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ORIGINAL RESEARCH

The Association of Circulating Selenium Concentrations with Diabetes Mellitus

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Purpose: The relationship between circulating selenium and diabetes mellitus (DM) remains inconsistent. Therefore, the relationship between circulating selenium and DM was investigated in the present study.

Patients and Methods: All participants (aged ≥18 years) were included from the National Health and Nutrition Examination Survey (NHANES) 1999–2006. Selenium concentrations from the fasting serum samples were determined using inductively coupled mass spectrometry, then grouped into quartiles. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by using multivariate logistic regression analysis and the results were stratified by age and sex.

Results: A total of 2,903 (61.9±13.7 years old) participants (49.3% males) were enrolled, and 580 (19.97%) of them had DM. The mean levels of selenium were 136.4±19.6 μg/L. Patients with DM (138.76±20.02 vs 135.88±19.44, P=0.002) had higher selenium levels compared to those without DM. The OR for DM was 1.12 (95% CI=1.01–1.24; P=0.0270) for each 10 μg/L increment in selenium, and subjects in the highest quartile of selenium levels (>147.00 uμg/L) had 2.82 (95% CI=1.55–5.11; P=0.0007) times higher risk of DM compared to the lowest quartile of selenium levels. Subgroup analysis showed that selenium was independently associated with DM only in female aged <65 years.

Conclusion: Circulating selenium levels were positively associated with the odds of DM, but difference in sex and age.

Keywords: diabetes mellitus, selenium, relationship

Introduction

Diabetes mellitus (DM) has become a public burden worldwide.[1] To elucidate the pathogenesis of DM, some previous studies have suggested the roles of trace elements.[2–6] Selenium serves as the redox center for the form of selenoproteins, and is an essential trace element in the human and animal's diet.[7,8] The roles of selenium in the maintenance of human health has attracted attention from researchers.[9–12] Selenium forms part of the active site of peroxide-destroying enzyme glutathione peroxidase, and involves antioxidant decency, biotransformation, inflammatory progress, detoxification, and immune response.[13,14] Epidemiological, experimental and clinical studies have provided evidence for the roles of selenium in coronary heart disease,[15] hypertension,[16] metabolic syndrome,[17] and dyslipidemia prevention.[18] In addition, selenium was significantly associated with disease prognosis,[19,20] and the use of high-dose selenium might be associated with a reduced risk of 28-day mortality in critically ill patients.[21] However, a systematic review of randomized controlled trials showed no evidence to support Se supplementation in treating people with diabetes.[22]

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Many previous studies have shown that circulating selenium may play an important role in the pathogenesis of abnormal glucose metabolism.[23,24] Although a large number of studies have analyzed the relationship between selenium and diabetes, findings are highly controversial, and only few studies have analyzed the age or sex-specific relationship between selenium and DM. Therefore, the purpose of this study is to analyze the association of circulating selenium level with DM, and further explore their relationship through sex and age subgroups.

Patients and Methods

Study Population

Data was extracted from the 1999–2006 National Health and Nutrition Examination Survey (NHANES, n=41,474). The NHANES study was designed to provide a representative sample of non-institutionalized civilian population and assess the health and nutritional status of adults and children in the United States.[25,26] Subjects who was missing selenium data (n=19,721) and aged <18 years (n=18,850) were excluded. Participants from NHANES aged ≥18 years and with data on circulating selenium were included in the present analysis (n=2,903). The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (protocol #98-12 and protocol #2005-2006). Written informed consent was obtained from all participants.

Date Collection and Definition

All participants have provided information on demographics, data on physical examination, and disease history. Total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), and C-reactive protein were determined according to standardized method. Serum TG and TC were measured enzymatically, while HDL-C was measured by direct immunoassay or precipitation. LDL-C was calculated by Friedewald formula if TG ≤400 mg/dL.[27] Body mass index (BMI) was defined as mass (kg) divided by the square of height (m^2).[28] HbA1c levels were measured using HPLC (Bio-Rad DIAMAT glycosylated hemoglobin analyzer system).[29] Diabetes (FBG ≥126 mg/dL or self-report or taking hypoglycemic drugs or HbA1C ≥ 6.5%)[30] and hypertension (blood pressure ≥140/90 mmHg or self-report)[31] were identified from laboratory analysis or self-reported status.

Measurement of Selenium

The laboratory method for detecting circulating selenium in NHANES was described in detail previously.[32] Selenium concentrations were determined using inductively coupled mass spectrometry from the morning fasting serum sample. In brief, circulating selenium was measured at the Trace Elements Laboratory at the Wadsworth Center of the New York State Department of Health (Albany, NY, USA) using inductively coupled plasma–dynamic reaction cell–mass spectrometry, a multi-element analytical technique capable of trace level elemental analysis.

