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Low Serum Selenium Is Associated with Anemia Among Older Women Living in the Community: The Women's Health and Aging Studies I and II

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Abstract

Anemia is common among older adults, and a substantial proportion of anemia in the older population is of indeterminate cause. Low selenium levels have been associated with anemia in animals, but this relationship has not been well characterized in humans. The objective was to determine whether low serum selenium concentrations are associated with anemia among older women. We conducted a cross-sectional analysis of participants in the Women's Health and Aging Studies, a population-based sample of women living in the community in Baltimore, MD, USA. Of 632 women, aged 70–79 yr, 14.1% of women were anemic (hemoglobin <120 g/L). The prevalence of anemia among women in the lowest to highest quartile of serum selenium was 22.4%, 14.6%, 11.9% and 6.6%, respectively ($p < 0.0001$). An increase in $\log_e$ selenium was associated with a reduced risk of anemia (odds ratio per 1 SD increase = 0.63, 95% confidence interval = 0.47–0.84), adjusting for age, education, chronic diseases, iron status, and serum interleukin-6. We conclude that low serum selenium is independently associated with anemia among older women living in the community.

Index Entries

Aging; anemia; hemoglobin; selenium; women

INTRODUCTION

Anemia is common among older adults, and the prevalence of anemia increases with age (1) Major causes of anemia in older adults include iron, folate, and vitamin B₁₂ deficiencies, renal insufficiency (2), and chronic inflammation (3) In the third National Health and Nutrition Examination Survey (1988–1994), one-third of the anemia among adults 65 yr and older occurred in persons free of iron, folate, or vitamin B₁₂ deficiencies, chronic inflammation, or chronic renal disease and was considered unexplained (1) Understanding anemia in older people is important because anemia is associated with fatigue (4), decreased muscle strength and muscle mass (5,6), decline in physical performance (7), disability (5), frailty (8), and increased mortality (9)

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Selenium is an essential trace element and a normal constituent of the diet. Selenium is a component of selenoproteins, including selenoenzymes such as glutathione peroxidase, selenoprotein-P, and thioredoxin reductase (10) The impact of selenium deficiency has not been well characterized in the older population. Serum selenium concentrations seem to decrease with age (11,12) and are lower in people with chronic diseases (12) Low serum selenium concentrations have been associated with increased mortality from cancer (13,14) Low activity of glutathione peroxidase, a major selenoenzyme, was associated with increased risk of cardiovascular events among adults with suspected coronary artery disease (15)

Animal and human studies suggest that there is a link between selenium deficiency and anemia. Among animals, selenium deficiency is associated with anemia in hens (16) and cattle (17), but not rats (18) In humans, selenium deficiency might contribute to anemia among dialysis patients (19) and adults with pulmonary tuberculosis (20) Little is known about the relationship between selenium deficiency and anemia in older adults. We hypothesized that low serum selenium was associated with anemia among older adults. To examine this hypothesis, we characterized serum selenium and hemoglobin concentrations in the Women's Health and Aging Studies I and II, two population-based studies involving older women with and without disability living in the community in Baltimore, MD, USA.

SUBJECTS AND METHODS

Participants in this study were women, aged 70–79 yr, who participated in the Women's Health and Aging Studies (WHAS) I and II, two complementary, population-based studies designed to evaluate the causes and course of physical disability in older women living in the community. WHAS I was recruited from an age-stratified random sample of women aged 65 yr and older selected from Medicare enrollees residing in 12 contiguous zip code areas in Baltimore (21) Women were screened to identify self-reported physical disability that was categorized into four domains by reported difficulty with tasks in the following areas: (1) mobility, (2) upper extremity function, (3) higher functioning household management, and (4) self-care. WHAS I enrolled the one-third most disabled women ages 65 yr and older who had disability in two or more domains. Of the 1409 women who met study eligibility criteria, 1002 agreed to participate in the study in 1992. There were no major differences in sociodemographic or reported health characteristics between eligible participants and those who declined (21) Standardized questionnaires were administered in the participant's home by trained interviewers. Two weeks later, a trained registered nurse conducted an examination of each subject in the participant's home, using a standardized protocol that included physical performance measures and a physical examination. Approximately 75% of the women also consented to phlebotomy performed during a separate visit by a trained phlebotomist who followed a standardized protocol.

