REVIEW ARTICLE

The Role of Selenium in Human Immunity

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ABSTRACT

Selenium is a trace element that plays a role in human immunity. As an essential cofactor in selenoproteins, selenium is required forendogenous enzymatic activities that protect cells againsttoxic free oxygen radicals. Oxidative stress occurs in several pathological states, including selenium deficiency, so it has been postulated that selenium has a role in immune function. Immune dysfunction, susceptibility to viral infections and increased mortality are some of the outcomes associated with selenium deficiency.

INTRODUCTION

Jons Jacob Berzelius a Swedish national discovered Selenium (Se) in 1817.[1,2]Amounts of Se present in the soil fluctuate and it is incorporated into the food chain via uptake into plant crops.[3]Eggs, meat and fish contain the highest (87.6-737µg/kg) Se levels and the lowest being fruits and vegetablesat 1.7-24.9µg/kg.[4]Brazil nuts contain up to 254g/100g while crabmeat has about 84g/100g.[1]

Se in the form of selenite, selenate, or selenocysteine is absorbed in the duodenum.[1]Red blood cells rapidly absorbSe. In the presence of thiols, Se is reduced to hydrogen selenide and it is transported bound to alpha and beta globulins.[1]Se is also found in small amounts in liver (0.63g/g) andkidney0.39g/g tissues.[1]

In this review, we will analyse what is known of the in vitro immune effects of selenium, and how it impacts on disease conditions. We searched the Cochrane Library and PubMed on the 14th of February 2013 for data published during the last 10 years. We used the search terms "selenium", "immunity" and "humans".Out of 680,969 records we found 14 controlled trials and out of 7,694, 2 reviews were found. Due to this limited result, we have included other articles deemed useful.

Selenium and human requirements

Although the essential role of Se in human health is established, the actual human body requirement is still uncertain. Brown and Arthurreport that a human body weight of about 60kg needs 41µg of Se per day.[5]A study by Baum and co-workersdefined Se deficiency as a serum concentration level of 85µg/l.[6]Fairweather-Tait and colleagues report that dietary Se intake varies from 7µg/day to about 4990µg/day.[7]In the USA, dietary Se intake stands at 70µg/day for men and 55µg/day in women.[8]In Europe, a reduction over several years of average serum Se concentrations to 0.63-1.69µmol/l has been interpreted as an reflection of the reduction in imported wheat with high Se content from North America.[5]The observed uncertainty in Se requirements is a consequence of differences in the amounts present in food chains and soils.[9]Rayman suggests that on average, women need about 53µg/day while men about 60µg/day.[10]Data from Finland indicate that 70µg/day Se supplementation increase serum Se concentrations.[5]

The role of Selenium in human physiology

Selenium and oxidative stress

Selenium can be incorporated in selenoproteins in form of a modified amino acid, selenocysteine. Selenocysteineis further incorporated in proteins of the liver where it is bound and transported by albumin.[5]About 100 selenoproteins have been thought to exist in mammalian tissues, of which about 30 have been characterised in full. Se dependent enzymes include classical glutathione peroxidase, (GPx1), gastrointestinal glutathione peroxidase (GPx2), plasma glutathione peroxidase

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(GPx3) and phospholipid hydrogen peroxide glutathione peroxidase (GPx4).[5,11]The marked preponderance of antioxidant enzymes among Se dependent enzymes strongly suggests that Se has important antioxidant effects. $H_2O_2$is toxic to all cells, especially whenSe is deficient.[5]Adequatedetoxification of free radicals results in a decrease in oxidative stress due to reactive oxygen species (ROS) with a consequent decrease in cellular pathology.[5]

