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No effect of selenium supplementation on serum glucose levels in men with prostate cancer

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Abstract

Background—Literature indicates a relationship between selenium supplementation and risk of diabetes. However, since these data are inconclusive we investigated the effect of selenium supplementation on serum glucose levels in men with prostate cancer enrolled in a clinical trial testing of the effect of selenium on prostate cancer progression.

Methods—Subjects were randomized to receive placebo (N = 46), selenium 200 µg/day (N = 47) and selenium 800 µg/day (N = 47). Serum glucose levels were obtained every six months for up to five years. Longitudinal analysis was carried out 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.

Results—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 = 0.56) or selenium 800 µg/day (p = 0.91) treatment groups.

Conclusion—These results do not support a relationship between selenium supplementation and changes in serum glucose levels. Recommendations regarding selenium supplementation and risk of diabetes will require more definitive studies.

Keywords

Selenium supplementation; serum glucose; prostate cancer

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Introduction

Although, selenium supplementation has been reported to be inversely associated with prostate cancer risk ¹⁻³, recent reports indicate it may increase the risk of Type-2 diabetes. In secondary analyses of data from the Nutritional Prevention of Cancer (NPC) study, 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]) ⁴. Results were prominent in the highest tertile of baseline selenium (hazard ratio: 2.70 [95% CI: 1.30, 5.61]) ⁴. In a cross-sectional study, Bleys *et al* reported an odds ratio of 1.57 (95% CI: 1.16, 2.13) for diabetes (N = 8,876) ⁵.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a phase 3 randomized 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 men ⁶. Interim review indicated that selenium did not prevent prostate cancer in this population ⁶. A statistically non-significant increased risk of Type 2 diabetes was observed in the selenium group ($p = 0.16$) but not in the selenium + vitamin E group ⁶.

Each study has its limitations. In secondary analysis of NPC, diabetes was not the primary outcome and it was self reported ⁴. In the SELECT analysis, not only was the diabetes status self reported, but the relative risk was not statistically significant ⁶. 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 design ⁵. The objective of the current study was to investigate the effect of selenium supplementation on serum glucose levels in a cohort of men with biopsy-proven prostate cancer on active surveillance for their disease. Selenium is an important nutritional trace element, hence understanding its effect on biological processes is essential before public health recommendations can be made.

Methods

A secondary analysis was carried out using data from a pre-existing randomized clinical trial ⁷ designed to investigate the effects of selenium on prostate cancer progression (Watchful Waiting Trial). Subjects had biopsy proven, non-metastatic prostate cancer and had elected to be followed by active surveillance (watchful waiting) for their disease. A total of 140 men were randomized to placebo (n = 46), 200 µg selenium/day (n = 47), or 800 µg selenium/day (n = 47) and followed every three months for up to five years. 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 spectrophotometry. 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. Thirteen subjects reported having diabetes at baseline and six others reported being diagnosed with diabetes during the trial. These 19 subjects were not included in the longitudinal analysis. Subjects in the three treatment groups achieved steady state concentrations of selenium in a dose-dependent manner within the first two years (figure 1). Therefore, treatment groups were used as a proxy for serum selenium levels for longitudinal analysis. 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 the mixed effects model to account for variability in fasting status as been done by Bleyer *et al* ⁸.

Mixed-effects models ⁹ were used to assess the effect of selenium supplementation on glucose levels over time. 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, pack-years of smoking, body mass index (BMI), fasting status, baseline serum glucose and Gleason score. Sensitivity analyses using only fasting serum glucose data were performed to assess the robustness of findings¹⁰. Thirty-six men had all fasting serum glucose measurements (time since last meal $\geq$ eight hours). Sensitivity analysis was conducted on these 36 subjects to compare the results with the model used for the total population adjusted for fasting status.

