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Selenium supplementation has no effect on serum glucose levels in men at high risk for Prostate Cancer

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Abstract

Background—Current literature regarding the effect of selenium supplementation on risk of diabetes is inconclusive. Hence a longitudinal study was conducted to investigate the effect of selenium supplementation on serum glucose levels in elderly men.

Methods—Data were obtained from 699 men participating in a randomized, double-blind, placebo-controlled Phase 3 clinical trial investigating the effect of two doses of selenium (200 and 400 µg/day) compared to placebo on incidence of prostate cancer. Subjects were followed every six months for up to five years. Serum glucose levels were obtained every six months. Mixed effects regression models were used to assess if rate of change of serum glucose levels was significantly different in the selenium supplemented groups as compared to placebo. Sensitivity analyses were performed to assess the robustness of findings and to minimize the possibility of residual bias due to fasting status.

Results—Of the total 2893 glucose measurements, 734 were carried out when the subject had been fasting for 8 hours. The changes in serum glucose levels during the course of the trial were not statistically significantly different as compared to placebo for the selenium 200 µg/day ($p = 0.98$) or selenium 400 µg/day ($p = 0.81$) treatment groups. Sensitivity analyses demonstrated comparable results for models using the total population and models restricted to subjects with only fasting glucose data.

Conclusion—These results do not support a relationship between selenium supplementation and risk of diabetes. Hence recommendations regarding selenium supplementation based on increased risk of diabetes seem premature.

Keywords

selenium supplementation; serum glucose; prostate cancer

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Introduction

Results from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) and the Nutritional Prevention of Cancer (NPC) study indicate that selenium may be associated with increased risk of type-2 diabetes. SELECT was a Phase 3 randomized, placebo-controlled, double-blind clinical trial conducted to assess whether supplementation with 200 µg/day selenium and/or 400 IU/day vitamin E would prevent prostate cancer in average risk men¹. Although the study concluded that selenium did not prevent prostate cancer in this population, they reported a statistically non-significant increased risk of type 2 diabetes in the selenium group (relative risk: 1.07 (99% CI: 0.94–1.22), $p = 0.16$) but not in the selenium + vitamin E group¹. A secondary analysis of data from the NPC study indicated that 58 subjects in the selenium supplemented group ($n = 600$) and 39 subjects in the placebo group ($n = 602$) developed Type-2 diabetes (hazard ratio: 1.55 [95% CI: 1.03, 2.33])². This association was more prominent in the highest tertile of baseline selenium (hazard ratio: 2.70 [95% CI: 1.30, 5.61])². In a cross-sectional study using data from 8,876 adults participating in the Third National Health and Nutrition Examination Survey (NHANES III) Bleys *et al* reported an increased risk for diabetes in subjects having high serum selenium concentrations [odds ratio (OR) and 95% CI: 1.57 (1.16, 2.13)]³.

However, using a longitudinal study design our group was able to demonstrate in a small study ($N = 140$) that serum glucose trajectories of men with biopsy-proven prostate cancer supplemented with 200 or 800 µg of selenium per day for up to five years were not statistically significantly different from placebo (p -values 0.56 and 0.91 respectively)⁴.

Results such as these have led to uncertainty amongst physicians regarding appropriate recommendations for their patients with regards to selenium and diabetes. Selenium is an essential micronutrient that plays an important role in many biologic systems and processes⁵; hence a thorough understanding of its effect on biological processes is needed for accurate public health recommendations. To expand on previous results, we conducted a longitudinal study to determine the effect of selenium supplementation on serum glucose levels using data from 699 men enrolled in a Phase 3 clinical trial of selenium supplementation (average duration = 3 years) in the setting of prostate cancer prevention for men at high risk for this disease.

