*** *Logistic model for 1856 subjects adjusted for age, gender, BMI, education, smoking, alcohol consumption, and physical activity. **ANCOVA model for 1784 subjects without the use of antidiabetic medication adjusted for age, gender, BMI, education, smoking, alcohol consumption, and physical activity.

note that the Se levels in different cohorts differed by the geographic location of the study population, and Se measurements using different biological samples might limit the comparison of the results. Furthermore, most studies investigated Se-replete populations from developed countries, and data on Se-deplete populations from developing countries are limited. A recent meta-analysis using data from five observational studies indicated a significantly higher prevalence of T2DM in the highest blood Se category compared with the lowest level category [*OR*=1.63 (1.04-2.56)], and a positive association between serum Se levels and T2DM was observed in populations with relatively low levels (<97.5 μg/L) and high levels (>132.5 μg/L) of serum Se, suggesting a U-shaped non-linear dose-response relationship between serum Se and T2DM[18].

The inconsistent results from different studies may be due to differences in the study design (cross-sectional versus longitudinal), age distribution of the study participants, differences in the Se levels, or differences in the distribution of diabetes-related confounders, including lifestyle and genetic susceptibility to diabetes. Therefore, more longitudinal studies, including extensive investigations on confounders, are necessary.

To date, most population-based studies have only considered the outcome effect of plasma glucose or T2DM; however, the association between Se and insulin resistance has been little explored. In this study, we observed a positive relationship between Se and HOMA-IR, which is consistent with the results of a recent cross-sectional study, which found a positive correlation between Se and insulin, and between Se and HOMA-IR in Polish men aged 50 to 75 years[19]. Similar results were reported in several other population-based studies[20-21]. This finding suggests that higher Se levels may contribute to metabolic disorders. In this context, a growing body of evidence on the association between Se levels and insulin levels or insulin resistance is found in experimental studies. In mice models, the overexpression of Se-dependent glutathione peroxidase-1 (GPX1) and selenoprotein P (SEPP1) induced insulin resistance[22]. Furthermore, the maximal expression of selenoproteins and selenoprotein deficiency promoted the development of a T2DM-like phenotype[23]. In a rat model used in a recent study[24], a diet of 3.0 mg of Se per kg of body weight induced hyperinsulinemia, insulin resistance, and glucose intolerance in the dams at late gestation and on day 14 postpartum and in the offspring aged 112 days. Further evidence has been found in pig models[25].

Although the mechanism underlying the association between high Se and diabetes is still unclear, recent population-based and experimental studies indicate a potential oxidative stress pathway. A population-based study[26] that evaluated gene-environment interactions indicated a nonlinear dose-response relationship between Se exposure and oxidative stress biomarkers, suggesting that high Se levels increase oxidative stress in some biological processes. A recent study explored the effect of high Se levels on insulin sensitivity and the possible underlying mechanisms using rat and rat hepatocyte models[27] and found that high Se-activated selenoproteins weakened insulin-stimulated 'good' reactive oxygen species (ROS) signals and attenuated insulin signaling. Another study indicated that high-dose selenite treatment exacerbated hepatic insulin resistance in a T2DM mouse model, at least in part via an oxidative stress-mediated JNK pathway, and this result provides new mechanistic insights into the pro-diabetic effect of selenite in T2DM[28]. In this context, herein we did not measure oxidative stress markers and consequently did not explore the possible underlying mechanisms. Therefore, other population-based studies are needed to elucidate this mechanism considering the effect of oxidative stress.

Our study has some strengths. First, it evaluated the association between Se exposure and diabetes in an Asian population. Second, the Se level in the study population without Se supplementation was relatively low. For life-long rural residents who consume local food products, nail Se levels closely reflect the life-long level of exposure to Se[29]. Third, Se was measured in nail samples, which provided a relatively long-term measure of exposure compared with blood or urine samples, and the Se level in nails does not fluctuate significantly with the daily intake of Se in the diet.

Our study has some limitations. The first is its cross-sectional design. Therefore, longitudinal studies are necessary to confirm our results. In addition, our study sample included subjects aged 65 years or older. Therefore, the association between Se and diabetes in younger populations is unknown. Third, this study did not consider genetic factors or other environmental factors that might influence the association between Se level and the risk of diabetes.

In conclusion, our results suggest that long-term

higher levels of exposure to Se may be associated with a higher risk of diabetes in an older population in rural China. Future studies that include other biomarkers will elucidate the association between Se and insulin resistence and its underlying mechanisms.

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***Conflict of Interest*** The authors declare that no conflicts of interest are associated with this research.

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