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A Comparative Study of Serum Selenium and Vitamin E Levels in a Population of Male Risk Drinkers and Abstainers

A Population-Based Matched-Pair Study

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ABSTRACT

Depressed selenium and Vitamin E levels may contribute to hepatic injury through lipid peroxidation. To study the effect of moderate alcohol drinking (32.4 ± 23.6 g ethanol/d) on serum selenium and serum vitamin E concentrations, we conducted a matched-pair study of 73 healthy, well-nourished risk drinkers and healthy controls with little or no alcohol consumption. Among risk drinkers, serum selenium was significantly lowered (1.49 vs 1.67 μmol/L; $p < 0.001$) compared with controls. Difference in α-tocopherol concentrations did not, however, reach statistical significance (22.8 vs 24.9 μmol/L; $p = 0.06$). Nutritional and life-style factors differed very little between the two groups. We conclude that even moderate alcohol consumption lowers selenium status. Selenium may thus represent a link joining the hepatotoxic and nutritional backgrounds of alcoholic liver disease.

Index Entries: Selenium; α-tocopherol; alcohol; liver disease.

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INTRODUCTION

The causes of alcohol-induced liver disease are not fully understood. Hepatotoxic qualities of ethanol and acetaldehyde as well as a number of nutritional deficiencies are considered to be of etiological importance (*1*). Experiments have shown that ethanol metabolism leads to increased free-radical activity in liver cells (*2,3*), and biopsy specimens from alcoholic subjects show evidence of lipid peroxidation (*4*). Interest has therefore been focused on the oxygen radical scavenging nutrients selenium and vitamin E. Selenium is incorporated by covalent bonding into the primary amino acid structure of glutathione peroxidase (GSH-Px), an enzyme using glutathione (GSH) as an electron donor, when reducing hydrogen peroxide and other lipoperoxides in the hepatocyte (*5*). Vitamin E, of which α-tocopherol has the greater biologic activity, acts intracellulary to prevent oxidative damage to polyunsaturated fatty acids in biological membranes by terminating chain reactions of lipid peroxides (*6*). Selenium and vitamin E deficiency have also been demonstrated to cause liver necrosis in nonalcoholic experimental animals (*7*).

Studies have demonstrated low selenium and vitamin E levels in diagnosed alcoholics compared to control subjects (*8–10*). These studies, however, were done in inebriated alcoholics, or in alcoholics where little or no information on other dietary items exist. We therefore conducted a matched-pair study, comparing serum concentrations of selenium and vitamin E, as well as multiple nutritional and life-style factors, in a group of healthy, socially adequate, well-nourished risk drinkers and healthy controls with little or no alcohol consumption.

METHODS

Subjects

For the present analyses, we used data from the third Tromsø Study, a population survey of cardiovascular risk factors. Height, weight, blood pressure, nonfasting serum lipid concentrations, and γ-glutamyltransferase (GGT) were measured in 21,826 subjects, i.e., 81.3% of the eligible population invited to the screening. A questionnaire on cardiovascular disease risk factors was completed, and extra blood samples for future analyses were drawn and stored at −80°C. Twenty thousand and twenty-five participants (92%) returned a second questionnaire later by mail on education, dietary habits, alcohol consumption (five categories), use of drugs, and mental and sleeping problems. After the initial screening, men aged 20–61 yr with a serum GGT between 50 and 200 U/L, and self-reported beer, wine, or liquor consumption at least two to three times a week or an alcohol intake on one occasion corresponding to one bottle of wine at least one to two times per month were classified as risk

drinkers, and selected for an alcohol intervention study (*11*). They were interviewed by a psychiatrist on average daily ethanol consumption, and hospital records for all subjects were scrutinized. Excluded were all subjects with diagnosed alcoholism, hepato-biliary diseases, major psychiatric disorders, and subjects on antiepileptic medication. That left 338 men, who after giving informed consent, were eligible for the trial. Of these, 73 men (22%) were randomly selected for the present study. They were matched pairwise to healthy nondrinking men (included abstainers [40%] and subjects who only occasionally drank alcohol, all with GGT < 35 U/L), according to age (within 5 yr), daily consumption of cigarets (nonsmoker, 1–10, 11–20, 21–30, or more than 30 cigarets a day), smoking years (within 1 yr), and total cholesterol level (within 0.5 mmol/L). Since active drinking may produce spuriously low values for trace metals and vitamins, all blood samples were drawn when cases were not actively drinking. These blood samples were then analyzed for selenium, α-tocopherol, and albumin.

