Higher toenail selenium is associated with increased insulin resistance risk in omnivores, but not in vegetarians

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Research

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Abstract

Background The relationship between selenium (Se) and insulin resistance remains unclear. We aim to evaluate the association between toenail Se levels and insulin resistance in China.

Methods In this cross-sectional study, 220 vegetarians and 220 age-sex- matched omnivores from Shanghai were included. The toenail Se levels were measured by inductively coupled plasma mass spectrometry method. Dietary Se intakes were assessed by the 24-hour dietary recall questionnaire. Blood samples were collected to examine fasting blood glucose and fasting insulin concentrations. Insulin resistance index (HOMA-IR) and insulin secretion index (HOMA-B) were calculated to assess insulin resistance. The multilinear regression models were performed, and the following covariates were included in the models: age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber).

Results Toenail Se levels were not associated with insulin resistance among vegetarians but were positively associated with fasting insulin levels (β=1.030, 95% CI: 0.393, 1.667) and HOMA-IR (β=0.245, 95% CI: 0.098, 0.392) in omnivores. Stratifying the results by Se intake levels in the omnivores revealed a significant association among those with dietary Se intake ≥ 60 μg/d; insulin level (β=1.053, 95% CI: 0.415, 1.691) and HOMA-IR (β=13.271, 95% CI: 4.433, 22.109) but not in those with < 60 μg/d ; insulin level (β=2.146, 95% CI: -0.710, 5.002) and HOMA-IR (β=13.766, 95% CI: -46.868, 74.400).

Conclusions Higher toenail Se levels were associated with increased insulin resistance risk in Chinese omnivores, but not in vegetarians.

Background

Type 2 diabetes mellitus (T2DM) is a global health concern that represents an increasing burden on healthcare systems and economies (1). In 2017, the International Diabetes Federation estimated that there were 451 million people with diabetes worldwide, and these figures were expected to exceed 690 million by 2045 (2). China has the world's largest diabetes epidemic where approximately 11% of the Chinese adult population are affected (3).

Previous studies have suggested that a vegetarian diet may have positive effects on the prevention of T2DM and the improvement of insulin resistance (4–6). One meta-analysis detected an inverse association between adherence to plant-based dietary pattern and the risk of T2DM (relative risk = 0.77, 95% CI: 0.71, 0.84) (4). In China, vegetarians showed a higher insulin sensitivity and lower fasting insulin level in comparison with the matched omnivores (7). The potential mechanisms for the protective effect of vegetarian diet from the development of T2DM may include higher consumption of plant foods rich in antioxidants, vitamins, and minerals in addition to lower consumption of red and processed meat (4).

Selenium (Se) is a key component of glutathione peroxidase, an antioxidant enzyme that prevents cells from being damaged by free radicals and lipid peroxides (8). The association between Se and T2DM is still contradictory. A recent meta-analysis of experimental and non-experimental studies showed that Se may increase the risk of T2DM across a wide range of exposure levels (9). However, Park et al. combined data from two large U.S. cohort studies: the Nurses' Health Study and the Health Professionals Follow-Up Study and concluded that higher toenail Se levels were associated with lower risk for T2DM (10). Moreover, the association between Se nutritional status and insulin resistance, a hallmark and a pathophysiological factor of T2DM, was inconsistent across studies (11, 12).

Therefore, this study was conducted to evaluate the association between toenail Se levels and insulin resistance among Chinese vegetarians and omnivores. To the best of our knowledge, this is the first study to investigate the relationship between Se and insulin resistance among Chinese vegetarians.

Methods

Population

In this cross-sectional study, vegetarians were recruited from Shanghai, China through vegetarian restaurants, vegetarian social activities and online advertisements during the period between March 2016 and May 2016. To be eligible, participants had to 1) be ≥18 years; 2) reside in Shanghai ≥6 months; 3) follow a vegetarian diet for ≥ 1 year; 4) understand the questionnaire. Those with history of severe nutritional malabsorption and those with history of pregnancy or breastfeeding within the preceding 12 months were excluded. Omnivores were recruited by the friends and relatives of the included vegetarians and were matched respectively for age (±1 year) and gender. This study was approved by the Institutional Review Board of the Shanghai Jiao Tong University School of Medicine, and all participants provided written informed consent.

Anthropometric, clinical and dietary assessment

Using a questionnaire, all subjects were questioned about their personal and socio-demographic characteristics including age, gender, income, alcohol consumption, smoking, physical activity, sedentary time, sleep duration, vegetarian pattern (vegan or lacto-ovo-vegetarian), and vegetarian duration. Vegetarians were defined as people who followed a vegetarian diet at all daily meals for at least 1 year; otherwise, they were defined as omnivores. Vegans were defined as those who did not consume any sort of foods of animal origin, while those who consumed meat, eggs, dairy products or fish were defined as "lacto-ovo-vegetarians".

