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Original article

Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults

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SUMMARY

Background & aims: Mortality resulting from influenza (flu) virus infections occurs primarily in the elderly through declining immunity. Studies in mice have suggested beneficial effects of selenium (Se) supplementation on immunity to flu but similar evidence is lacking in humans. A dietary intervention study was therefore designed to test the effects of Se-supplementation on a variety of parameters of anti-flu immunity in healthy subjects aged 50–64 years.

Methods: A 12-week randomized, double-blinded, placebo-controlled clinical trial (ClinicalTrials.gov NCT00279812) was undertaken in six groups of individuals with plasma Se levels <110 ng/mL. Four groups were given daily capsules of yeast enriched with 0 μg Se/day (SeY-0/d; $n = 20$), 50 μg Se/d (SeY-50/d; $n = 18$), 100 μg Se/d (SeY-100/d; $n = 21$) or 200 μg Se/d (SeY-200/d; $n = 23$). Two groups were given onion-containing meals with either <1 μg Se/d (SeO-0/d; $n = 17$) or 50 μg Se/d (SeO-50/d; $n = 18$). Flu vaccine was administrated at week 10 and immune parameters were assessed until week 12.

Results: Primary study endpoints were changes in cellular and humoral immune responses. Supplementation with SeY and SeO affected different aspects of cellular immunity. SeY increased Tctx-ADCC cell counts in blood (214%, SeY-100/d) before flu vaccination and a dose-dependent increase in T cell proliferation (500%, SeY-50/100/200/d), IL-8 (169%, SeY-100/d) and IL-10 (317%, SeY-200/d) secretion after *in vivo* flu challenge. Positive effects were contrasted by lower granzyme B content of CD8 cells (55%, SeY-200/d). SeO (Se 50 μg/d) also enhanced T cell proliferation after vaccination (650%), IFN-γ (289%), and IL-8 secretion (139%), granzyme (209%) and perforin (190%) content of CD8 cells but inhibited TNF-α synthesis (42%). Onion on its own reduced the number of NKT cells in blood (38%). These effects were determined by comparison to group-specific baseline yeast or onion control groups. Mucosal flu-specific antibody responses were unaffected by Se-supplementation.

Conclusion: Se-supplementation in healthy human adults with marginal Se status resulted in both beneficial and detrimental effects on cellular immunity to flu that was affected by the form of Se, supplemental dose and delivery matrix. These observations call for a thorough evaluation of the risks and benefits associated with Se-supplementation.

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Abbreviations: APC, allophycocyanin; ECD, energy coupled dye; flu, influenza; IFN-γ, interferon gamma; Ig, immunoglobulin; IL, interleukin; LAK, lymphokine activated killer; LGL, large granular lymphocytes; MNC, mononuclear cells; NK, natural killer; Se, selenium; SeMet, selenomethionine; SeMSC, γ-glutamyl-methylselenocysteine; SeY, selenium-yeast; SeO, selenium-onion; TNF-α, tumor necrosis factor alpha.

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1. Introduction

Selenium status is known to influence ability of the immune system to respond to infections [1]. Evidence for the importance of adequate Se intakes is provided by the impact that Se deficiency has on the immune system, reportedly reducing proliferation of T cells [2], lymphocyte-mediated toxicity and NK cell activity [3], all of which are important for antiviral immunity. While the mechanisms by which Se exerts its antiviral effects are unknown, Se/selenoproteins regulate cellular redox balance and it is known that the establishment and progression of viral infections are influenced by the redox state of the host cell [4]. Dietary Se is mainly present in organic complexes, such as selenomethionine (SeMet) found in meat, cereals and plant foods, and Se-methylselenocysteine (SeMSC) in Se-accumulator plants such as onions and brassica vegetables, with smaller quantities of inorganic Se derived from dietary supplements. One of the proposed consequences of marginal Se status is impaired immune function. With regard to anti-viral response the benefits of higher Se intake have been demonstrated solely in the recall responses to polio virus vaccination of healthy volunteers with marginal selenium status [5]. This prompted us to evaluate the effects of Se supplementation on a set of immunological parameters that pertain to both cellular and humoral immunity to a different type of virus, such as the influenza (flu) virus. The reason for this investigation is twofold. First, the polio virus is an enteric pathogen and does not undergo the rapid antigenic drifts seen in flu virus; as such, the benefits in recall responses to attenuated polio vaccination cannot therefore be extrapolated to flu virus infections. Secondly, flu infection has very high socio-economic cost worldwide [6] and to identify food supplements with the ability to potentiate immunity in at risk populations, such as the elderly and chronically ill may have an important impact on overstretched healthcare systems worldwide. Indeed, in annual flu epidemics 5–15% of the population is affected with upper respiratory tract infections that result in three to five million cases of severe illness and between 250,000 and 500,000 deaths every year around the world [6]. The aims of this study were to measure both cellular and humoral immune responses to flu vaccine in healthy older (50–64 years) individuals with marginal Se status after Se supplementation.

