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Dose-Dependent Effects of Selenized Yeast on Total Selenium Levels in Prostatic Tissue of Men With Prostate Cancer

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Although a negative association between serum selenium (or selenium supplementation) and prostate cancer risk has been widely reported (1–8), very little is known about the effects of oral supplementation with selenized yeast on selenium levels in prostate tissue of men with prostate cancer.

In 2003, Gianduzzo et al. reported results of a prospective trial enrolling 51 men with benign prostatic hyperplasia randomized to receive 200 μ g selenized yeast or placebo daily for 1 mo (9). Prostate tissue selenium levels were statistically significantly higher in the

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supplemented group as compared to placebo (supplement group median = 241 and control group median = 196 ng/gm, $P = 0.016$) at the end of the study. In another study, Sabichi and colleagues supplemented 66 men with organ-confined prostate cancer with 200 μg selenomethionine (SeMet) or placebo for 14 to 31 days (10). Although baseline serum selenium was similar in the two groups ($P = 0.64$), post-intervention mean serum selenium level was 15% higher and selenium concentration within the prostate was 22% higher in the SeMet arm as compared to placebo ($P = 0.001$ and $P = 0.021$, respectively). The first study was conducted on men with benign prostatic hyperplasia, where it is possible that the tissue environment was different than that found in a prostate with carcinoma. The second study used SeMet, a form of selenium shown to have no effect on prostate cancer incidence in results from the SELECT study (11).

While the above studies do give insight into the uptake of various selenium forms by prostate tissue, critical data regarding the uptake of total selenium from selenized yeast in men with prostate cancer are missing. Results from the current study not only address this deficiency in the literature but are also complementary to the Gianduzzo and Sabichi studies, allowing us to compare uptake of various forms of selenium in different prostatic conditions.

A randomized, double-blind, placebo-controlled Phase 2 clinical trial was conducted. Men enrolled in this trial had to be diagnosed with biopsy-proven, non-metastatic adenocarcinoma of the prostate; they had to undergo open radical prostatectomy for treating their prostate cancer, and they were receiving no other treatment for prostate or any other cancer. Furthermore, all men were less than 80 yr of age with prostate specific antigen (PSA) levels less than 50 ng/ml and were not taking more than 50 micrograms of selenium per day as a dietary supplement from non-study sources. Fifty-three subjects were randomized to receive placebo ($n = 17$), 200 μg of high selenized yeast ($n = 19$), or 400 μg of selenized yeast ($n = 17$) per day. Study agent was supplied by Cypress Systems, Inc., Fresno, CA (SelenoPrecise). Subjects were instructed to take daily supplement pills for 4–6 wk until the day before their surgery. Blood was collected at baseline and end of study for determination of serum selenium levels. Prostate tissue sample was obtained at surgery for assessment of prostate tissue selenium level.

Serum and prostate tissue selenium level was determined by automated electrothermal atomic absorption spectrophotometry using a Perkin-Elmer Zeeman 3030 instrument (Perkin-Elmer Corp., Norwalk, CT) (2). To assess differences between treatment groups, analysis of variance (ANOVA) was conducted for continuous variables (age, baseline serum selenium, duration of exposure, Gleason score, and selenium concentration in prostate tissue) and chi-square test for the categorical variable (race). Since 90.6% our population were Caucasian, the race variable was dichotomized as Caucasian/non-Caucasian. Paired t -tests were carried out to determine if selenium concentration in prostate tissue was statistically significantly different in the selenium supplemented groups as compared to placebo. Multivariate linear regression was used to assess if concentrations of selenium were significantly different in the treatment groups after adjusting for other variables such as baseline serum selenium, age, duration of exposure, race, and Gleason sum score.

Selenium concentration in prostate tissue at prostatectomy was statistically significantly different among the three treatment groups (Table 1). Pair-wise *t*-tests show that the selenium concentration in prostate tissue at prostatectomy in the 200 $\mu\text{g/day}$ and 400 $\mu\text{g/day}$ groups were statistically significantly higher as compared to placebo (*P* values: 0.046 and < 0.001 , respectively). The serum selenium concentrations at the end of the study were also significantly different between the 3 treatment groups ($P < 0.001$). None of the other variables (baseline serum selenium levels, age, duration of exposure, Gleason score, and Caucasian race) were statistically significantly different between treatment groups.

Results from linear regression models (adjusted for age, duration of exposure, baseline serum selenium, Gleason score, and Caucasian race) demonstrate that subjects supplemented with 200 or 400 μg selenium per day had statistically significantly higher selenium levels in their prostate tissue at prostatectomy (Fig. 1). Additionally, prostate selenium levels were statistically significantly higher in the 400 μg group as compared to the 200 μg group ($P = 0.006$). Stratified analysis based on median baseline serum selenium concentration was carried out to determine if baseline serum selenium levels had a differential effect on the results due to selenium supplementation. Results demonstrated that tissue selenium levels in the 200- μg selenium group were not statistically significantly different than placebo in men with baseline serum selenium levels less than or equal to 135 ng/ml ($P = 0.479$); whereas they were statistically significantly different ($P = 0.047$) in men with serum selenium level > 135 ng/ml. Tissue levels in men supplemented by 400 μg of selenium were significantly higher than placebo in both strata ($P = 0.001$ and 0.002 , respectively). The trend for dose effect was statistically significant in both strata ($P = 0.001$ and 0.002 , respectively). Correlation coefficients for the association between serum selenium and prostate tissue selenium were 0.0016, -0.0184 , 0.2323 , and 0.1806 for placebo, 200 μg group, 400 μg group, and the total population, respectively.

