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Epidemiology

Association between serum selenium level and the prevalence of diabetes mellitus in U.S. population

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ABSTRACT

Objective: Selenium seems to be a risk factor for diabetes mellitus (DM) in recent studies, opposite to the previous expectation that it may contribute to prevent DM. The authors aimed to ascertain the relationship between selenium and DM.

Methods: Data were collected from the National Health and Nutrition Examination Survey conducted from 2011 to 2014. A multivariate logistic regression analysis with adjustment for age, sex, race/ethnicity, hypertension, dyslipidemia and body mass index was conducted to evaluate the odds ratio for DM.

Results: The total number of subjects was 19,931. Large proportion of subjects were excluded due to young age (< 20 years) and missing data. The data of 3406 participants were analyzed, and a total of 604 had DM. In a multivariate logistic regression model, the increase of 10 μg/L in selenium increased the prevalence of DM by 12% (OR: 1.12; 95% CI: 1.06–1.18). Further analysis with 1:1 propensity score matching data with age and sex showed a similar results (OR: 1.08; 95% CI: 1.01–1.15). In addition, the restricted cubic spline regression showed a dose-dependent relationship between selenium level and DM. Subgroup analysis showed a dose-dependent relationship between selenium level and DM regardless of sex or race/ethnicity

Conclusions: This large population study clearly demonstrates a positive association between selenium level and DM. This finding could have implications for nutritional supplementation in clinical settings.

1. Introduction

Selenium (Se) is a basic component of selenoproteins, which are a group of critically important enzymes [1]. Its role ranges from antioxidant and anti-inflammatory effects to the synthesis of DNA and thyroid hormone [2]. Because of their anti-oxidative properties, a number of studies have been conducted to identify the relationship between Se level and metabolism associated with increased oxidative stress and inflammation [3–5]. Hyperglycemia is associated with the production of excess levels of reactive oxygen species. Oxidative stress has a huge impact on the onset and progression of type 2 diabetes mellitus (DM) [6,7]. Hence, Se had been assumed to be helpful in the prevention and therapy of type 2 DM [8–10].

However, in 2007, Stranges et al. found an excess risk of type 2 DM among subjects receiving Se supplementation compared with placebo, following a secondary analysis of the Nutritional Prevention of Cancer trial [11]. Two cross-sectional studies on the US National Health and Nutrition Examination Surveys (NHANES) [12,13] and several other observational studies [14–16] showed that high serum Se levels are positively associated with the risk of DM. Additionally, some laboratory studies mentioned that a few Se forms and selenoproteins adversely affect glucose metabolism and provide biological plausibility for an effect on DM occurrence [17–19].

Although some clinical trials [20,21] and observational studies [22,23] reported no increased risk of DM associated with Se exposure, a recent randomized controlled trial [24] and two meta-analyses [25,26] showed positive association between Se exposure and risk of DM. A cross-sectional analyses of 1727 participants from the Selenium Trial, a

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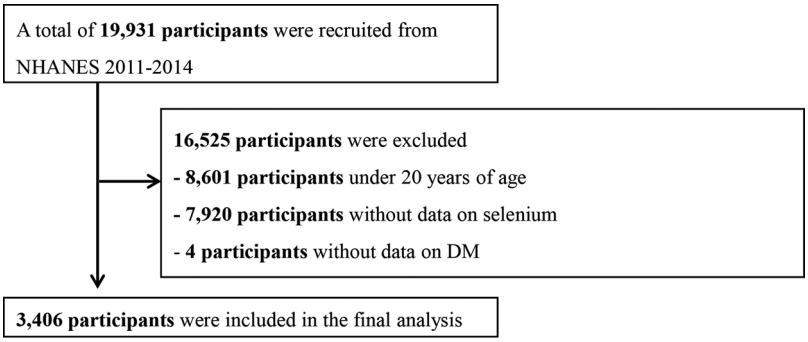

Fig. 1. Flow chart for participant selection in the study.