Methods

Data for this study were obtained from samples collected during the Negative Biopsy Trial (NBT), a randomized, double-blind, placebo-controlled, multi-center, Phase 3 clinical trial of selenium supplementation for prevention of prostate cancer⁶. Men enrolled in this trial were at high risk of prostate cancer as evidenced by prostate specific antigen (PSA) > 4 ng/ml and/or suspicious digital rectal examination and/or PSA velocity (rate of PSA change over time) > 0.75 ng/ml/year. Additionally, subjects were required to have undergone a prostate biopsy negative for cancer within 12 months of enrollment. A total of 699 subjects were randomized to receive placebo ($N = 232$), selenium 200 µg/day ($N = 234$), or selenium 400 µg/day ($N = 233$). They were followed every six months for up to five years. Serum selenium concentrations and PSA were measured at baseline and at each follow up visit. Detection of biopsy-proven prostate cancer was the primary endpoint of the NBT. Results indicated that as compared to placebo, the risk of developing prostate cancer was not statistically significantly different in the selenium 200 µg/day or the selenium 400 µg/day groups (Hazard ratio and 95% confidence intervals 0.94 [0.52, 1.7] and 0.90 [0.48, 1.7])⁶. Out of the 699 men enrolled in the NBT, 73 men were diagnosed with prostate cancer on subsequent biopsy.

Serum glucose levels were measured at baseline and at alternate follow-up visits by Sonora Quest Laboratories (Tucson, AZ). Plasma selenium was measured at baseline and at every follow-up visit using electrothermal atomic absorption spectrophotometry⁷. Glucose values were transformed using the logarithmic function in order to correct for skewed distribution. Questionnaires at baseline and at every follow-up visit recorded diabetes status. A total of 99 subjects reported being diagnosed with diabetes at baseline (N = 68) or during the course of the study (N = 31). The time of blood collection and time since last meal were noted at the time of blood collection; and these data were used to create a variable to determine the fasting status (≥ 8 hours since last meal) of each subject at each visit. This variable was included in statistical models to account for variability in fasting status as been done by Bleyer et al⁸.

The effect of selenium supplementation on glucose levels over time was assessed using mixed-effects regression models⁹. Statistical significance of an interaction term between treatment group and time-on-study was used to assess the significance of association between selenium supplementation and change in glucose levels over time. Models were adjusted for race, age, fasting status and baseline selenium. Subjects diagnosed with diabetes before or during the trial were included in this analysis. Sensitivity analyses using only fasting serum glucose data were performed to assess the robustness of findings¹⁰. Fasting serum glucose measurements (time since last meal ≥ eight hours) were available from 278 subjects (734 individual glucose measurements). Sensitivity analysis was conducted on these data to compare the results with the model using data from the total population.

Results

Table 1 shows baseline descriptive statistics for three treatment groups and indicates that treatment groups were statistically balanced at baseline. Table 2 demonstrates mean and standard deviation (SD) of serum glucose levels for each visit by treatment groups for the total population as well as for subjects having fasting blood glucose data. In the total population, as compared to placebo, changes in the serum glucose levels in the selenium 200 and 400 µg/day treatment groups were not statistically significantly different (*p*-values 0.98 and 0.81 respectively). Sensitivity analysis conducted on subjects with all fasting glucose data also demonstrated no effect of selenium supplementation on serum glucose levels (*p*-values were 0.14 and 0.97 respectively) and concurred with the findings from the total population. In this dataset 734 glucose measurements from 278 subjects were available. However, for calculating the effect of selenium supplementation on blood glucose, measurements from only those subjects that had at least two serum glucose measurements were used. This was done as at least two measurements are needed to calculate PSA velocity. This resulted in 590 individual serum glucose measurements from 192 subjects, as serum glucose measurements from subjects having only one glucose measurement were excluded. Table 3 demonstrates a sub-set analysis using data from subjects diagnosed with diabetes before or during the conduct of the parent clinical trial. These results also concur with the results obtained from data from the total population and conclude that as compared to placebo, selenium supplementation does not statistically significantly affect serum glucose levels (*p*-values 0.86 and 0.33 respectively for 200 and 400 µg/day treatment groups) in men diagnosed with diabetes.