Statistical Analysis

All continuous variables were presented as mean±standard deviation, and categorical variables were presented in frequency or as a percentage according to baseline levels of circulating selenium in quartiles. The One-Way ANOVA, Kruskal Wallis *H*-test and chi-square tests were used to determine any statistical differences between subgroups. Circulating selenium levels were grouped by quartiles (Q1: <124.00 μg/L; Q2: 124.00–134.90 μg/L; Q3: 135.00–146.90 μg/L; and Q4 > 147.00 μg/L). Odds ratios (ORs) and 95% confidence intervals (CIs) for DM were estimated by multivariate logistic regression analysis with the lowest quartile as the reference. A logistic regression model was used to evaluate association between selenium and DM. Age, sex, BMI, SBP, TC, TG, LDL-C, CRP, smoking, race, and hypertension were adjusted in regression models. Results of the logistic regression model were also stratified by sex and age. A 2-sided $P<0.05$ was considered as statistically significant. All statistical analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

A total of 2,903 subjects (mean age=61.94 years, 49.29% male) were divided into two groups according to diabetes status at baseline. The mean selenium levels of the study population were 136.43±19.60 μg/L. The baseline features of the study population are shown in Table 1. In brief, DM patients have higher selenium levels (138.76±20.02 vs 135.88±19.44; $P=0.002$) compared to those without DM. When stratifying the clinical characteristics by selenium levels in quartiles in Table 2, the mean HbA1C (5.67±0.81 vs 5.76±0.93 vs 5.80±1.00 vs 6.00±1.40; $P<0.001$) and the

Table 1 Baseline Demographic and Clinical Parameters Between Diabetes and Without Diabetes

	All (n=2903)	Without Diabetes (n=2301)	Diabetes (n=580)	*P*-value
Age (years)	61.94±13.73	60.96±14.03	65.55±11.74	<0.001
BMI (kg/m^2)	28.69±5.89	28.13±5.65	30.86±6.34	<0.001
SBP (mmHg)	123.01±15.67	122.73±15.80	124.28±15.25	0.098
DBP (mmHg)	70.64±13.18	71.59±12.46	66.32±15.48	<0.001
HbA1C (%)	5.81±1.07	5.45±0.32	7.24±1.65	<0.001
FBG (mg/dL)	111.73±42.21	97.86±10.15	163.70±68.27	<0.001
TC (mg/dL)	207.05±43.49	208.07±42.34	202.53±46.89	0.006
TG (mg/dL)	160.49±139.12	147.35±103.71	209.72±220.54	<0.001
LDLC (mg/dL)	120.69±38.42	123.16±38.64	111.02±36.02	<0.001
HDLC (mg/dL)	54.32±16.29	55.34±16.47	50.13±15.00	<0.001
CRP (mg/dL)	0.72±1.56	0.72±1.56	0.76±1.59	0.544
Selenium (μg/L)	136.43±19.60	135.88±19.44	138.76±20.02	0.002
eGFR (mL/min/1.73m^2)	74.93±20.70	75.64±19.87	72.41±23.75	<0.001
Gender (n, %)				0.134
Male	1,431 (49.29%)	1,122 (48.76%)	303 (52.24%)	
Female	1,472 (50.71%)	1,179 (51.24%)	277 (47.76%)	
Smoking (n, %)				0.194
Non-smoker	1,327 (45.77%)	1,058 (46.04%)	259 (44.73%)	
Ex-smoker	1,019 (35.15%)	789 (34.33%)	220 (38.00%)	
Current smoker	553 (19.08%)	451 (19.63%)	100 (17.27%)	
Race (n, %)				<0.001
Black	510 (17.57%)	389 (16.91%)	119 (20.52%)	
Mexican American	561 (19.32%)	400 (17.38%)	160 (27.59%)	
Other Hispanic	76 (2.62%)	64 (2.78%)	11 (1.90%)	
Other race	112 (3.86%)	86 (3.74%)	26 (4.48%)	
White	1,644 (56.63%)	1,362 (59.19%)	264 (45.52%)	
Hypertension (n, %)				<0.001
No	1,483 (51.24%)	1,302 (56.76%)	170 (29.41%)	
Yes	1411 (48.76%)	992 (43.24%)	408 (70.59%)	

Note: Data are the means±standard deviation or number (%).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

prevalence of DM (17.27% vs 18.24% vs 19.41% vs 25.41%; *P*<0.001) were gradually increased in parallel with the quartiles of selenium. There were significant differences in BMI, FBG, TG, TC, LDL-C, CRP, sex, and smoking among the quartiles (all *P*<0.005).