Table 1
Clinical characteristics of the participants in NHANES 2011-2014.

	Normal (N = 2773)	Diabetes Mellitus (N = 633)	p- value
Age, years	46.0 ± 17.4	59.9 ± 13.3	< 0.001
Men	1342 (48.4%)	333 (52.6%)	0.062
Race/Ethnicity			< 0.001
Hispanic	562 (20.3%)	161 (25.4%)	
Non-Hispanic White	1184 (42.7%)	211 (33.3%)	
Non-Hispanic Black	587 (21.2%)	167 (26.4%)	
Other race	440 (15.9%)	94 (14.8%)	
Body mass index, Kg/m^2	28.2 ± 6.7	32.4 ± 7.8	< 0.001
Systolic blood pressure, mmHg	121.3 ± 17.5	130.3 ± 18.0	< 0.001
Diastolic blood pressure, mmHg	70.1 ± 12.2	69.9 ± 15.0	0.715
Fasting glucose, mg/dL	96.8 ± 9.8	146.7 ± 58.7	< 0.001
HbA1c, %	5.4 ± 0.4	7.2 ± 1.7	< 0.001
Triglycerides, mg/dL	132.1 ± 92.4	189.8 ± 156.6	< 0.001
Total cholesterol, mg/dL	191.9 ± 40.0	186.6 ± 44.9	0.006
Selenium, μg/L	129.0 ± 18.7	134.3 ± 21.1	< 0.001
Hypertension	1037 (38.5%)	493 (79.1%)	< 0.001
Dyslipidemia	1075 (39.1%)	468 (75.0%)	< 0.001

Data are the means ± Standard deviation or number (%).

Table 2
Adjusted ORs and 95% CIs for DM according to the increase of 10 μg/L in Se.

	Model 1[a]	Model 2[b]
	OR (95% CI)	OR (95% CI)
Total	1.12 (1.07-1.18)	1.12 (1.06-1.18)
Sex		
Men	1.09 (1.02-1.16)	1.07 (1.00-1.15)
Women	1,17 (1.09-1.25)	1.17 (1.09-1.26)
Race/Ethnicity		
Hispanic	1.20 (1.08-1.34)	1.22 (1.06-1.14)
Non-Hispanic White	1.08 (1.01-1.16)	1.08 (1.00-1.16)
Non-Hispanic Black	1.10 (0.99-1.22)	1.11 (0.99-1.24)
Other race	1.16 (1.04-1.30)	1.13 (1.00-1.28)

Abbreviations: DMdiabetes mellitus; Seserum selenium.
[a] Model 1 adjusted for age, sex and race/ethnicity.
[b] Model 2 further adjusted for body mass index, hypertension, and dyslipidemia.

randomized clinical trial of Se supplementation for colorectal adenoma chemoprevention, showed that higher plasma concentrations of Se were significantly associated with prevalent type 2 DM [25]. Wang et al. [24] analysed 43 observational studies and detected a positive association between serum Se levels and type 2 DM. Vinceti et al. [26] conducted the most recent meta-analysis and concluded that Se may increase the risk of DM with higher relative risks in nonexperimental studies compared with experimental studies.

Thus, we aimed at ascertaining the effect of Se concentration on the prevalence of DM by cross-sectional study using recently obtained NHANES data collected from 2011-2014.

2. Methods

2.1. Study population

The total number of subjects from all sources was 19,931. The following participants were excluded from this study: those younger than 20 years or those with missing data such as questionnaire, anthropometric, or laboratory data. The total number of eligible participants was 3406 (Fig. 1). Most excluded cases in adults were due to lack of data on Se because the Se measured only in a one third of adults.

2.2. Laboratory measurements

Whole blood specimens are processed, stored, and shipped to the Division of Laboratory Sciences, National Center for Environmental Health, and Centers for Disease Control and Prevention for analysis. Detailed instructions on specimen collection and processing can be found in the NHANES Laboratory/Medical Technologists Procedures Manual [27].