WHAS II was specifically designed to be a companion study for WHAS I and includes a cohort of women, aged 70–79 yr, selected to be representative of the two-thirds least disabled women living in the community. Participants were selected via age-stratified random samples from the same sampling frame as in WHAS I and were screened using the same four domains of physical function. Eligible women had either no disability or disability in only one domain. In 1994, 880 women were found eligible for WHAS II, and 436 consented to participate. Those agreeing were more highly educated and reported more diseases than those who refused, but they did not differ significantly in disability characteristics. An interview standardized to that performed in WHAS I was administered in the Johns Hopkins Functional Status Laboratory. Trained technicians then conducted a standardized examination that included a physical examination and physical performance measures. Phlebotomy was performed in 93% of WHAS II participants by a trained phlebotomist, following the same protocol as that used in WHAS I. Demographic characteristics, self-rated health, and information about appetite and

eating were measured in the WHAS questionnaires. Chronic diseases were adjudicated by WHAS co-investigators based on the questionnaire, physical examination, and physician contact (21)

Details on the study methods and sampling design of the WHAS studies are published elsewhere (21,22) For our analyses, the sample population was chosen using a methodology that has been developed by the WHAS research team (23) The overall sample from which this study was drawn consists of women participating in WHAS I ($n = 399$) and WHAS II ($n = 430$) who were 70–79 yr of age. Weights have been calculated to adjust for sampling probability and response rates. This pooled sample has been used in published studies of the association between mobility disability and insulinlike growth factor (23), serum carotenoids and sarcopenia (24), and obesity and frailty (25)

Laboratory Analysis

Nonfasting blood samples were obtained by venipuncture between 0900 and 1400 h. Processing, aliquoting, and freezing were carried out at the Core Genetics Laboratory of The Johns Hopkins University School of Medicine following a standardized protocol. Blood samples were delivered to Quest Diagnostics Laboratories (Teterboro, NJ) on the day of blood drawing for complete blood count and measurements of C-reactive protein, ferritin, folate, and vitamin B₁₂. Serum vitamin B₁₂ and folate were measured by radioimmunoassay (26) Aliquots of serum were stored at -70°C until the time of further analyses.

Serum selenium interleukin-6 (IL-6), and cytomegalovirus antibodies were measured in the laboratory of one of the investigators (R.D.S.). Serum selenium was measured by graphite furnace atomic absorption spectrometry using Perkin-Elmer AAnalyst 600 with Zeeman background correction. For selenium, samples were diluted 1 : 4 with a Triton-X (Sigma Chemical, St. Louis, MO) and nitric acid solution (Fisher Scientific, Pittsburgh, PA), and the matrix modifier was a palladium and magnesium nitrate solution (both Perkin-Elmer, Norwalk, CT). The instrument was calibrated daily using SeroNorm™ Trace Elements Serum Level 1 (Accurate Chemical and Scientific Corp., Westbury, NY). Serum IL-6 was measured using enzyme-linked immunosorbent assay (ELISA) (Quantikine Human IL-6; R & D Systems, Minneapolis, MN). Serum immunoglobulin G antibodies against cytomegalovirus were detected using a quantitative ELISA (CMV IgG ELISA; Zeus Scientific, Inc, Raritan, NJ). All samples were run in a masked fashion. The within-run and between-run coefficients of variation for selenium were 5.8% and 4.8%, respectively.

Statistical Analysis

Probability weights specific to WHAS I and II were used in the analysis in order to make inferences about community-dwelling women aged 70–79 yr based on our study sample. The procedures used to calculate the weights for the WHAS samples are described elsewhere (21, 23) Descriptive statistics were used to characterize the study population, give the distribution of biochemical measurements of micronutrients, and calculate the prevalence of deficiencies. All of the measurements of micronutrients and IL-6 had a skewed distribution and were analyzed using $\log_e$ transformation and are presented as geometric means and 95% confidence intervals (CIs). Chi-square and trend tests were used to examine the associations between anemia and dichotomized covariates. Univariate and multivariate logistic regression were used to examine the relationship between selenium and anemia, with sequential models adjusting for demographic, chronic disease, nutritional, and inflammation variables that were significant ($p < 0.05$) in univariate analyses. To assess the relative strength of associations between selenium and anemia, odds ratios (ORs) and 95% CIs associated with a one standard deviation increase in $\log_e$ selenium were reported.

Anemia was defined according to the World Health Organization definition of hemoglobin (<120 g/L among women) (1) Vitamin B₁₂ deficiency and folate deficiency were defined using standard cutoffs of <300 pg/mL and <5.0 ng/mL, respectively (27) A serum creatinine concentration >1.4 mg/dL was considered consistent with renal disease (21) Quartiles of selenium were defined as <1.38, ≥1.38 to <1.53, ≥1.53 to <1.68, and ≥1.68 μmol/L (<109.5, ≥109.5 to <120.7, ≥120.7 to <132.3, and ≥132.3 μg/L). The statistical programs used were SAS (SAS Institute, Cary, NC) (28) for data management and Stata (Stata Corporation, College Station, TX) (29) for weighted analyses. *p*-Values of ≤0.05 were considered statistically significant.