Participants' height, body weight, waist circumference, and hip circumference were obtained from the physical examination by trained dietitians in accordance with the standardized protocol. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Waist-to-hip ratio was calculated as the measured waist circumference divided by hip circumference.

A 24-hour diet recall questionnaire was used to assess their daily consumption of different nutrients. Daily nutrient intakes were calculated from the 24-hour dietary recall data using Nutrition Calculator v2.5

software, which was developed by the Institute of Nutrition and Food Safety of the Chinese Centre for Disease Control and Prevention and Beijing B-win Technology Co. Ltd.

Sample collection and biochemical analyses

Participants were asked to provide toenail clippings from all ten toes and return them to the researchers. The concentrations of toenail Se were measured according to inductively coupled plasma-mass spectrometry from the National Standard for Food Safety Determination of Multi Elements in Food (GB 5009.268-2016). Toenail samples of a total of 220 vegetarians and 220 matched omnivores who met the inclusion criteria were included in this study. Peripheral venous blood samples were collected after 12 hours of fasting. Fasting blood glucose (FG) and fasting insulin (FI) concentrations were tested by the Clinical Laboratory Center of Shanghai Xinhua Hospital.

Insulin resistance indices

Insulin resistance and *B*-cell function were evaluated by the homeostasis model assessment (HOMA) method (13), in which FI (mU/L) and FG (mmol/L) were used

HOMA-IR= FI (mU/L) ×FG (mmol/L)/22.5 (11, 14), HOMA-B (%)= 20×FI (mU/L)/[FG (mmol/L) - 3.5] (11, 14). Insulin resistance was defined as HOMA-IR > 2.60 (13, 15).

Statistical analysis

All statistical analyses were performed with the use of Stata software version 14.0 (StataCorp, College Station, TX, USA), and two-sided P values <0.05 were considered as statistically significant. The continuous variables were shown as mean ± standard deviation (SD), while the categorical variables were expressed as number and percentage (%). To compare the differences between vegetarian group and omnivore group, the paired Student's t-test study for continuous variables and paired chi-square test for categorical variables were used. Covariance analysis was used to test the differences in glucose metabolism and insulin resistance between the vegan group and the lacto-ovo-vegetarian group after controlling the covariates, including age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber). Then multilinear regression models were used to investigate the association between nail concentrations of Se and insulin resistance after adjusting for all major confounders.

Results

The characteristics of the participants are shown in Table 1. In total, 220 vegetarians and 220 matched omnivores met the inclusion criteria. The mean age of vegetarians and omnivores were 35.96 ± 8.73 years and 35.23 ± 8.93 years, respectively. In the vegetarian group, 76 of the vegetarians were vegans, 144 were lacto-ovo vegetarians, and they had adhered to a vegetarian diet for 5.61 ± 5.04 years. Of them, 180 (81.8%) were female and 40 (18.2%) were male. Vegetarians had a lower BMI, waist-to-hip ratio values, alcohol consumption, daily intakes of energy, protein, and fat, but higher-income, physical activity, and daily intakes of fiber compared with omnivores (all $P < 0.05$). In addition, the level of FG, FI, HOMA-IR and dietary Se intake were significantly lower in vegetarians than in omnivores (all $P < 0.05$) while the number of participants under recommended nutrient intake Se level were higher in vegetarians than in omnivores ($P < 0.05$). The proportion of participants with insulin resistance was also lower in vegetarians than in omnivores (1.36% versus 5.45%; $P < 0.05$). The mean concentration of Se in toenails of vegetarians was 0.53 ± 0.16 μg/g, which was significantly lower than that of omnivores (0.69 ± 0.53 μg/g, $P < 0.05$). There was also a significant difference in toenail Se between the vegan group (0.46 ± 0.11 μg/g) and the lacto-ovo-vegetarian group (0.56 ± 0.17 μg/g).