Fasting plasma concentrations of glucose were measured using Hexokinase-mediated reaction Roche/Hitachi Cobas C Chemistry Analyzer. Hemoglobin A1C (HbA1c) was measured using a Tosoh G8 Glycohemoglobin Analyzer. Serum Se concentrations are determined using blood multi-element analysis by inductively coupled plasma - the dynamic reaction cell-mass spectrometry (ICP-DRC-MS).

DM was investigated with a structured questionnaire or laboratory data. DM was defined as having ≥1 of the following conditions: a self-report of current use of hypoglycemic agents or insulin, fasting plasma glucose ≥ 126 mg/dL or random glucose ≥ 200 mg/dL

2.3. Statistical analysis

Summary statistics are presented as mean and standard deviation (SD) or prevalence (%). The *t*-test and Pearson's chi-squared test were used to compare each variable according to DM status. A multivariate logistic regression analysis was carried out to evaluate the odds ratio (OR) and 95% confidence interval for the risk of DM according to the Se level. Because of the heterogeneity of demographic characteristics by DM, we conducted an additional analysis through 1:1 propensity score matching with age and sex performed a subgroup analysis by sex and race/ethnicity. The graphical relationships were also evaluated with restricted cubic spline plots with 5 knots according to Se level. The analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and R version 3.1.0 (the R Foundation for Statistical Computing, Vienna, Austria).

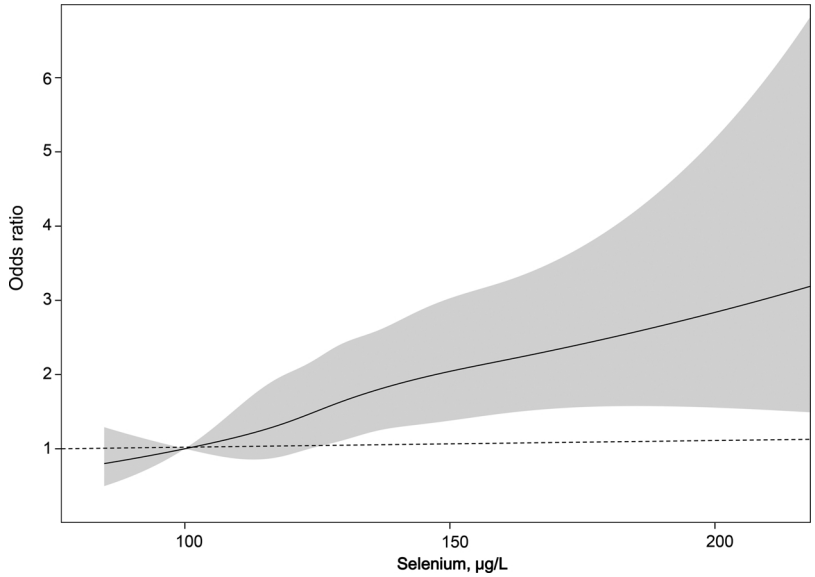

Fig. 2. The relationship between serum selenium level and the odds ratio for DM Adjusted for age, sex, race/ethnicity, body mass index, hypertension, and dyslipidemia.

3. Results

3.1. Association between Se and the risk of DM

The data of the 3406 participants were assessed, and a total of 604 had DM. The general characteristics of the participants according to diabetic status are summarized in Table 1.

In a multivariate logistic regression model, the increase of 10 μg/L in Se increased the prevalence of DM by 12% (OR: 1.12; 95% confidence interval (CI): 1.06–1.18, Table 2). Further analysis with 1:1 propensity score matching data with age and sex showed a similar results (OR: 1.08; 95% CI: 1.01–1.15). In addition, the restricted cubic spline regression showed a dose-dependent relationship between Se and DM (Fig. 2).