Transcriptional effects of selenium

Nuclear factor KB (NF-$_{\kappa}$B) controls the transcription of pro-inflammatory cytokine genes.[12,13]Increased replication of several viruses is seen when NF-$_{\kappa}$B is activated.[14]A study was conducted in Japan on 141 healthy individuals. The aim was to demonstrate the regulatory effect of Se on NF-$_{\kappa}$B.[15]Hepatoma cell lines from humans were grown for 3 days in medium containing 2% fetal calf serum. Following this, cells were cultured in the same type of medium containing sodium selenite for another 3 days.[15] Se, at a concentration of 0.51mol/l which is about half the serum concentration for healthy individuals, was sufficient for maximum inhibition of activated NF-$_{\kappa}$B. As Se concentrations in this range are common in the serum of subjects with elevated C-reactive proteins (CRP) levels, they postulated that low Se may contribute to NF-$_{\kappa}$B-mediated inflammation.[15]

Impact of selenium on immunity

Innate immunity

Se deficiency has been shown to impair the phagocytic function of neutrophils and macrophages. Although the number of circulating neutrophils was normal in Se deficient experimental animals,their ability to kill an ingested organism was compromised, and this defect was attributed to a drop in the cytosolic GPx1 activity in the neutrophils.[16]Thus instead of the organism being killed, neutrophils were killed.

In another experimental system, *Listeria monocytogenes* was administered to mice orally to assess the effect of Se on innate immunity.[17]Mice were infected with *L. monocytogenes*and categorised into four classes as follows: Group I, non-infected Se-adequate; Group II,non-infected Se-deficient; Group III, infected Se-adequate;and Group IV, infected Se-deficient.Glutathione activity was lowered in Se deficient mice as compared to replete mice, and*L. monocytogenes* persisted in-group IV compared to group III. These data suggest that the innate immune response in Se deficient mice is defective in *L. monocytogenes* infection.[17]Another interesting outcome of this experiment was the discovery of increased numbers of natural killer cells and production in the Se supplemented mice.

Humoral immunity

A study conducted in rats infected with *Trypanosomabruceibruceisuggested that Se supplementation can play a role in the humoral immune response. Antibody titers were increased* in supplemented rats compared tothe control group ($P<0.05$). Mortality was 100% death in the infected unsupplementedgroup but was reduced to 40% in rats that received 4 and 8 part per million (ppm) selenium in feeds.[18]

In a double-blinded study conducted by Broome *et al*., 22 individuals with a low plasma Se measure were chosen as study participants. These participants were allocated to receive either a 50μg, or 100μg or placebo every day for a period of 15weeks.[19] An oral live attenuated polio vaccine was administered at week 6 to all twenty-two subjects. Se supplementation increased poliovirus antibody titers in adults challenged with the poliovirus.

T cells immunity

Several studies highlight the importance of Se to proper functioning of the immune systemand particularly in CD4 T cell functioning and mounting responses against infection.

In the aforementioned study by Broome *et al*, a T lymphocyte (CD3+) immune response was enhanced in persons that received the sodium selenite by day 7 giving rise to an effective cellular elimination of the poliovirus. An increase in the clearance of the poliovirus in subjects that received the sodium selenite was made possible by an increased proliferation and differentiation of the T cells and CD4+ cells.[19]However, in participants receiving placebos there was no detectable increase in Se plasma

level or change in T cells. A mutation also occurred in the polio viral genome of the placebo group, giving rise to a more virulent form of a virus, whichdid not occur in the supplemented group. Interferon gamma (IFN-) increased in both groups (placebo and supplemented), but the increase was much higher in the group that received 100µg Se/day. Still in the supplemented group, peak levels for IFN- production was at day 7 while in the placebo group the reported peak was at day 14.[19]

In another study, mice were randomised to receive low (0.08 mg/kg), medium (0.25 mg/kg), or high (1.0 mg/kg) Se diets for 8 weeks.[20]These mice were challenged with Lymphocytic choriomeningitis (LCMV) gp66–77 withthe aim of assessing the role of Se on CD4 T cell proliferation and maturation. There was a skewing towards a Th1 response with an increase inIFN- production in mice on a high Se diet as opposed to the other two groups. IFN- was also found to play a role in macrophage activation and increased inhibition of viral replication