Clinical and Laboratory Measurements

Blood pressure was recorded using an automatic device (Dinamap, Critikon, Tampa). Body weight was measured with an electronic scale, with the subjects wearing light clothing. Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric methods with commercial kits (CHOD-PAP for cholesterol and GPO-PAP for triglycerides; Boehringer Mannheim, Mannheim, GER). Serum high-density lipoprotein (HDL) cholesterol was measured after the precipitation of serum with phosphotungstic acid and magnesium chloride (*12*). The measurements of GGT were performed according to the recommendations of the Scandinavian Enzymes Committee (*13*). Selenium concentrations were determined by electrothermal atomic absorption spectroscopy after dilution with a nickel matrix modifier (*14*). All analyses were done in duplicate and in random order. Calibration was done against standards based on human serum with a known content of selenium (*15*). Quality assurance was ensured using a certified reference serum as a control (*16*). The coefficient of variation for the reference serum between series was 0.85%. Serum α-tocopherol levels were measured by high-performance liquid chromatography (*17*), and serum albumin by standard laboratory methods.

Statistical Analyses

The mean differences between cases and controls were tested for significance with a *t*-test for paired samples. Differences in selenium and vitamin E concentrations according to consumption of dietary items were tested by analysis of variance. Correlation coefficients were calculated by Pearson's formula, and qualitative data were tested using the chi-square

test. Results are given as means ± SD. All statistical tests were considered to be significant at the $p = 0.05$ level. The Statistical Package for the Social Sciences (SPSSX) was used (*18*).

RESULTS

Baseline characteristics of risk drinkers and controls (Table 1) indicate a successful matching. Risk drinkers consumed on average 32.4 ± 23.6 g ethanol/d. They had higher blood pressure ($p < 0.001$), relative weight ($p = 0.002$), and heart rate ($p = 0.026$) than controls. They had breakfast less regularly ($p < 0.05$), and ate less bread ($p < 0.05$) and more fat ($p < 0.01$). Consumption of fat and lean fish, vegetables, fruits, coffee, and salt was equal in the two groups. No differences in years of education, employment rate, social network, ability to cope with difficult situations, use of analgesics or sedatives, or physical activity were detected. Risk drinkers, though, reported more sleeping problems ($p < 0.05$) and depressions ($p < 0.01$) than controls. Their perception of their own health was not as good as controls ($p < 0.01$), something reflected by an elevated number of sick days ($p < 0.02$).

Serum selenium concentrations were lower in risk drinkers (1.49 vs 1.67 μmol/L; $p < 0.001$) compared with controls. This difference remained significant ($p < 0.001$) after adjustment for bread consumption, the only dietary variable associated with increased serum selenium levels ($p < 0.03$). Difference in serum α-tocopherol concentrations did not, however, reach statistical significance (22.8 vs 24.9 μmol/L; $p = 0.06$). The log-10 GGT difference between subjects drinking alcohol and nondrinking controls was highly statistically significant ($p < 0.001$). No difference was observed between albumin in the two groups ($p = 0.4$). These results are shown in Table 2.

No differences in α-tocopherol levels according to consumption of dietary variables were found. No significant correlation was found between alcohol consumption and serum concentrations of selenium or α-tocopherol, nor were there any correlations between albumin and selenium or albumin and vitamin E (Table 3).

DISCUSSION

Our study shows that even modest ethanol consumption leads to reduced serum selenium concentrations. This may be related to poor dietary intake, but except for bread consumption, little difference between dietary habits was found in the two groups. Ethanol-induced intestinal malabsorption, well documented for a number of nutrients (*19*), may cause selenium depletion. Increased urinary loss of selenium, however, is not observed during alcohol drinking (*20*). Low serum selenium concentrations in alcohol drinkers reflect low liver selenium val-