Association of Selenium Concentration with Diabetes Mellitus

As shown in Table 3, for every 10 uμg/L increment in selenium concentration, the risk for DM increased by 12% (95% CI=1.01–1.24, *P*=0.0270) after being adjusted for age, sex, BMI, SBP, TC, TG, LDL-C, CRP, smoking, race, and hypertension history. Moreover, when using the lowest quartile of selenium as a reference, the ORs for DM increased in parallel with the quartiles of selenium (ORs were 1.15 (95% CI=0.65–2.03; *P*=0.6257), 1.49 (95% CI=0.83–2.70; *P*=0.1842), and 2.82 (95% CI=1.55–5.11; *P*=0.0007) from the second to the fourth quartiles, respectively, *P*<0.001 for trend).

Subgroup Analysis

As shown in Table 4, for every 10 uμg/L increment in selenium concentration, associated with an increased risk of DM in men (OR=1.07; 95% CI=0.93–1.22; *P*=0.3362) and in women (OR=1.21; 95% CI=1.02–1.43; *P*=0.0260), in participants aged <65 years (OR=1.43; 95% CI=1.21–1.69; *P*<0.001), and aged ≥65 years (OR=0.99; 95% CI=0.86–1.13; *P*=0.8659), respectively. When selenium was treated as a categorical variable, patients in Q4 had a significantly elevated risk for DM compared with those

Table 2 Baseline Demographic and Clinical Parameters Among Participants

Selenium Quartiles (ug/L)	Q1 <124.00	Q2 124.10–134.90	Q3 135.00–146.90	Q4 >147.00	*P*-value
Number	696	746	721	740	
Age (years)	61.25±14.13	61.62±13.83	62.36±13.41	62.49±13.55	0.259
BMI (kg/m^2)	29.17±6.82	28.91±5.96	28.63±5.36	28.07±5.30	0.003
SBP (mmHg)	122.20±16.94	122.26±15.47	123.21±15.46	124.31±14.73	0.119
DBP (mmHg)	69.93±14.30	70.50±12.99	70.80±13.26	71.31±12.15	0.431
HbA1C (%)	5.67±0.81	5.76±0.93	5.80±1.00	6.00±1.40	<0.001
FBG (mg/dL)	104.74±26.48	109.50±36.99	112.64±42.27	119.73±55.84	<0.001
TC (mg/dL)	197.01±47.87	203.72±39.37	210.48±40.54	216.48±43.59	<0.001
TG (mg/dL)	154.32±177.24	143.69±88.09	167.30±142.59	177.87±138.88	0.006
LDL-C (mg/dL)	115.57±45.63	118.32±36.13	124.08±36.09	124.85±34.94	0.004
HDL-C (mg/dL)	53.65±16.45	54.13±16.05	54.33±15.85	55.14±16.80	0.373
CRP (mg/dL)	0.98±2.12	0.70±1.34	0.67±1.38	0.56±1.25	<0.001
Selenium (μg/L)	114.15±8.50	129.43±3.10	140.10±3.49	160.86±17.04	<0.001
eGFR (mL/min/1.73m^2)	76.00±22.47	74.91±21.31	74.44±19.15	74.42±19.78	0.439
Gender (n, %)					<0.001
Male	290 (41.67%)	347 (46.51%)	380 (52.70%)	414 (55.95%)	
Female	406 (58.33%)	399 (53.49%)	341 (47.30%)	326 (44.05%)	
Smoking (n, %)					<0.001
Non-smoker	289 (41.58%)	340 (45.70%)	354 (49.17%)	344 (46.49%)	
Ex-smoker	207 (29.78%)	257 (34.54%)	261 (36.25%)	294 (39.73%)	
Current smoker	199 (28.63%)	147 (19.76%)	105 (14.58%)	102 (13.78%)	
Race (n, %)					<0.001
Black	192 (27.59%)	145 (19.44%)	101 (14.01%)	72 (9.73%)	
Mexican American	72 (10.34%)	152 (20.38%)	156 (21.64%)	181 (24.46%)	
Other Hispanic	21 (3.02%)	21 (2.82%)	26 (3.61%)	8 (1.08%)	
Other race	31 (4.45%)	30 (4.02%)	19 (2.64%)	32 (4.32%)	
White	380 (54.60%)	398 (53.35%)	419 (58.11%)	447 (60.41%)	
Hypertension (n, %)					0.356
No	365 (52.52%)	396 (53.23%)	353 (49.23%)	369 (50.00%)	
Yes	330 (47.48%)	348 (46.77%)	364 (50.77%)	369 (50.00%)	
Diabetes (n, %)	119 (17.27%)	135 (18.24%)	139 (19.41%)	187 (25.41%)	<0.001