Time of sample collection was used to create a variable “Time of day” which was coded as 0 = AM (< 12 noon) and 1 = PM (>12 noon). This variable was included in mixed effects regression model to determine if time of sample collection had an effect on the association between selenium supplementation and serum glucose levels. Results from this analysis indicate that as compared to placebo, the serum glucose levels of subjects supplemented with selenium were not statistically significantly different (*p*= 0.65 and 0.99 respectively).

These results did not change upon stratifying the analysis by the “time of day”. This indicates that time of day did not have an effect on relationship between selenium supplementation and serum glucose levels in this analysis. In a subset analysis, the percentage of men diagnosed with prostate cancer was lower among diabetics as compared to non-diabetics (3.7% vs 11.3%). This difference however was not statistically significant ($p=0.2$). These results are consistent with results previously reported by other research groups¹¹.

Analysis was conducted to determine if proportion of normal, pre-diabetic and diabetic subjects changed during the course of the study. If selenium supplementation had an effect on serum glucose, you would expect these proportions to be different between the beginning and end of this study. This classification was based on fasting blood sugar levels (<100 classified as normal, 100–126 classified pre-diabetic and >126 classified as diabetic). Proportions of each of the three groups at the beginning and end of the study were compared (table 4). These results indicate no statistical difference in the proportions between the beginning and end of the study. Serum glucose levels before selenium supplementation and at the end of the study were also compared to determine the effect of selenium supplementation on serum glucose (table 5). These results also did not indicate a statistically significant difference adding more evidence that selenium supplementation has no effect on serum glucose levels.

Discussion

A longitudinal study conducted to investigate the effect of selenium supplementation on serum glucose levels in a cohort of men at high risk for prostate cancer (PSA > 4 ng/ml and/or suspicious digital rectal examination and/or PSA velocity >0.75ng/ml/year) indicates that as compared to placebo, supplementation with 200 or 400 µg/day of selenium does not statistically significantly affect serum glucose levels. These results are similar to the results reported earlier by us in a population of men diagnosed with prostate cancer⁴. Interestingly, these results do not support the association between selenium and diabetes that has been reported by other investigators^{1–3}. These studies had some limitations. In a secondary analysis of the NPC study, diabetes was not the primary outcome and it was self-reported² whereas in the SELECT analysis, not only was the diabetes status self-reported, but the relative risk was not statistically significant¹. Thirdly, in the analysis by Bleys *et al*, temporal association between serum selenium and serum glucose levels could not be definitively established due to its cross-sectional study design³.

In our study, we attempt to address some of the shortcomings that were present in previous reports. Because serum glucose values were used as an outcome in this study, there was reduction in bias associated with self-report and misclassification associated with diagnosis of diabetes, both of which were limitations for SELECT and secondary analysis of the NPC study. Measuring serum glucose every six months provided more accurate characterization of the change in glucose levels over time and a more powerful estimate than could be obtained using measurement at a single time point. The longitudinal study design also addressed the issue of temporality of the association between selenium and serum glucose levels, which was a limitation in the earlier cross-sectional study by Bleys and colleagues³. In this study, mean baseline serum selenium levels were statistically significantly higher for the total population as well as for each of the tertiles as compared to the NPC study ($p < 0.001$ for the total population and each tertile)⁶. If the hypothesis held true that selenium supplementation leads to an increase in serum glucose levels; the likelihood of seeing this effect would be higher in a population with higher baseline selenium supplemented with a higher dose of selenium (400 µg/day in this study). Data from the current study do not reflect this.