Selenium and Disease Conditions

Cardiomyopathy and Coxsackie virus

In China, Keshan and Kashin-Beck diseases are human conditions that areassociated with Se deficiency.[21,22,23]This may be as a result of a direct effect of Se deficiency on cardiac muscle, but Keshan and Kashin-Beck diseases may also result from defective surveillance allowing the pathogenic coxsackie virus to develop enhanced virulence.[19]

Beck and colleagues carried out an experiment in Se insufficient mice.Se deficient mice were inoculated with a benign strain of coxsackie type of the virus.A virulent type of a virus evolved following mutations in its genome. The resulting virus was reported to cause a type of myocarditis in mice similar to that of humans.When isolated, the mutated virulent virus was inoculated in mice that had sufficient Se.Heart damage was still induced, which demonstratedthat Se deficiency causes permanent damage or mutation to the virus.[24]

HIV

During HIV infection a number of micronutrient deficiencies occur, perhaps resulting from malabsorption. Malabsorption of trace elements and micronutrient is attributed to gastrointestinal tract infections,mucosal damage, and altered metabolism.[25]

Observational data

Several studies report observational data. Raymanhas reported a correlation between low Se and reduced CD4 T cells of HIV infected individuals.

Death rates in HIV infected persons with lower levels of Se is 20 times higher ($P<0.0001$) than HIV infected individuals with sufficient Se levels (6).It seems plausible that this mortality effect might be mediated through oxidative stress (6), although it is possible that both are merely markers of some other pathophysiological process. Glutathione activityincreases T helper cell count, and cytotoxic cell activities that act against the HIV virus replication rate and lower HIV viral load (2). However, direct evidence for this is conflicting. We found 3 randomised controlled trials of Se supplementation, and one observational study.

A cross-sectional study was conducted in 400 HIV-1 seropositive women to assess, among other things, the relationship between plasma Se level and CD4 count. In univariate analysis, an association existed between low Se and low CD4 count (26).

No association was found using multivariate analysis

During HIV infection interleukin-2 and IFN- levels are reduced. IL-2 is required in differentiation and activation of effector cells. Activation and proliferation of natural killer cells is equally dependant on IL-2 production. A compromise in IL-2 cytokine level leads to rapid progression of HIV disease and a decrease in T lymphocytes (27). Therefore, in HIV infected individuals Se supplementation is a plausible adjunct for therapy and combating free radicals constantly produced following chronic immune activation (27, 26).

Clinical trial data

In a double-blinded randomised controlled trial conducted by Hurwitz and colleaguesin Miami, 200g of Se was given to 262 participants for 9 months. 121 received supplementation (dose of 200µg selenium) over a 9-month follow-up assessment while 141 received a

placebo. An increase of 32.2 +/- 24.5g/L in serum Se concentration was recorded in the treatment group as opposed to 0.5 +/- 8.8g/L in placebo. HIV viral load was reduced (P< .02) and CD4 counts increased (p< .04) compared to placebo (28).

Furthermore, 200µg supplementation every day resulted in an increased CD4 cell count and a reduction in the viral load (28).There were no side effects attributed to supplementation. In the same study, the number of hospitalisations reduced (RR = 0.38; p = .002) (28).

In contrast, a study that was carried out in Tanzania on HIV positive pregnant women, using the same amount of supplementation (200µg) did not show any reduction in the viral load nor an increase in CD4 cell counts but reduced the chances of CD4 decline to >50 cells/mm3(29). A decrease in the mortality rates and a slight increase in the birth weight of the infants born from HIV positive women were reported (29). This reduction was attributed to the increased supply of Se via the umbilical cord, placenta and breast milk to the infants.