Results indicate that supplementation with selenized yeast for 4–6 wk significantly increases tissue selenium levels within the prostate gland as compared to placebo in a dose-dependent manner. Baseline serum selenium levels differentially affect the selenium retention ability of the prostate. It is of interest that serum selenium levels were a poor indicator of prostate tissue selenium levels.

Selenized yeast is the form of selenium that has been observed to be associated with lower risk for prostate cancer in the original studies by Clark (1,2,12). The exact mechanism by which selenium may inhibit prostate carcinogenesis is not known, but proposed mechanisms include a protective role of selenoproteins, induction of apoptosis, immune system effects, detoxification of antagonistic metals, inactivation of nuclear transcription factors, regulation of lipoxygenases, reduction of oxidative stress, induction of Phase 2 drug metabolizing enzymes, androgen receptor downregulation, inhibition of DNA adduct formation, and cell cycle arrest (13).

Hence, it is of interest to note that tissue selenium levels within the prostate increase significantly after supplementing with selenized yeast. Sabichi et al. report a 22% increase in prostate tissue selenium concentrations after supplementation with 200 μg SeMet per day for 14–31 days (1.80 vs. 1.47 ppm) (10). The comparable supplementation group in the current

study (200 μg selenized yeast per day) demonstrated a 34% increase in prostate selenium as compared to placebo (177 vs. 132 ng/g), whereas the high concentration dose (400 μg selenized yeast per day) demonstrated a 92% increase in prostate selenium as compared to placebo (254 vs. 132 ng/g). Increased selenium uptake in the prostate after supplementation with selenized yeast as compared to SeMet may potentially explain differences in results between the original Clark studies and SELECT. The selenized yeast used in this trial and the original studies by Clark, contains a number of other selenium species in addition to SeMet, the purified form of selenium used in SELECT. Interestingly, studies in animal models have demonstrated different effects for selenized yeast as compared to SeMet (14–16). In addition to the reasons presented above, any putative protective effect of selenized yeast may also be due to unknown reasons.

This study is complementary to the studies conducted by Gianduzzo et al. and Sabichi et al. and provides a critical piece of the puzzle, i.e., the effect of selenized yeast on prostate selenium content in men with prostate cancer. Comparing the results obtained from this study with those seen by Gianduzzo and colleagues, we can assess the effect of selenized yeast on supplementation in a population with prostate cancer or BPH; whereas by comparing results of the current study with those seen by Sabichi et al., we can assess the effect of selenized yeast or SeMet supplementation on selenium levels in the prostate of men with prostate cancer. It is interesting to note that although there was an increase in serum selenium levels post-supplementation, these levels correlate poorly with levels within the prostate tissue, suggesting that serum measurements are a poor indicator of prostatic selenium content. This has also been noted by other authors (9).

The end-of-study selenium concentration in serum was statistically significantly different between the three treatment groups ($P < 0.001$). The fact that the concentration in the 400 μg group was lower than that observed in the 200 μg group is of interest. Although the exact reason for this cannot be elucidated, it could potentially be due to fluctuations in selenium metabolism perhaps due to single nucleotide polymorphisms in the glutathione peroxidase (17). The data have been thoroughly investigated to rule out the effect of data entry or sample processing errors. We do recognize several limitations of this study. The sample size was relatively small due to difficulties in recruitment to a clinical trial with this study design, but it is comparable to other published studies (9,10). Also, while establishment of prostate selenium concentrations prior to supplementation would have been ideal, it was not possible since the tissue obtained at a prostate biopsy is not sufficient for quantitative analysis using current methods. Previous literature indicates that it may take up to three months or more for selenium to achieve steady state concentration in blood (18,19). Duration of the current trial was 4–6 wk and therefore may have been too short to establish a steady state concentration in blood or the prostate tissue. Hence the steady state concentration in this trial may turn out to be higher than that reported in this paper.

This is the first study to demonstrate that supplementation with selenized yeast for 4–6 wk significantly increases prostate tissue selenium levels in patients with prostate cancer in a dose-dependent manner. These data address a major deficiency in current literature and will help to further our understanding of the association between selenium and prostate cancer.

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FIG. 1. Adjusted prostate selenium levels by treatment groups (mean $\pm$ SEM). A: Total population, B: Subjects with baseline selenium ≤ 135 ng/ml, and C: Subjects with baseline selenium > 135 ng/ml. Results in panel A are adjusted for baseline selenium, age, duration of exposure, Gleason score, and race. Results in panels B and C are adjusted for age, duration of exposure, Gleason score, and race.

TABLE 1

Descriptive statistics for all treatment groups

Variable	Total (N = 53)	Placebo (n = 17)	Se 200 (n = 19)	Se 400 (n = 17)	P value
Baseline age (yr)	62.4 (7.0) ^a	62.7 (7.0)	61.1 (6.1)	63.4 (8.0)	0.636
Duration of exposure (days)	44.7 (34.4) ^a	43.5 (23.9)	49.6 (51.0)	40.8 (50.6)	0.769
Gleason score	6.2 (0.7) ^a	6.1 (0.8)	6.5 (0.9)	6.0 (0.4)	0.136
Caucasian race	48 (90.0) ^b	16 (88.9)	17 (89.9)	15 (93.8)	0.871
Baseline serum selenium level (ng/ml)	135.2 (19.7) ^a	132.4 (18.0)	138.1 (25.0)	135.0 (14.5)	0.698
End of study serum selenium level (ng/ml)	172.2 (47.6) ^a	132.5 (23.2)	206.7 (40.2)	165 (39.9)	< 0.001
Selenium concentration in prostate tissue at prostatectomy (ng/g)	185.3 (83.5) ^a	132.1 (68.8)	177.65 (65.02)	254.3 (72.1)	< 0.001

^a Mean (SD);

^b N (%).