2. Subjects and methods

2.1. Subjects and study design

A randomized, double-blind, placebo-controlled study was undertaken in adults aged 50–64 years with suboptimal Se status (plasma Se < 110 ng/mL), to determine the effects of Se supplementation on immune responses to flu vaccine. The study was approved by the Norfolk Research Ethics Committee (ref 05/Q0101/32) and registered as a clinical trial (ClinicalTrials.gov NCT00279812). Volunteers were excluded if they had abnormal hematology, blood chemistry, blood pressure measurements, or BMI <18.5 or >35 kg/m^2. They had to be non-smokers, not on prescription medication for a chronic ailment or taking any immunosuppressive drugs, antacids or laxatives. Any dietary or herbal supplements being used had to be forfeited from at least one month prior to the start of the study and for its duration. People that had donated blood within 16 weeks of the first study sample and/or were due to do so less than 16 weeks after the last study sample were excluded. Neither immunizations during the study period nor antibiotic use from within four weeks prior to starting the study until the study end were permitted. Concurrent participation in another research project was discouraged. Anyone who needed more than 2 weeks' absence from the study were also excluded. Allergy to eggs or egg products, chicken protein, the antibiotic gentamicin or history of Guillain-Barré syndrome were also exclusion criteria. More detailed information can be found in Hurst et al. [7]. Briefly, each subject was randomly assigned to one of six groups by the study scientists and given tablets containing SeMet in yeast matrix (SeY) at a daily dose of either 0 (SeY-0/d; $n = 20$), 50 (SeY-50/d; $n = 18$), 100 (SeY-100/d; $n = 21$) or 200 (SeY-200/d; $n = 23$) μg Se or test meals three times a week made with Se-enriched onions (SeO) containing SeMSC with the equivalent of 50 μg Se/day (SeO-50/d; $n = 18$) or unenriched onions (SeO-0/d; $n = 17$), for a period of 12 weeks. Se-containing yeast tablets were prepared and Se-enriched onions were grown as described elsewhere [7]. A computerized random number generator was used for the allocation of volunteers. The double-blind coding was not revealed until the completion of final data analyses.

2.2. Flu vaccination process and monitoring of pre- and post-vaccination responses

At week 10 participants were vaccinated with a trivalent influenza vaccine (Solvay Pharmaceuticals, Weesp, The Netherlands) developed according to World Health Organization (WHO) guidelines. Vaccines were administered intramuscularly in the deltoid region of the arm by the study nurses. The flu vaccine strains used were determined according to annual recommendations by the WHO. Vaccines contained the following: influenza A strain subtype H1N1/New Caledonia (years 1 and 2), Solomon Islands (year 3); subtype H3N2/California (year 1), Wisconsin (years 2 and 3); Influenza strain B subtype Jiangsu (year 1), Malaysia (years 2 and 3). Strains of H1N1 (A), H3N2 (A) and B viruses were administered in equal amounts (15 μg of each in 0.5 mL). Fasting blood samples (65 mL) were drawn at weeks 0 (baseline), 10 (Se-intervention, pre-vaccination), 11 (Se-intervention, post vaccination week 1) and 12 (Se-intervention, post vaccination week 2). Enrollment and all study procedures involving human volunteers were performed at the Human Nutrition Unit at the Institute of Food Research, Norwich, UK.

2.3. Volunteer randomization and dietary intervention

Volunteers were randomly allocated to one of six study groups. A computerized random number generator was used (URL: http://www.randomizer.org/form.htm) to generate 3 digit numbers with the group codes A, B, C, D, E or F to facilitate allocation of volunteers. This was done by the study statistician. Yeast supplements were supplied in coded form as either A, B, C, or D. The supplements were taken with a meal on a daily basis. Onions for the study meals were grown at the University of Nottingham, Sutton Bonington, Leicestershire, UK. Their Se content was analyzed by inductively coupled mass spectroscopy. Study meals were also blinded in that the onions supplied by the University of Nottingham were labeled simply as white or yellow onions. Meals made with the yellow onions were designated group E and those made with white onion as group F. Meals were prepared to contain the right weight of onions to achieve 117 μg Se/meal and three meals were consumed per week by each participant in group E or F as an average of 50 μg Se/d. Although volunteers in the onion meal groups could not be blinded, the type of onion in their meal was blinded. The identities of intervention codes used were not known to the researchers, volunteers, statistician or study nurses. Randomization data were kept confidential until study end and completion of data analyses.

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