Table 1
Characteristics of the study population

	Vegan (n = 76)	Lacto-ovo-vegetarian (n = 144)	Vegetarian (n = 220)	Omnivore (n = 220)
Age (y)	36.84 ± 8.51	35.49 ± 8.85	35.96 ± 8.73	35.23 ± 8.93
Female, %	77.63	84.03	81.82	81.82
Vegetarian duration (y)	5.79 ± 4.46	5.52 ± 5.33	5.61 ± 5.04	-
BMI(kg/m^2)	20.72 ± 2.27	21.17 ± 2.67	21.02 ± 2.54*	22.53 ± 3.48
Waist-to-hip ratio	0.81 ± 0.05	0.81 ± 0.05	0.81 ± 0.05*	0 .84 ± 0 .05
No alcohol, %	98.68	93.75	95.45*	81.36
No smoking, %	86.84	90.97	89.55	90.45
Physical activity (min/wk)	151.97 ± 181.98	93.16 ± 108.48	113.48 ± 140.75*	82.86 ± 114.39
Income (Yuan/month), %				
< 3000	17.11	19.44	18.64*	25.45
3000 ~ 5000	22.37	17.36	19.09*	20
5000 ~ 8000	18.42	29.17	25.45*	24.10
> 8000	42.10	34.03	36.82*	30.45
Energy (Kcal/d)	1536.32 ± 541.52	1496.98 ± 503.67	1510.57 ± 516.17*	1792.88 ± 583.46
Protein (g/d)	48.50 ± 23.94	44.48 ± 18.92	45.87 ± 20.83*	71.52 ± 31.64
Fat (g/d)	39.49 ± 21.22	43.02 ± 21.31	41.80 ± 21.30*	68.14 ± 34.66
Carbohydrate (g/d)	237.96 ± 90.39	227.55 ± 84.11	231.14 ± 86.26	217.14 ± 75.72
Fiber (g/d)	19.36 ± 11.89	13.63 ± 7.56**	15.61 ± 9.65*	12.04 ± 7.12

* Statistical significance when comparing vegetarian and omnivore groups.

**Statistical significance when comparing vegan and lacto-ovo-vegetarian groups.

(1)Data were assessed with covariance controlling for age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber)

Abbreviations: BMI, body mass index; FG, fasting blood glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function.

	Vegan (n = 76)	Lacto-ovo-vegetarian (n = 144)	Vegetarian (n = 220)	Omnivore (n = 220)
FG (mmol/L)	4.58 ± 0.29	4.66 ± 0 .80	4.63 ± 0.67*	4.82 ± 0.40
FI(mU/L)	4.76 ± 2.67	4.96 ± 2.08	4.89 ± 2.30*	6.03 ± 3.11
HOMA-IR	0.98 ± 0.56	1.05 ± 0.60	1.03 ± 0.59*(1)	1.30 ± 0.71
HOMA-β (%)	91.26 ± 58.47	94.85 ± 42.97	93.61 ± 48.78	97.86 ± 62.42
Insulin resistance (%)	1.32	1.39	1.36%*	5.45
Dietary Se intake(μg/d)	25.28 ± 23.89	25.83 ± 15.03	25.64 ± 18.52*	55.14 ± 37.51
Toenail Se (μg/g)	0.46 ± 0.11	0.56 ± 0.17**	0.53 ± 0.16*(1)	0.69 ± 0.53
* Statistical significance when comparing vegetarian and omnivore groups.				
**Statistical significance when comparing vegan and lacto-ovo-vegetarian groups.				
(1)Data were assessed with covariance controlling for age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber)				
Abbreviations: BMI, body mass index; FG, fasting blood glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function.				

The associations between toenail Se levels and glucose metabolic indices are presented in Table 2. The multi-linear regression results showed that omnivore diet was positively associated with FI (β = 1.030, 95% CI: 0.393, 1.667) and HOMA-IR (β = 0.245, 95% CI: 0.098, 0.392) after adjusting for age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber). No significant differences were found between vegetarian diet and FI as well as HOMA-IR.

Table 2
Multiple regression analysis for associations between toenail Se levels and glucose metabolic indexes in vegetarians and omnivores.

		Vegetarian(n = 220)		Omnivore(n = 220)	
		β (95% CI)	P	β (95% CI)	P
FG	Model 1	0.340 (-0.224, 0.905)	0.24	0.079 (-0.022, 0.180)	0.13
	Model 2	0.303 (-0.278, 0.885)	0.31	0.029 (-0.065, 0.122)	0.55
FI	Model 1	1.427 (-0.503, 3.357)	0.15	1.294 (0.532, 2.056)	< 0.01
	Model 2	1.190 (-0.707, 3.086)	0.22	1.030 (0.393, 1.667)	< 0.01
HOMA-IR	Model 1	0.358 (-0.136, 0.851)	0.16	0.319 (0.144, 0.493)	< 0.01
	Model 2	0.288 (-0.201, 0.776)	0.25	0.245 (0.098, 0.392)	< 0.01
HOMA-B	Model 1	13.560 (-27.543, 54.663)	0.52	8.991 (-6.671, 24.653)	0.26
	Model 2	8.568 (-32.381, 49.517)	0.68	9.995 (-4.444, 24.434)	0.18

Model 1: unadjusted regression;

Model 2: adjusted for age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber)

FG, fasting blood glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function.