In another double-blind, randomized trial conducted among 400 HIV-1 women, McClelland tested whether multivitamin plus selenium supplementation decreases genital HIV-1 shedding. The odds of detection of vaginal HIV-1-infected cells were higher (2.5-fold; P = 0.001) among women who received micronutrients in comparison to placebo. Supplementation also resulted in higher CD4 (+23 cells/mL, P = 0.03) and CD8 (+74 cells/mL, P = 0.005) counts compared with placebo but did not alter the plasma viral load (30).

During HIV infection, selenium deficiency increases susceptibility and fast progression of the disease. To confirm that selenium supplementation can be used to increase body selenium, two small studies were conducted in France and U.S on people living with HIV. In a study conducted in France, reduced serum Se levels increased from an average of 0.75 +/- 0.27µmol/L to 1.63 +/- 0.27µmol/L following 21days of selenium supplementation (2). Whilst in the U.S, serum Se in people living with HIV increased from a mean of 1.55 +/- 0.38µmol/L as compared to 2.47 +/- 0.25µmol/L in the control group (2). Based on these and other related trials, it is probable that supplementation could be useful in boosting the serum Se levels (19, 2).

Conclusions and Recommendation

The effects of Se on human immunity are clearly complex, but only limited data are available on human immunology. There is a need for more research, especially in deficient populations, and intervention studies. This would provide more insight on the role of Se in immunity.

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REFERENCES

1. Bowrey, D.J., Morris-Stiff, G.J and Puntis, M.C. A. Selenium Deficiency and Chronic Pancreatitis" Disease Mechanism and Potential for Therapy. *HPB Surgery*, 1999; 11:207-216.
2. Stone, C.A., Kawai, K., Kupka, R., Fawzi, W.W. The Role of Selenium in HIV Infection. *Nutr Rev*. 2010; 68(11): 671–681
3. Peters, U and Takata, Y. Selenium and the Prevention of Prostate and Colorectal Cancer. *MolNutr Food Res*. 2008; 52 (11): 1261-1272
4. Ventura, M.G., Freitas, M.C., Pacheco, A., Meerten, T.V., Wolterbeek, H.T. Selenium content in selected Portuguese foodstuffs. *Eur Food Res Technol*224:395-401
5. Brown, K. M and Arthur J. R Selenium, selenoproteins and human health: a review. *Public Health Nutrition*: 2001; 4: 593-599
6. Baum, M.K., Shor-Posner, G., Lai, S et al. High risk of HIV-related mortality is associated with selenium deficiency. *J AcquirImmunDeficSyndr* 1997; 15:370-374
7. Fairweather-Tait, S. J., Bao, Y., Broadley, M. R et al. Selenium in human health and disease. *Antioxid Redox Signal* 2011; 14: 1337–83.
8. Khan, M.S, Dilawar, S, Ali I and Rauf N. The Possible Role of Selenium Concentration in Hepatitis B and C Patients. Saudi J Gastroenterol2012; 18:106-10