The current study analyzes data from 699 subjects. Multiple measurements of serum glucose from the same subjects resulted in 2893 separate data points for serum glucose, which increased the statistical power of this study as compared to studies having data from only one time point. It would have been ideal if all glucose measurements were determined under fasting conditions. However, this was not part of the IRB-approved protocol for the parent clinical trial due to potential negative effects on adherence and subject participation. Thus, models were adjusted to take this into account in a manner similar to that carried out by Bleyer et al⁸. We performed sensitivity analyses¹⁰ to assess the robustness of our results. These analyses demonstrate comparable results between an analysis of the total population and an analysis restricted to subjects with fasting glucose measurements. Another sub-set analysis conducted to investigate the effect of selenium supplementation on serum glucose levels in men diagnosed with diabetes also yielded similar results. These results are specific to men at high risk of prostate cancer and may not be generalizable to the total population.

Results from this study do not support conclusions drawn in earlier reports that indicate selenium supplementation may increase the risk of diabetes. Randomized controlled trials specifically designed to test this association are required before definitive statements and public health recommendations about effect of selenium supplementation on risk of diabetes can be made.

Acknowledgments

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The significant finding(s) of this study

- In this longitudinal analysis serum glucose levels in men supplemented with selenium did not change significantly as compared to placebo.
- This indicates that selenium supplementation did not influence serum glucose levels in these men

This study adds

- This longitudinal study indicates selenium supplementation does not alter serum glucose. Therefore, it seems unlikely that selenium supplementation increases the risk of diabetes as suggested by prior literature

Table 1

Descriptive statistics by treatment group

Variable	Total population (N= 699)	Placebo (N = 232)	Se 200µg (N = 234)	Se 400µg (N =233)	p-value
Age at enrollment (mean, SD, years)	65.4 (7.7)	65.5(7.4)	65.2(8.0)	65.5(7.7)	0.84
Baseline PSA (mean, SD, ng/ml)	6.8(5.5)	6.4(5.6)	7.2(6.2)	6.9(4.5)	0.41
Baseline Selenium (mean, SD, ng/ml)	126.1(25.5)	124.5(24.7)	126.6(26.9)	127.2(24.8)	0.51
End of study selenium (mean, SD, ng/ml)	166.4 (44.8)	131.3(21.2)	166.7(43.5)	202.7(70.9)	<0.001
Caucasians (n, %)	577(83.5)	192(84.2%)	195(83.7%)	190(82.6%)	0.90
Baseline Serum glucose levels (mean, SD, ng/ml)	100.7(23.5)	102.3(23.2)	100.5(26.5)	99.2(20.4)	0.72
Diabetes prevalence at baseline (N, %)	68 (9.7)	23 (9.9)	22 (9.4)	23 (9.8)	0.98
Diabetes incidence during study	31 (4.4)	7 (3.0)	12 (5.1)	12 (5.2)	0.44

Note: To calculate p-value, ANOVA used for continuous variables and chi-square for categorical variables.

Table 2

Table showing mean (SD) for serum glucose (ng/ml) levels at each visit

Visit	Total		Placebo		Se 200µg/day		Se 400µg/day	
	N	Serum Glucose	N	Serum Glucose	N	Serum Glucose	N	Serum Glucose
Total population								
1	581	107.5 (37.1)	190	109.6 (41.4)	198	107.5 (37.3)	193	105.4 (32.0)
2	581	109.5 (37.7)	190	108.4 (36.5)	198	111.8 (41.1)	193	108.1 (35.4)
3	489	110.4 (37.9)	161	108.9 (35.4)	169	110.6 (41.9)	159	111.6 (36.2)
4	409	107.7 (34.7)	140	105.1 (31.8)	130	112.3 (43.4)	139	105.9 (27.6)
5	331	109.3 (37.4)	118	110.8 (40.7)	109	108.1 (36.9)	104	108.9 (34.3)
6	259	107.1 (33.6)	93	106.6 (36.4)	81	107.1 (28.7)	85	107.7 (35.1)
7	183	109.4 (35.8)	65	111.6 (33.4)	61	106.0 (24.2)	57	110.6 (47.5)
8	44	116.3 (42.5)	17	123.2 (52.3)	15	106.9 (27.3)	12	118.3 (48.9)
9	10	126.8 (67.3)	4	160.5 (101.5)	5	103.4 (23.9)	1	109.0
10	4	135.8 (91.6)	3	154.3 (102.5)	1	80.0	1	NA *
11	1	199.0	1	199.0	0	NA *	0	NA *
12	1	240	0	240	0	NA *	0	NA *
Total	2893		983		967		943	
p-value**				Reference		0.98		0.81
Fasting subjects								
1	192	104.3 (30.0)	70	105.8 (34.6)	58	101.6 (23.5)	64	105.6 (30.8)
2	192	105.1 (27.7)	70	103.8 (30.2)	58	110.5 (31.1)	64	101.7 (20.2)
3	109	104.9 (21.8)	35	102.5 (19.7)	35	105.9 (22.7)	39	106.3 (23.2)
4	59	104.4 (18.2)	22	106.5 (14.8)	14	101.6 (17.6)	23	104.1 (21.7)
5	25	106.7 (20.0)	9	110.8 (20.3)	5	103.2 (19.6)	11	104.9 (21.3)
6	10	109.2 (27.3)	4	103 (6.58)	3	124.3 (52.3)	3	102.3 (8.32)
7	3	114 (21.4)	2	122.5 (21.9)	1	97	0	NA
Total	590		212		174		204	
p-value**				Reference		0.14		0.97