3.2. Risk of DM according to sex and race/ethnicity

We performed a subgroup analysis to examine the association between Se level and DM status according to sex and race/ethnicity to correct the heterogeneity of demographic features. In men, the increase of 10 μg/L of Se increased the prevalence of DM by 7% (OR: 1.07; 95% CI: 1.01–1.15) and in women by 17% (OR: 1.17; 95% CI: 1.09–1.26; Table 2). In the subgroup analysis by race/ethnicity, Hispanic and non-Hispanic Whites but not non-Hispanic Blacks showed a positive association between high Se levels and DM (Table 2). However, the restricted cubic spline regression showed a dose-dependent relationship between Se level and the prevalence of DM regardless of sex or race/ethnicity (Figs. 3 and 4).

4. Discussion

This large population-based study showed that higher concentrations of Se were significantly associated with the prevalence of developing DM with dose dependent manner. The subgroup analysis according to sex and race/ethnicity showed similar result.

DM is characterized by varying degrees of peripheral insulin resistance and defects in insulin secretion. Although the mechanisms that underlie insulin resistance and DM are not fully understood, several studies point to the role of oxidative stress in the onset and progression of DM [23]. Recent experimental studies have revealed an association between high Se intake and insulin resistance or type 2 DM [28–32]. High Se exposure led to insulin resistance in rodents and pigs [33]. The high Se exposure might affect the expression of key regulators of glycolysis and gluconeogenesis. This action might potentially be mediated by the selenoprotein glutathione peroxidase 1 (GPx1) [33], as demonstrated by a study in experimental animal models [34] that showed overexpression of GPx1 caused obesity and insulin resistance. In skeletal muscles of pigs, high Se exposure led to an increase in GPx1 activity and expression of both forkhead box O1 and peroxisomal proliferator-activated receptor-γ coactivator 1α genes. It also led to a decrease in the expression of the gene for the glycolytic enzyme pyruvate kinase [32]. Reversely, reduced GPx1 expression showed decreased obesity and insulin resistance in mice [35].

The first large randomized trial was the Nutritional Prevention of Cancer (NPC) Trial, in which 200 μg Se per day or a matched placebo was administered to evaluate whether it could reduce the risk of nonmelanoma skin cancer [36]. Stranges et al. performed the secondary analyses with the NPC data and showed an increased risk of type 2 DM among those in the Se intervention group compared to those in the placebo group [11]. Subsequently, the Selenium and Vitamin E Cancer Prevention Trial (SELECT), the largest prostate cancer prevention trial with 35,533 participants showed a statistically non-significant increase in type 2 DM occurred after supplementation with 200 μg/day of Se compared to placebo (RR = 1.07, p = 0.16) [20], but the positive association decreased over time at the end of the supplementation period [37]. Previous studies using NHANES database also showed positive associations between Se and DM [12,13]. A most recent dose–response meta-analysis showed a fairly consistent pattern of positive association between Se concentration and risk of type 2 DM [26]. It was noteworthy since it demonstrated a dose-dependent association between Se and the risk for type 2 DM based on meta-analysis of numerous experimental and nonexperimental studies. The authors ascertained the positive association between Se and DM using recent NHANES data.

In this study, women showed higher OR than men in association between high Se concentration and DM. Recent large studies reported similar [25,26] or even higher risks [21] in women, opposite to previous studies [11–13,38]. Racial differences were also found in this study. Hispanic and non-Hispanic White showed higher risk than non-Hispanic Black. Results from previous NHANES studies [13,14] and a recent randomized trial [25] showed similar racial differences.