Note: Data are the means±standard deviation or number (%).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Q, quartiles.

in Q1 among females (OR=5.51, 95% CI=2.11–14.37; *P*=0.0005) and those aged <65 years (OR=5.87, 95% CI=2.52–13.65; *P*<0.0001), but this difference did not reach statistical significance in male subjects (OR=1.87, *P*=0.1272) and those aged ≥65 years (OR=1.40; 95% CI=0.57–3.45; *P*=0.4680).

Discussion

The present study demonstrated that DM patients had higher selenium levels than those without DM among the general US population. The subgroup analysis according to sex showed significant results only in females aged <65 years.

These results were in agreement with a meta-analysis of 20 observational studies suggesting that higher concentrations of selenium (from blood, nail, urine, and dietary intake) were an independent risk factor for the DM.[23] However, a meta-analysis also showed a modest association between blood selenium and DM, and further indicating a likely U-shaped relationship between blood selenium and DM.[33] Although our findings suggested an obvious correlation between an increased exposure to selenium and DM, data from clinical trials of selenium supplementation have not been conclusive. A meta-analysis of randomized controlled trials on selenium supplementation and the risk of type 2 DM showed no significant relationship.[34] In

Table 3 The Association Between Selenium and Diabetes in Different Models

Outcomes	Crude Model	Minimally Adjusted Model	Fully Adjusted Model
Diabetes	**OR (95% CI) *P*-value**	**OR (95% CI) *P*-value**	**OR (95% CI) *P*-value**
Selenium (per 10 μg/L changed)	1.07 (1.03–1.12) 0.0016	1.10 (1.05–1.15) <0.0001	1.12 (1.01–1.24) 0.0270
Selenium quartiles			
Q1	1.0	1.0	1.0
Q2	1.07 (0.81–1.40) 0.6311	1.13 (0.84–1.50) 0.4204	1.15 (0.65–2.03) 0.6257
Q3	1.15 (0.88–1.51) 0.3001	1.20 (0.90–1.61) 0.2085	1.49 (0.83–2.70) 0.1842
Q4	1.63 (1.26–2.11) 0.0002	1.89 (1.43–2.49) <0.0001	2.82 (1.55–5.11) 0.0007
P for trend	<0.001	<0.001	<0.001

Notes: Data are the ORs and 95% CIs. Crude model adjust for: none. Minimally adjusted model adjust for: age, sex and BMI. Fully adjusted model adjust for: age, sex, BMI, SBP, TC, TG, LDL-C, CRP, smoking, race, and hypertension.
Abbreviations: OR, odds ratios; CI, confidence interval; Q, quartiles.

addition, in our study, the association between higher selenium concentration and higher the risk of DM might be attributed by the levels of blood lipids.

In the present study, we also found selenium to be an independent risk factor for DM only in women and the young population. Our results were similar to a previous study, where female subjects seemed to have higher risk for DM.[35,36] However, a cross-sectional study among Chinese middle-aged and older adults suggested no significant association between selenium intake and DM both in males and