RESULTS

There were 632 of 829 women in WHAS I and II, aged 70–79 yr, who participated in the blood drawing and had hemoglobin and other laboratory measures available for the analysis. Women who did not participate in the blood drawing had a significantly lower income and had a higher proportion of self-reported poor appetite, poorer self-perceived health, and higher rate of disability than women who participated in the blood drawing, as reported elsewhere (30) Overall, 89 of 632 women (14.1%) were anemic (hemoglobin <120 g/L). The demographic, health, and nutritional characteristics of women with and without anemia are shown in Table 1. A significantly higher proportion of women with anemia were black and had education <12 yr, diabetes mellitus, cardiovascular disease, positive cytomegalovirus serostatus, elevated serum IL-6, ferritin <30 mg/L, and lower serum selenium compared to women without anemia. The prevalence of anemia among women in each quartile of serum selenium is shown in Fig. 1. The prevalence of anemia decreased with increasing quartile of selenium ($p < 0.0001$). We also show the prevalence of anemia among women in each quartile of serum selenium when women with iron, folate, and/or vitamin B₁₂ deficiencies are excluded and that the prevalence of anemia decreased with increasing quartile of selenium ($p < 0.0001$) (Fig. 1).

Multivariate logistic regression models were used to examine the relationship between different risk factors and anemia (Table 2). Selenium was strongly and significantly associated with anemia in models that adjusted for demographic factors (model 1), demographic factors and chronic diseases (model 2), and demographic factors, chronic diseases, serum ferritin, and IL-6 (model 3).

DISCUSSION

This study shows that low serum selenium is an independent risk factor for anemia among older women living in the community based on cross-sectional analyses. Selenium deficiency has not usually been considered as a possible cause of anemia in older adults (1,31) and has only been implicated in anemia among patients on hemodialysis (19) or with pulmonary tuberculosis (20) However, a strong and direct correlation between low plasma selenium concentrations and low hemoglobin has also been noted in the British National Diet and Nutrition Survey among 1134 men and women aged 65 yr and older (12)

A potential biological mechanism by which selenium could contribute to anemia is through maintenance of an optimal concentration of glutathione peroxidase, a key antioxidant selenoenzyme, in erythrocytes (32) Glutathione peroxidase protects hemoglobin against oxidation in erythrocytes (33) Although there is little direct evidence that serum selenium is related to erythrocyte and hemoglobin stability in humans, there is a possible relevant example of erythrocyte damage resulting from increased oxidative stress in animals (34) and possible protection by selenium. Livestock that forage on *Brassica* (mustard, rape) are susceptible to brassica anemia, in which oxidative stress causes excessive erythrocyte damage (35) and

selenium supplementation has been shown to protect animals against erythrocyte damage (36–38)

The dietary intake of selenium varies widely worldwide, as selenium concentrations in plant-based foods reflect the concentrations of selenium in the soil where the plants were grown. The selenium concentrations in animal sources of food, in turn, depend on the selenium content of the plants used for forage or whether animal feed was fortified with selenium. Clinical selenium deficiency is rare and is seen in keshan disease, an endemic cardiomyopathy found in low selenium areas of China where affected persons might have serum selenium $<0.25 \mu\text{mol/L}$ ($20 \mu\text{g/L}$) (27,39). The current dietary requirements for selenium by the Food and Nutrition Board of the Institute of Medicine are based in part on maintenance of optimal levels of selenoproteins in blood, especially plasma glutathione peroxidase (39). The selenium requirement for prevention of chronic disease has not yet been definitively determined (40). It is thought that serum selenium concentrations should be at least $1.27 \mu\text{mol/L}$ ($100 \mu\text{g/L}$) in order to have optimal activity of glutathione peroxidase, a major antioxidant enzyme (27). The baseline serum selenium concentrations at which there appeared to be a protective effect of selenium supplementation against cancer in two US trials was $1.34\text{--}1.54 \mu\text{mol/L}$ ($106\text{--}147 \mu\text{g/L}$) (40). About half of the women in WHAS in the present study had serum selenium levels $<1.54 \mu\text{mol/L}$. Except for overt clinical selenium deficiency, the health consequences of an inadequate selenium intake are incompletely understood and selenium requirements for older adults are largely extrapolations from middle-aged adults (39).

This study raises a potentially important public health question: Has selenium deficiency been overlooked as a cause of anemia among older adults? Except for the present study and the British National Diet and Nutrition Survey (12), little has been done to examine the relationship between serum selenium and anemia. To our knowledge, it is not known whether improving dietary selenium intake will increase hemoglobin concentrations among older adults with low serum selenium concentrations.