The considerable strengths of this study are that a number of populations were included, and predefined subgroup analyses could be

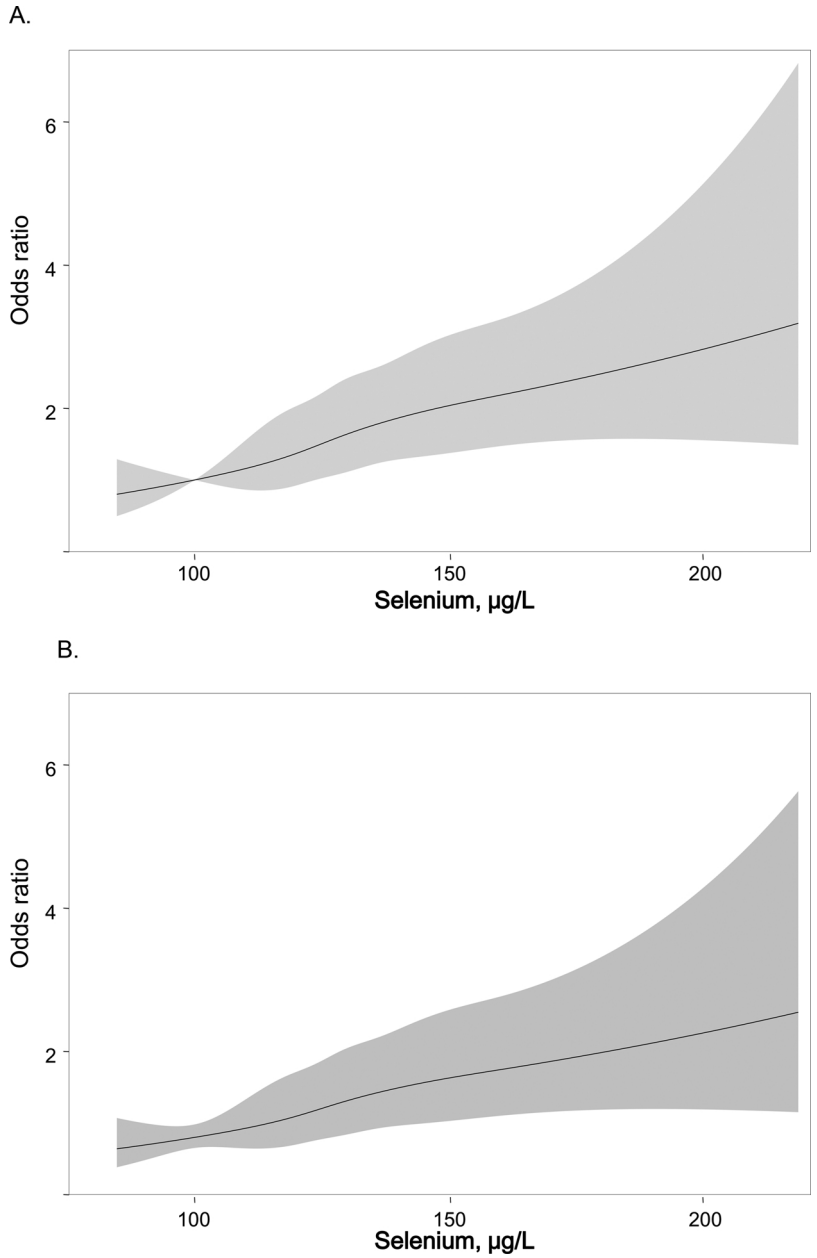

Fig. 3. The relationship between serum selenium level and the odds ratio for DM according to sex.
A, men; B, women
Adjusted for age, race/ethnicity, body mass index, hypertension, and dyslipidemia.

performed by sex and race/ethnicity. However, the present study has several potential limitations. First, since this study is not a prospective study but a cross-sectional study, the authors could analyze only the association between Se level and the prevalence of DM, not the causal relationship. Second, there might be selection bias because large proportion of participants were excluded due to lack of data. Third, the authors were unable to differentiate participants with type 1 DM from those with type 2 DM.