Table 4 The Association Between Selenium and Diabetes in Subgroups

	Male	Female	<65 Years	≥65 Years
	OR (95% CI) *P*-value	**OR (95% CI) *P*-value**	**OR (95% CI) *P*-value**	**OR (95% CI) *P*-value**
Crude model				
Selenium (per 10 μg/L changed)	1.10 (1.04–1.18) 0.0024	1.04 (0.98–1.11) 0.2178	1.15 (1.08–1.24) <0.0001	1.02 (0.96–1.08) 0.5360
Selenium quartiles				
Q1	1.0	1.0	1.0	1.0
Q2	0.95 (0.64–1.43) 0.8195	1.17 (0.81–1.69) 0.4063	1.41 (0.92–2.15) 0.1129	0.89 (0.62–1.28) 0.5285
Q3	1.09 (0.74–1.60) 0.6799	1.20 (0.82–1.75) 0.3566	1.59 (1.04–2.43) 0.0323	0.88 (0.62–1.27) 0.5063
Q4	1.63 (1.13–2.35) 0.0089	1.55 (1.07–2.24) 0.0208	2.36 (1.58–3.53) <0.0001	1.21 (0.85–1.71) 0.2859
P for trend	0.003	0.026	<0.001	0.2813
Minimally adjusted model				
Selenium (per 10 μg/L changed)	1.13 (1.06–1.21) 0.0002	1.07 (1.00–1.14) 0.0601	1.19 (1.11–1.29) <0.0001	1.05 (0.99–1.12) 0.1166
Selenium quartiles				
Q1	1.0	1.0	1.0	1.0
Q2	0.98 (0.64–1.51) 0.9335	1.27 (0.86–1.88) 0.2285	1.58 (1.01–2.46) 0.0449	0.91 (0.62–1.34) 0.6319
Q3	1.21 (0.80–1.82) 0.3673	1.19 (0.79–1.79) 0.4105	1.78 (1.13–2.79) 0.0125	0.91 (0.62,–.34) 0.6461
Q4	1.92 (1.30–2.84) 0.0011	1.82 (1.22–2.72) 0.0031	2.91 (1.89–4.49) <0.0001	1.41 (0.97–2.03) 0.0688
P for trend	<0.001	0.007	<0.001	0.0657
Fully adjusted model				
Selenium (per 10 μg/L changed)	1.07 (0.93, 1.22) 0.3362	1.21 (1.02, 1.43) 0.0260	1.43 (1.21, 1.69) < 0.0001	0.99 (0.86, 1.13) 0.8659
Selenium quartiles				
Q1	1.0	1.0	1.0	1.0
Q2	0.84 (0.37–1.90) 0.6686	1.87 (0.80–4.36) 0.1455	1.67 (0.73–3.86) 0.2264	0.85 (0.3–1.93) 0.6908
Q3	0.97 (0.42–2.22) 0.9341	2.97 (1.18–7.48) 0.0208	2.66 (1.11–6.37) 0.0281	0.91 (0.39–2.16) 0.8386
Q4	1.87 (0.84–4.18) 0.1272	5.51 (2.11–14.37) 0.0005	5.87 (2.52–13.65) <0.0001	1.40 (0.57–3.45) 0.4680
P for trend	0.071	<0.001	<0.001	0.4092

Notes: Data are the ORs and 95% CIs. Crude model adjust for: none. Minimally adjusted model adjust for: age, sex, BMI. Fully adjusted model adjust for: age, sex, BMI, SBP, TC, TG, LDL-C, CRP, smoking, race, and hypertension.
Abbreviations: OR, odds ratios; CI, confidence interval; Q, quartiles.

females.[37] We speculated that, on the one hand, the population selection and race of the study population were different. On the other hand, the difference mechanisms for hormonal control in females may also play a role in selenium metabolism. Moreover, sex-specific nutritional and health behaviors may contribute to observed discrepancies in selenium levels between men and women.[38] Finally, selenoprotein biosynthesis was sexually dimorphic in the liver, indicating that hepatic metabolism of dietary selenium may differ in males and females.[39,40] In this study, the average age of the patients was older than 60 years, suggesting that the effect of estrogen on secretion function of female patients have significantly reduced, and estrogen has played an important role in liver metabolism.[41]

Selenium has multiple and complex effects on the development of DM. The potential mechanism of action for any linkage between selenium and T2D may be mediated in part via the selenoprotein glutathione peroxidase-1 (GPx-1).[42] Basic researchshowed that overexpression or prolonged activation of GPx-1 may result in dysregulation of insulin signaling and cause insulin resistance.[43,44] Moreover, selenium metabolism is accompanied by oxidative stress, and the metabolites of oxidation could have toxic effects on pancreatic β cells.[45] However, more researches are needed to clarify the relationship between selenium and diabetes.

There are some limitations in the present study. First, DM and hypertension history were obtained from self-reported data. Second, the present study was the cross-sectional design that did not reveal causal relationships between selenium concentrations with DM. In addition, dietary habits, living environment of the subjects, ethnicity, and medication use (such as vitamins, trace element supplements, diuretics) data were missing in this study. Finally, the lack of information about selenium supplementation would be an issue.

Conclusion

In conclusion, the present study suggested that circulating selenium concentrations were significantly associated with DM in the US adult population, but the association differed by sex and age. However, the potential mechanism between selenium levels and DM were not elucidated, and further research is needed to make this causal relationship clear.

Ethics Approval and Informed Consent

The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention (Protocol #98-12, Protocol #2005-06). Written informed consent was obtained from all subjects.

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Disclosure

The authors declare that they have no conflicts of interest.

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