The associations between toenail Se levels and glucose metabolic indices according to dietary Se intake in omnivores are displayed in Table 3. The concentration of Se in toenails was positively associated with FI (β = 1.053, 95% CI: 0.415, 1.691), HOMA-IR (β = 0.237, 95%CI: 0.079, 0.395), and HOMA-β (β = 13.271, 95%CI: 4.433, 22.109) in omnivores with dietary intake of Se ≥ 60 ug/d (China recommended nutrient intake (RNI) level), however, no association was observed, when the dietary Se intake was < 60 ug/d, after multivariable adjustment for age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber).

Table 3
Multiple regression analysis for associations between toenail Se levels and glucose metabolic indexes according to dietary Se intake in omnivores

Dietary Se intake(μg/d)	**< 60 (n = 155)**			**60(n = 65)**	
		β (95% CI)	P	β (95% CI)	P
FG	Model 1	0.391 (0.059, 0.723)	0.06	0.034 (-0.072, 0.140)	0.53
	Model 2	0.166 (-0.159, 0.491	0.32	-0.025 (-0.123, 0.073)	0.62
FI	Model 1	2.330 (-0.410, 5.070)	0.10	1.161 (0.469, 1.853)	< 0.01
	Model 2	2.146 (-0.710, 5.002)	0.14	1.053 (0.415, 1.691)	< 0.01
HOMA-IR	Model 1	0.614 (0.001, 1.227)	0.05	0.279 (0.112, 0.445)	< 0.01
	Model 2	0.504 (-0.140, 1.148)	0.13	0.237 (0.079, 0.395)	< 0.01
HOMA-B	Model 1	-4.121 (-63.969, 55.726)	0.89	11.041 (0.670, 21.412)	< 0.01
	Model 2	13.766 (-46.868, 74.400)	0.66	13.271 (4.433, 22.109)	< 0.01

Model 1: unadjusted regression;

Model 2: regression with age, sex, BMI, alcohol consumption, income, and daily dietary intakes (energy, protein, fat, carbohydrate, and fiber) controlled;

Abbreviations: FG, fasting blood glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function.

Discussion

In the present study, no association was observed between toenail Se levels and insulin resistance in vegetarians, yet high toenail Se levels were associated with increased insulin resistance risk in omnivores. This positive relationship remained significant in the omnivores who had dietary intake of Se≥ 60 μg/d, but not < 60 μg/d.

To the best of our knowledge, this was the first study to investigate the relationship between Se and insulin resistance among Chinese vegetarians. Our findings were supported by a recent cross-sectional study that showed that higher nail Se levels were associated with higher HOMA-IR in older people in rural

China (12). The adjusted odds ratio for the highest Se quartile group (≥0.568 μg/g) was 0.34 (95% CI: 0.08, 0.80) compared with the lowest Se quartile group (<0.320 μg/g) (12). Another study found positive correlations between serum Se levels and HOMA-IR in aging Polish men with metabolic syndrome, which were also consistent with our findings (16). Unlike the previous studies that focused on older participants (12, 16), our research offered some vital insights into the association between toenail Se levels and insulin resistance in younger populations. This finding also accords with the previous work, which showed that higher level of toenail Se might be associated with the higher risk of diabetes (8, 12).

However, our findings disagree with previous studies which have suggested that higher levels of toenail Se associated with a decreased risk of diabetes in U.S. Men and Women (10). In addition, the ORDET cohort study observed that toenail Se was not associated with the incidence of diabetes (17).

The inconsistent results across studies may be explained by the variant outcomes. For example, the outcome of our study was insulin resistance, while the studies with contradictory findings used the incidence of diabetes as their outcome. Insulin resistance had been identified as one of risk factors for the incidence of diabetes (18). Since increased physical activity and weight reduction would improve insulin resistance, it may result in the decrease of the incidence of diabetes (19), and lead to inconsistent conclusions from different studies. Besides, another explanation may be due to the differences in the distribution of related insulin resistance and diabetes confounders, including lifestyle factors and genetic susceptibility to insulin resistance and diabetes (20).