Results

There were no statistically significant differences in glucose levels during the course of the trial in men supplemented with selenium as compared to those on placebo. The *p*-values comparing changes in glucose levels during the course of the trial for selenium 200 and 800 μ g/day treatment groups with placebo were 0.56 and 0.91 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 0.21 and 0.76 respectively).

Comment

Serum glucose levels in subjects supplemented with 200 or 800 μ g/day of selenium were not statistically significantly different than those observed in subjects on placebo. These results do not support previous conclusions regarding association between selenium and diabetes in other studies^{4–6}. The current analysis does provide distinct advantages over previous studies. 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 NPC. 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. Based on adherence (Figure 1), bias due to differential rates of compliance was not a confounding factor. 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 colleagues⁵.

In the NPC trial, the odds ratio for the association between diabetes and selenium supplementation was strongest in the highest tertile of baseline selenium (hazard ratio = 2.70 [95% CI, 1.30 to 5.61])⁴. In our 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)¹. If the hypothesis that selenium supplementation leads to an increase in serum glucose levels held true; the likelihood of seeing this effect would be higher in a population with higher baseline selenium supplemented with a higher dose of selenium (800 μ g/day in the Watchful Waiting trial). Current data do not reflect this.

Although a sample size of 140 is relatively small, repeated measures for serum glucose (*n* = 853) increase the statistical power as compared to studies having only one time point. It would have been ideal if the blood for measuring glucose was collected after all the subjects had fasted for at least eight hours. But this was not part of the IRB-approved protocol when the parent study was instituted. Models were statistically adjusted to take this into account as has also been done by Bleyer et al⁸. Sensitivity analyses were performed to assess the robustness of findings¹⁰. Results from these analyses demonstrated comparable results for

analysis conducted for the total population and the analysis restricted to subjects with only fasting data.

These results indicate the putative diabetes risk associated with selenium supplementation may be unfounded. Definitive studies need to be performed before recommendations can be made.

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Figure 1.

Mean serum selenium levels (upper panel) and glucose levels (lower panel) at each quarterly clinic visit for subjects receiving placebo (●), 200 µg/day selenium (■), or 800 µg/day selenium (▲) during the Watchful Waiting Trial. Table indicates number of subjects contributing data at selected clinic visits.

Table 1
Descriptive statistics by treatment group for men enrolled in the Watchful Waiting Trial

Variable	Total population (n = 140)	Placebo (n = 46)	Se 200 µg/day (n = 47)	Se 800 µg/day (n = 47)	p-value [*]
Baseline Age (mean, SD, years)	72.8 (6.65)	72.9 (6.5)	73.6 (6)	72 (7.5)	0.50
Baseline Body Mass Index (mean, SD, Kg/m ²)	26.9 (4.1)	27.0 (4.3)	25.7 (3)	27.8 (4.6)	0.03
Baseline PSA (mean, SD, ng/ml)	7.9 (6.2)	7.4 (5.6)	8.0 (7.0)	8.3 (6.2)	0.79
Baseline Selenium (mean, SD, ng/ml)	134.5 (41.5)	127.9 (17.3)	129.8 (21.3)	145.7 (65.3)	0.07
Baseline Pack-years of smoking (mean, SD)	23.3 (29.8)	22.3 (27.6)	21.2 (27.6)	26.5 (34.1)	0.67
Baseline Glucose (mean, SD, mg/dl)	100.4 (26.4)	101.9 (26.1)	102.9(28.4)	96.6 (25.0)	0.48
Caucasians (n, %)	123 (87.86%)	40 (86.96%)	42 (89.36%)	41 (87.23%)	0.93
Diabetes at baseline (n, %)	13 (9.3%)	6 (13.0%)	4 (8.5%)	3 (6.4%)	0.51
Diagnosed with diabetes during the trial (n, %)	6 (4.3%)	2 (4.4%)	1 (2.1%)	3 (6.4%)	0.70

* ANOVA used for continuous variables and Fisher's exact test used for categorical variables.