* Did not have subjects in these categories to calculate mean and SD.

** p-values were determined using mixed effects regression models. Please see statistical analysis section for further detail. N = number of glucose measurements

Table 3

Table showing mean (SD) for serum glucose (ng/ml) levels at each visit for subjects diagnosed with diabetes before or during the course of the study

Visit	Total		Placebo		Se 200µg/day		Se 400 µg/day	
	N	Serum Glucose	N	Serum Glucose	N	Serum Glucose	N	Serum Glucose
1	92	145.4 (63.1)	25	159.2 (83.2)	34	142.2 (58.1)	33	138.2 (49.6)
2	92	147.4 (63.0)	25	146.8 (72.1)	34	149.0 (69.6)	33	146.3 (48.8)
3	80	155.0 (59.9)	21	158.3 (63.4)	31	159.3 (60.0)	28	147.9 (58.5)
4	67	143.4 (60.1)	18	143.9 (55.4)	23	156.1 (76.8)	26	131.7 (44.5)
5	56	138.8 (62.6)	16	155.6 (80.2)	19	133.1 (54.9)	21	131.3 (54.0)
6	46	136.2 (50.5)	13	139.9 (67.8)	15	138.0 (41.8)	18	132.1 (45.2)
7	27	152.6 (69.3)	7	172.4 (57.9)	7	152.6 (30.3)	13	141.9 (89.0)
8	10	171.4 (56.9)	4	207.0 (38.5)	2	147.5 (43.1)	4	147.8 (69.3)
9	2	204 (134.4)	1	299	0	NA *	1	109
10	1	272	1	272	0	NA *	0	NA *
11	1	199	1	199	0	NA *	0	NA *
12	1	240	1	240	0	NA *	0	NA *
Total	475	133		Reference	165		177	
p-value **						0.86		0.33

* Did not have subjects in these categories to calculate mean and SD.

** p-values were determined using mixed effects regression models. Please see statistical analysis section for further detail. N = number of glucose measurements.

Table 4

Proportion of normal, pre-diabetic and diabetic subjects at baseline and end of study

Category	Baseline, N(%)	End of study, N(%)	p-value
Normal	61 (56.5%)	40 (54.1%)	0.54
Pre-diabetic	33 (30.6%)	25 (33.8%)	0.78
Diabetic	14 (12.9%)	9 (12.2%)	0.79
Total	108 (100%)	74 (100%)	

Table 5

Serum glucose levels at baseline and end of study

Category	Baseline (ng/ml)	End of study (ng/ml)	p-value
Normal	88.5 (10.3)	92.1 (7.3)	0.06
Pre-diabetic	108.4 (5.1)	107.6 (6.8)	0.09
Diabetic	169 (63.4)	144.7 (37.8)	0.53