As expected, our study observed a positive correlation between dietary Se intake and toenail Se level among the subjects, after adjusting for major confounding factors. In other words, dietary Se intake affects the toenail Se level, while the toenail Se level reflects dietary Se intake. Taking into account the practical guidance on dietary Se intake, our study divided omnivores into two groups according to 60 μg/d (China RNI level), to investigate the associations between toenail Se levels and glucose metabolic indexes among omnivores, as displayed in Table 3. Interestingly, when dietary Se intake was above 60 μg/d, the increased toenail Se levels were positively associated with FI and HOMA-IR. However, no significant association was observed in subjects when the dietary intake of Se under 60 μg/d. Previous studies have suggested that high levels of Se may be associated with insulin resistance and the increased risk of diabetes (20). Our finding was in accordance with the ORDET cohort study, which observed that the odds ratio for diabetes comparing the highest quantile of Se intake (55 μg/d) to the lowest one (32 μg/d) was 1.74, (95% *CI*: 1.12, 2.72; *P* for linear trend 0.001), after adjusting for age, education and menopausal status (21). These findings raise additional concerns about the association of dietary Se intake above 60 μg/d with insulin resistance risk in the Chinese omnivores. Therefore, more studies with larger participants in different populations are required to explore the safe range of dietary Se intake.

In the present study, no statistically significant differences between toenail Se levels and insulin resistance were found in the vegetarian group. This result may partly be explained by the low dietary Se intake in vegetarians. The mean dietary Se intake of vegetarians was 25.64±18.52 μg/d, which was significantly lower than that of omnivores (55.14±37.51, $P<0.05$). Previous studies have observed a U-shaped relationship between serum Se level and the risk of diabetes (22). Therefore, when the Se levels were relatively low, the association between Se levels and insulin resistance may not be observed. Another possible explanation for this finding is that the vegetarian diet may have a potential protective effect on the improvement of insulin resistance. A plant-based diet with various foods rich in antioxidants and phytochemicals, which may have a direct effect on alleviating oxidative stress and inflammation, may account for the lower insulin resistance among vegetarians (23). A recent prospective study indicated that higher consumptions of phytochemical-rich foods may improve the development of IR (23). Hence, the effect of Se on insulin resistance was reduced because of the protective effect of a vegetarian diet. Future studies are needed to investigate the potential underlying mechanisms.

There are a few possible metabolic explanations as to why Se affects insulin resistance. Se might affect insulin resistance via multiple mechanistic routes including insulin-like action, oxidative stress, and inflammatory cytokines (11). In experimental animal studies, high Se diets had a positive effect on the release of glucagon, which in return promotes hyperglycemia, or may induce elevated expressions of glutathione peroxidase-1 and other anti-oxidant selenoproteins leading to insulin resistance as well as obesity (21). Similarly, a significantly positive association between glutathione peroxidase activity and insulin resistance was observed in non-diabetic women during normal pregnancy (24). From the mechanistic perspective, dietary Se intakes above the recommended level for the optimal activity of antioxidant selenoproteins like glutathione peroxidases (55 μg/d), will lead to the non-specific incorporation of selenomethionine replacing methionine in both albumin and other proteins (25, 26). The metabolic pathways including this extra pool of Se are still poorly understood and may account for some adverse effects of high Se exposure on insulin resistance.

One of the strengths of this study is that Se was measured via toenail samples, which reflected a relatively long-term measure of Se exposure, in comparison with serum or urine samples. In addition, the Se levels in toenail did not fluctuate remarkably with the daily dietary Se intake (27). Secondly, many major confounding factors were controlled, ensuring the findings in this study to be more accurate. Thirdly, dietary assessments were conducted by trained and professional Chinese registered dietitians, and strict quality control measures were adopted throughout the study.

Some potential limitations in the present study need to be acknowledged. Firstly, our study sample was relatively small, so larger studies are warranted. Secondly, the findings were limited by the use of a cross-sectional design. Thirdly, this study did not consider genetic factors or other environmental factors that might influence the association between Se levels and the risk of insulin resistance. Therefore, more researches need to be undertaken before the association between Se and insulin resistance is more clearly understood.

Conclusions

In conclusion, our findings revealed a significantly positive association of toenail Se levels with insulin resistance in Chinese omnivores after adjusting for major confounding factors. This positive relationship between toenail Se levels and insulin resistance remains significant in the omnivores, whose dietary Se intake was above 60 μg/d, but not in the participants below 60 μg/d. These results raise additional concerns about the association of dietary Se intake above 60 μg/d with insulin resistance risk.

List Of Abbreviations

BMI, body mass index; FG, fasting blood glucose; FI, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function; T2DM, Type 2 diabetes mellitus; Se, Selenium.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Shanghai Jiao Tong University School of Medicine.Written informed consents from all patients were obtained prior to the enrolment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XS contributed to study concept and design; WC and QT contributed to assist the research design and field survey; BW, XC, and KD contributed to conduct the research; QG and XC contributed to data analysis; QG and XS wrote the manuscript. All authors approved the final version of the report.

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