In conclusion, this large population-based study clearly demonstrates a dose-dependent positive association between serum Se level and the prevalence of DM. Although the mechanism remains unclear, our findings could have implications for nutritional supplementation in clinical settings.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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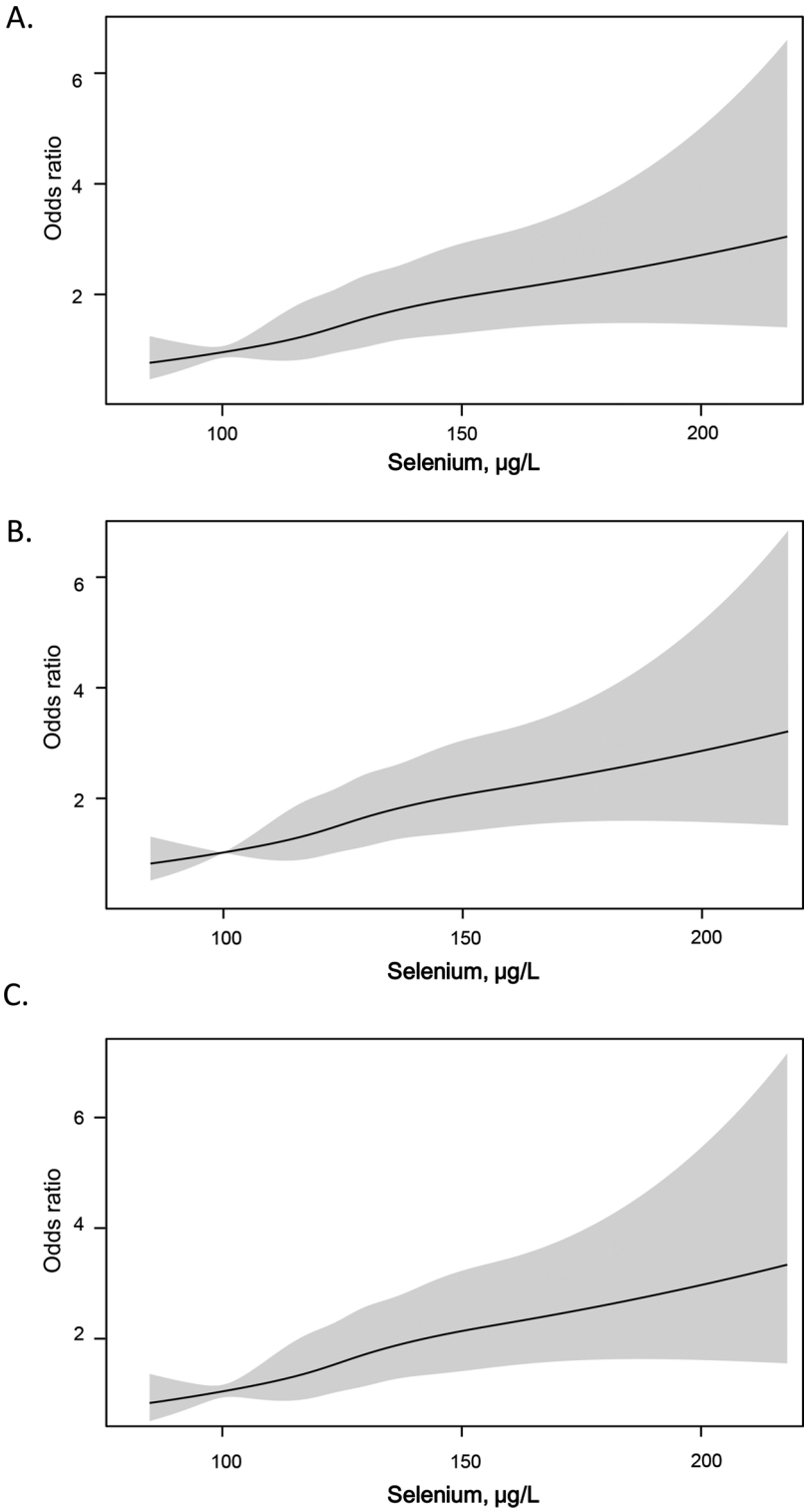

Fig. 4. The relationship between serum selenium level and the odds ratio for DM according to race/ethnicity.
A, Hispanic; B, non-Hispanic White; C, non-Hispanic Black
Adjusted for age, sex, body mass index, hypertension, and dyslipidemia.

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