In conclusion, low serum selenium was independently associated with anemia among older women living in the community. This study might represent a first important step toward determining whether selenium deficiency is a potential cause of anemia among older adults. Further work is needed to corroborate these findings in other populations, provide evidence for longitudinal causal associations, identify underlying biological mechanisms, and determine whether improving selenium status has an impact on anemia in older adults.

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Fig. 1.

Prevalence of anemia by quartile of selenium. Black bars indicate total study population ($N = 632$). Gray bars indicate subsample in which women with iron, folate, and vitamin B₁₂ deficiencies were excluded ($N = 511$) ($p < 0.0001$ by the Mantel-Haenszel χ^2 test, for both).

Table 1

Characteristics of Women With and Without Anemia (Hemoglobin <120 g/L) in the Women's Health and Aging Studies I and II, Age 70–79

Characteristic ¹	Anemic N = 89	Non-Anemic N = 543	P
Age (years)	74.6	74.1	0.2
Race, black (%)	49.4	16.9	<0.0001
Body mass index, kg/m ² (%)			
<18.5	5.8	4.9	0.0002
18.5–24.9	23.7	33.2	
25.0–29.9	32.9	36.1	
≥30	37.7	25.8	
Education <12 years (%)	62.5	39.0	0.0002
Current smokers (%)	7.2	12.9	0.12
Taking multivitamins (%)	19.4	22.8	0.53
Fair/poor appetite (%)	21.1	15.1	0.16
Diabetes mellitus (%)	27.4	9.32	<0.0001
Cardiovascular disease (%)	33.1	19.6	0.007
Osteoarthritis (%)	35.8	35.5	0.96
Chronic pulmonary disease (%)	11.5	19.6	0.08
Cancer (%)	12.3	8.4	0.23
Rheumatoid arthritis (%)	4.3	1.6	0.08
Renal disease (%)	16.5	3.0	<0.0001
Positive CMV serostatus (%)	96.0	85.7	0.02
IL-6 (pg/L) ²	4.26 (3.66–4.97)	3.32 (3.13–3.52)	0.003
C-reactive protein level ≥6 mg/L (%)	27.4	10.5	0.16
Ferritin (mg/L) ²	59.6 (46.5–76.4)	79.0 (74.1–84.8)	0.03
Ferritin <30 mg/L (%)	26.1	10.5	<0.0001
Selenium (μg/L) ²	112 (108–116)	122 (120–124)	<0.0001
Folate (nmol/L) ²	22.3 (19.3–25.8)	21.8 (20.6–23.1)	0.10
Folate level <6.7 nmol/L (%)	2.1	1.6	0.72
Vitamin B ₁₂ (pg/mL) ²	447 (387–513)	437 (419–495)	0.82
Vitamin B ₁₂ level <150 pg/mL (%)	4.0	1.9	0.35

¹Population-weighted means and percentages.

²Geometric mean (95% CI).

Table 2
Multivariate Logistic Regression Models of Risk Factors for Anemia

Variable	OR ¹	95% CI	P
<u>Crude Model</u>			
Log selenium	0.58	0.46–0.73	<0.0001
<u>Model 1</u>			
Log selenium	0.60	0.47–0.75	<0.0001
Age (years)	1.06	0.96–1.17	0.26
Education <12 years	2.29	1.34–3.91	0.002
<u>Model 2</u>			
Log selenium	0.57	0.44–0.75	<0.0001
Age (years)	0.98	0.87–1.12	0.82
Education <12 years	1.52	0.76–3.05	0.23
Body mass index	1.00	0.96–1.05	0.92
Diabetes mellitus	2.92	1.31–6.47	0.009
Cardiovascular disease	1.38	0.71–2.72	0.34
Renal disease	4.82	1.58–14.7	0.006
Positive CMV serostatus	2.57	0.75–8.84	0.13
<u>Model 3</u>			
Log selenium	0.63	0.47–0.84	0.002
Age (years)	0.97	0.84–1.11	0.63
Education <12 years	1.55	0.76–3.16	0.23
Body mass index	1.00	0.95–1.05	0.92
Diabetes mellitus	3.34	1.50–7.42	0.003
Cardiovascular disease	1.62	0.81–3.25	0.17
Renal disease	5.18	1.70–15.8	0.004
Positive CMV serostatus	2.53	0.75–8.49	0.13
Ferritin <30 mg/L (%)	2.91	1.26–6.72	0.01
Log IL-6	0.84	0.49–1.40	0.50

¹ OR per 1 SD increase in log_e selenium.