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ScienceDirect
Journal of Trace Elements in Medicine and Biology 23 (2009) 272–280
Journal of Trace Elements in Medicine and Biology
www.elsevier.de/jtemb

NUTRITION

The effect of selenium supplementation on DTH skin responses in healthy North American Men

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Received 5 May 2008; accepted 29 April 2009

Abstract

The trace element selenium (Se) is essential for immune system development and function in animals. However, the exact functions of Se in the human immune system and the achievable health benefits from Se supplementation remain unclear. To test whether an increased intake of dietary Se affects immune function, we conducted a randomized, controlled trial of Se supplementation in healthy free-living men. Forty-two men were administered 300 μg of Se a day as high-Se Baker's yeast, or low-Se yeast for 48 weeks. Serum immunoglobulins, differential complete blood counts and lymphocyte sub-populations were measured every 6 weeks. Tests of delayed-type hypersensitivity (DTH) skin responses to mumps, candida, trychophyton, tuberculin-purified protein, and tetanus were performed at baseline and at the end of 48 weeks of treatment. Supplementation increased blood Se concentration by 50%. Surprisingly, consumption of the low-Se yeast induced anergy in DTH skin responses and increased counts of natural killer (NK) cells and T lymphocytes expressing both subunits of the high affinity interleukin-2 receptor (IL2R). DTH skin responses and IL2R + cells did not change in the high-Se group, suggesting Se supplementation blocked induction of DTH anergy. There were no differences between groups in quality of life indicators, number of days sick, other leukocyte phenotypes, serum immunoglobulins, or complement factors. These results suggest that Se plays a role in immunotolerization, a cell-mediated process involved in many aspects of immune function.
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Keywords: Selenium supplementation; Immune function; Immunotolerance; Natural killer cell; T-cell

Introduction

Selenium (Se) is an essential trace element required in microgram amounts by humans and by all animals in which it has been tested. Signs of selenium deficiency include liver necrosis in rats, pancreatic atrophy in chickens, nutritional muscular dystrophy in sheep, and skeletal myopathy in patients receiving total parenteral nutrition without supplemental Se [1]. The essential functions of Se in mammals are mediated by a group of 25 selenoproteins in which Se is in the form of selenocysteine (Sec), the Se-containing homolog of cysteine. Enzymatic activities have been assigned to 12 of these selenoproteins: four are forms of glutathione peroxidase, three are iodothyronine deiodinases, three are thioredoxin reductases, and there is one methionine sulfoxide reductase B and one selenophosphate synthetase. Most of these selenoprotein genes are expressed in white blood cells [2–4]. Selenium is the only element specified in the genetic code ("TGA") and Sec has become recognized as the 21st protein amino acid [5].

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0946-672X/$ - see front matter Published by Elsevier GmbH.
doi:10.1016/j.jtemb.2009.04.002

Se has multiple functions in the immune system and deficiency has pleiotropic effects on humoral and cellular immunity [6]. Se is essential for development of the bursa and supports development of the thymus in chicks [7]. Se is reported to prevent myocardial lesions from Coxsackie virus B3 infection, increase killing of and protection from *Candida albicans*, and increase antibody titers in mice [8–10]. Se increased splenocyte blastogenesis and protection against *C. albicans* and *S. aureus* in rats [11,12]. Se raised serum IgM and lymphocyte proliferation *in vitro* in lambs and increased chemotaxis in goat neutrophils [13–15]. Se improved humoral and colostral antibody titers, and protection from *E. coli*-induced mastitis in cattle, and increased IgG and hemagglutination titers in ponies [16–19]. Despite the number and variety of Se's effects on animal immune systems, little is understood about the underlying mechanisms.

Relatively few studies have investigated the role of Se in human immune function. Supplementation of Se-replete US subjects with 200 μg/d Se as sodium selenite for 8 weeks increased tumor cell lytic activity of natural killer (NK) cells and cytotoxic lymphocytes [20,21]. Se supplementation improved polio vaccination response and poliovirus handling in UK subjects with marginal Se status [22], and supplementation of elderly subjects with Se-enriched yeast increased *in vitro* lymphocyte proliferation in response to pokeweed mitogen [23]. Se deficiency was associated with increased mortality in HIV-positive intravenous drug users, HIV-positive children, and pregnant HIV-positive Tanzanian women [24–26].

In a prior study, we observed that healthy men fed high-Se foods for 99 days had 2–1/2 fold higher antibody titers in response to a second vaccination with a recall antigen compared to men fed low-Se foods [27]. That study suggested Se affected immunological memory, a T-cell-mediated process. In the present study, we supplemented healthy men with 300 μg/d Se as high-Se yeast for 48 weeks to test if Se supplementation alters immune status or cell-mediated immunity.

Subjects and methods

Subjects

The present study was part of a larger investigation into the metabolic effects of long-term, high-level Se supplementation in healthy men. Fifty-four healthy, non-smoking men, aged 18–45 years were randomly assigned to treatment with high-Se yeast or low-Se yeast in the main study. Forty-two subjects completed the 48 weeks supplementation period, including the DTH skin response testing. Only the results pertaining to immune function and cellular and humoral immune status are presented herein. Other aspects of the main study are reported elsewhere [28,29]. Potential volunteers were recruited through newspaper advertisements and public service announcements in the Davis and Sacramento, CA areas, given a physical examination by a nurse practitioner and determined to be in good health. Inclusion criteria were self-reported absence of disease and clinically normal blood count and blood chemistries. Exclusion criteria were tobacco smoking, positive blood test for HIV, hepatitis B, syphilis, or positive urine tests for drugs of abuse (barbiturates, benzodiazepines, cocaine metabolites, opiates, amphetamines, and cannabinoids), and Se supplements providing more than 50 μg/d. Subjects were paid for their participation. The study protocol was reviewed and approved by the Institutional Review Board of the University of California at Davis School of Medicine, and informed consent was obtained in writing from all subjects.

Experimental protocol

Potential subjects meeting the recruitment criteria were enrolled into a run-in period lasting 3–6 weeks, during which replicate baseline measurements were obtained and compliance was assessed. Non-compliant subjects were dismissed before randomization and are not reported further. Two subjects at a time were randomized to treatment from July 2000 to November 2002, with one subject from each pair randomly assigned to each treatment group by coin flip. Fifty-four men satisfactorily completed the run-in period and were randomized to receive low-Se yeast tablets or high-Se yeast tablets for 48 weeks. Neither the subjects nor the study staff were aware of subjects' treatment assignments. Subjects took their first tablet the same day that all baseline measurements were completed. Subjects visited the Center for duplicate blood draws 2 d apart every 6 weeks during the 48 weeks supplementation period, and then returned again for duplicate blood draws at follow-up visits at 72 and 96 weeks. Visits were scheduled relative to each subject's first day of supplementation. When visits were missed, the next visit was scheduled based on the first day of supplementation to restore the original schedule. Unused tablets were counted at each visit and were collected at the end of the treatment period to measure compliance. Subjects consumed $93 \pm 5.3\%$ of the pills assigned. Every subject kept a notebook in which they recorded pills missed, symptoms, side effects and days sick. At each visit, subjects were administered the Profile of Mood States and SF-36 Health Status questionnaires and were interviewed to determine the number of days each subject had been sick since his last visit.