9. Johnson, C.C., Fordyce, F.M., Rayman, M.P. Symposium on 'Geographical and geological influences on nutrition': factors controlling the distribution of selenium in the environment and their impact on health and nutrition. *ProcNutrSoc*2010; 69: 119–32
10. Rayman M.P. The use of high-selenium yeast to raise selenium status: how does it measure up? *Br J Nutr*2004; 92: 557–73.
11. Reeves, M.A and Hoffmann, P.R. The human selenoproteome: recent insights into functions and regulation *Cell Mol Life Sci*. 2009; 66(15): 2457–2478
12. Tak, P.P and Firestein G.S. NF-$_{\kappa}$B: A key role in inflammatory diseases. *Journal of Clinical Investigation* 2001; 107(1):7-11
13. Youn, H-S., Lim, J.H., Choi, Y.J., Lee, Y.J., Lee, Mi-Young and Ryu, J-H. Selenium supresses the activation of transcription factor NF-$_{\kappa}$B and IRF3 induced by TLR3 or TLR4 agonists. *International Immunopharmacology* 2008; 8:495-501
14. Schreck, R., Rieber, P andBaeuerle, P.A. Reactive oxygen intermediates as apparently widely used messengers in the acti- vation of the NF-kappa B transcription factor and HIV-1. EMBO Journal 1991; 10, 2247–2258.
15. Maehira, F., Miyagi, Eguchi and Y. Selenium regulates transcription factor NF-$_{\kappa}$B activation during the acte phase reaction. *ClinicaChimicaActa*2003; 334: 163-171
16. Arthur,J. R., Roderick C. McKenzie, R. C and Geoffrey J. Beckett, G. J. Selenium in the Immune System. J. Nutr. 2003; 133: 1457S–1459S
17. Wang, C., Wang, H., Luo, J., Hu, Y., Wei, L., Duan, M. and He, H. Selenium deficiency impairs host innate immune response and induces susceptibility to *Listeria monocytogenes* infection. *BMC Immunology* 2009, 10:55
18. Eze, J.I., Ngene, A.A., Anosa, G.N and Ezeh, I. O. Immnolomodulatory effect of dietary selenium supplementation on serum antibody response and leucocytic profile of trypanosome bruceibrucei infected rats. *African Journal of Biotechnology* 2011; 10(56) 12098-12106
19. Broome, C.S., McArdle, F., Kyle, J.A. M et al. An increase in selenium intake improves immune function and poliovirus handling in adults with marginal selenium status. *Am J ClinNutr*2004; 80:154–62
20. Hoffmann, F.W., Hashimoto, A.C., Shafer, L.A., Dow, S., Berry, M.J., and Hoffmann, P.R. Dietary Selenium Modulates Activation and Differentiation of CD4+ T Cells in Mice through a Mechanism Involving Cellular Free Thiols. *J. Nutr*. 140: 1155–1161, 2010.
21. Su, C., Gong, C., Li, J., Chen, L., Zhou, D. & Jin, Q.Preliminary results of viral etiology of Keshan disease. Chin. Med. J. 1979; 59: 466
22. Rayman M.P. Selenium and human health. *Lancet* 2000; 356:233–241.
23. Rayman MP. The importance of selenium to human health. *Lancet* 2012; 379:1256–68.
24. Beck, M.A., Esworthy, R.S., Ho, Y.S., Chu, F.F. Glutathione peroxidase protects mice from viral-induced myocarditis. *FASEB J* 1998; 12:1143
25. Semba R.D. and Tang A.M. Micronutrients and the pathogenesis of human immunodeficiency virus infection *British Journal of Nutrition* (1999), 81, 181–189
26. Drain, P.K., Baeten, J.M., Overbaugh, J., Wener, M.H., Bankson, D.D., Lavreys, L., Mandaliya, K., Ndinya-Achola, J.O and R McClelland, R.S. Low serum albumin and the acute phase response predict low serum selenium in HIV-1 infected women. BMC *Infectious Diseases* 2006; 6:85
27. Baum, M.K., Miguez-Burbano, M.J., Campa, A and Shor-Posner G.Selenium and Interleukins in Persons Infected with Human Immunodeficiency Virus Type 1. *JID* 2000; 182
28. Hurwitz, B.E., Klaus, J.R., Llabre, M.Met al. Suppression of Human Immunodeficiency Virus Type 1 Viral Load with Selenium Supplementation. *Arch Intern Med.* 2007; 167:148-154
29. Kupka, R.,Mugusi,F., Aboud, S., Msamanga, G.I., Finkelstein, J. L., Spiegelman, D and Fawzi, W.W. Randomized, double-blind, placebo-controlled trial of selenium supplements among HIV-infected pregnant women in Tanzania: effects on maternal and child outcomes. *Am J ClinNutr*. 2008; 87(6): 1802–1808
30. McClelland, R.S., Baeten, J.M., Overbaugh, J et al. Micronutrient Supplementation Increases Genital Tract Shedding of HIV-1 in Women. Results of a Randomised Trial. *Journal of Acquir Immune DeficSyndr.* 37:1657-1663