Table 1
Characteristics of Risk Drinkers and Matched Nondrinking Controls

Characteristic	Drinkers, $N = 73$	Nondrinkers, $N = 73$
Age (yr)[a]	39.5 ± 9.8[b]	40.7 ± 8.7
Cigarets (no. smoked/d)[a]	8.7 ± 10.4	7.1 ± 9.0
Smoking years[a]	20.0 ± 9.8	20.4 ± 8.9
Smoker (%)[a]	57.5	57.5
Total serum cholesterol (mmol/L)[a]	6.4 ± 1.1	6.3 ± 1.1
Serum HDL-cholesterol (mmol/L)	1.4 ± 0.4	1.3 ± 0.3
Serum triglycerides (mmol/L)	2.2 ± 1.2	2.0 ± 1.2
Systolic blood pressure (mm Hg)	136.2 ± 18.8	128.2 ± 13.4
Diastolic blood pressure (mm Hg)	83.6 ± 14.7	75.3 ± 9.8
Heart rate (beats/min)	75.2 ± 14.7	70.6 ± 12.0
Body-mass index (kg/m^2)	26.7 ± 3.4	25.2 ± 2.8
Years of education	11.4 ± 4.2	11.3 ± 3.5

[a]Matching criteria.
[b]Means ± SD.

Table 2
Mean Serum Concentrations of Selenium, α-Tocopherol, and Albumin in Risk Drinkers and Matched Nondrinking Controls

Characteristic	Drinkers, $N = 73$	Nondrinkers, $N = 73$	p-value
Selenium (μmol/L)	1.49 ± 0.16[a]	1.67 ± 0.22	<0.001
α-Tocopherol (μg/mL)	22.8 ± 5.9	24.9 ± 9.0	0.06
Albumin (g/L)	42.9 ± 2.1	43.2 ± 2.5	0.4

[a]Means ± SD.

Table 3
Correlations Between Serum Selenium, α-Tocopherol and GGT with Ethanol Consumption

	r	p-value
Serum selenium	.07	0.26
α-Tocopherol	−.13	0.13
GGT	.13	0.13

ues (*8*). GSH, critical for the activity of GSH-PX, is also lowered in alcohol drinkers (*21*). Experimental depletion of GSH from rat liver cells, has been found to lead to increased ethanol toxicity (*22*). If ethanol exerts its hepatotoxic action, at least partly, via activation of molecular oxygen, reactive oxygen species may be toxic mediators capable of depressing or distorting the protein synthesis, leading to low levels of selenoproteins and sulfur-containing proteins, whereas the collagen formation is in-

creased. Since selenium in serum and liver occurs essentially in protein-bound forms, a reduced synthesis of specific seleno-transport proteins may thus be the reason for the decreased selenium levels in alcohol drinkers. This theory is also supported by animal experiments; liver concentrations of selenium in ethanol-fed rats were reduced to 53–57% of control rats given an isocaloric diet containing the same amounts of selenium. This correlated positively by an almost parallel decrease in protein synthesis (*23*). Low vitamin E may further accentuate the hepatic damage. Although the α-tocopherol difference (2.1 μmol/L) in our study was not statistically significant (95% confidence interval = −0.1–4.2), reduced serum levels of α-tocopherol have been reported in alcoholics (*9,17*). Because of strong positive correlations between vitamin E and serum cholesterol (*24*), these former studies may be difficult to interpret, since no lipid adjustment was performed. No principal storage organ for vitamin E exists. Low α-tocopherol is therefore likely to result from reduced dietary intake. Increased hepatic metabolism of α-tocopherol is also a possibility, since this has been reported in ethanol-fed rats (*25*).

Serum selenium did not correlate with serum albumin. Although reported earlier (*8*), this is not surprising, because selenium is thought to be bound to nonalbumin proteins with mol wt between 50,000 and 100,000 (*23*). Positive correlations between selenium and prealbumin and prothrombin-time have been reported by others (*10,23*). This study also confirms that alcohol consumption is associated with elevated blood pressure and relative weight (*26*), known risk factors for cardiovascular disease morbidity and mortality. Low selenium and vitamin E levels in alcohol drinkers may even worsen cardiovascular disease risk, since antioxidants are believed to reduce oxygen-induced damage to lipids, lipoproteins, and endothelial tissue (*27*).

In conclusion, protection against ethanol-induced hepatic lipoperoxides and toxic oxygen species depends on several vitamins and enzyme-linked trace elements. Whether a cause or a consequence, moderate alcohol consumption lowers selenium status. This may have significant implications in the pathogenesis of liver disease in the alcoholic.

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