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Selenium status and immunity

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Selenium is found at the active centre of twenty-five selenoproteins which have a variety of roles, including the well-characterised function of antioxidant defense, but it also is claimed to be involved in the immune system. However, due to limited and conflicting data for different parameters of immune function, intakes of selenium that have an influence on immune function are uncertain. This review covers the relationship between selenium and immune function in man, focusing on the highest level of evidence, namely that generated by randomised controlled trials (RCT), in which the effect of selective administration of selenium, in foods or a supplement, on immune function was assessed. A total of nine RCT were identified from a systematic search of the literature, and some of these trials reported effects on T and natural killer cells, which were dependent on the dose and form of selenium administered, but little effect of selenium on humoral immunity. There is clearly a need to undertake dose–response analysis of cellular immunity data in order to derive quantitative relationships between selenium intake and measures of immune function. Overall, limited effects on immunity emerged from experimental studies in human subjects, though additional investigation on the potential influence of selenium status on cellular immunity appears to be warranted.

Key words: Selenium: Immune function: Infectious diseases

A total of twenty-five selenoproteins have been identified[(1)], all of which contain selenocysteine, the twenty-first amino acid in the genetic code. In the past two decades, there has been significant progress in characterising selenoproteins and understanding their physiological and pathological functions[(1)], but the identity and functions of some still remain unknown. Selenocysteine is located in several enzyme-active sites that play a crucial role in regulating reactive oxygen species (ROS) levels, energy metabolism, overall redox status and cellular processes involved in innate and adaptive immune responses[(2–5)]. The sub-families within the well-characterised selenoproteins are glutathione peroxidases (GPX), thioredoxin reductases (TXNRD), methionine sulphoxide reductase, selenoprotein P (SePP) and several selenoproteins in the endoplasmic reticulum[(6)]. GPX, TXNRD and selenoproteins located in the endoplasmic reticulum play an important role in controlling oxidative

Abbreviations: COVID-19, coronavirus disease 2019, GPX, glutathione peroxidase, NK, natural killer, RCT, randomised controlled trial, ROS, reactive oxygen species, Se, selenium, SePP, selenoprotein P, TXNRD, thioredoxin reductase.

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Table 1. Examples of selenoproteins involved in viral infections[9]

General function	Selenoproteins
Antioxidant/redox function	GPX1, GPX2, GPX3, GPX4, TXNRD1, TXNRD2, TXNRD3, MSRB1, SELENOP, SELENOW
Anti-inflammatory	GPX, TXNRD1, SELENOS
Immune cell function	GPX, TXNRD, MSRB1, SELENOK, SELENOS
Anti-viral effects	GPX, TXNRD, ER selenoproteins

GPX1, cytosolic glutathione peroxidase; GPX2, gastrointestinal glutathione peroxidase; GPX3, extracellular glutathione peroxidase; GPX4, phospholipid glutathione peroxidase; TXNRD1, cytosolic thioredoxin reductase; TXNRD2, mitochondrial thioredoxin reductase; TXNRD3, testis thioredoxin reductases; MSRB1, methionine sulphoxide reductase B1; SELENOP, selenoprotein P; SELENOW, selenoprotein W; SELENOK, selenoprotein K; SELENOS, selenoprotein S; ER selenoproteins, endoplasmic reticulum selenoproteins.

stress. It has been suggested that reduced selenoprotein expression may affect host defence against infectious diseases. For viral infections, it has been shown in animal models that the oxidative stress associated with host selenium deficiency leads to viral genome mutations, whereby benign or mildly pathogenic viruses may become highly virulent[7], but this has yet to be confirmed in human subjects.

ROS have an important role in host defence and immunity, for example phagocytic cells produce large amounts of ROS to eliminate a wide variety of pathogens without altering the host cell viability. Viruses are known to induce ROS-generating enzymes and viral infections are often accompanied by alterations in the intracellular redox state of the host cell[6]. Redox homoeostasis plays an important role in pathology because accumulation of ROS and/or depletion of scavenging systems leads to the development of oxidative stress, chronic activation of immune responses and inflammation[8]. However, when the innate or adaptive immune responses are activated in an uncontrolled way, the immune system itself can be responsible for the development of tissue damage.

The focus of this review is to examine the relationship between selenium intake, and its subsequent impact on selenium status, and changes in immune function in man, without covering direct antiviral (toxic) activity of selenium against viruses and other micro-organisms.

Role of selenium in susceptibility to infections

A number of selenoproteins (Table 1) are directly or indirectly involved in combatting viral infections through functions relating to antioxidant defence, redox signalling and redox homoeostasis[9]. A balance exists between the generation of ROS and their scavenging systems, and this equilibrium can be disturbed during viral infections, resulting in oxidative stress. Selenoproteins are involved in redox homoeostasis; for example, TXNRD1 modulates redox tone in immune cells through the regeneration of reduced cytosolic thioredoxin 1[10]. GPX enzymes use glutathione to catalyse the reduction of hydrogen peroxide and organic peroxides to form selenious acid as an intermediary or the corresponding alcohols[11]. They have an anti-inflammatory role; for example, they metabolise ROS to prevent activation and translocation of nuclear transcription factor NF-κB, essential for viral replication, to the nucleus and thus prevent it binding to pro-inflammatory cytokine genes[12]. GPX and TXNRD can reverse oxidative damage in immune cells[11] and influence viral pathogenicity by counteracting oxidative stress which can cause mutations in the viral genome[13].

Table 2. Dietary selenium recommendations for adults (μg/d) from different authorities

Authority/publication year	AR/EAR (M/F)	PRI/RDA/RNI (M/F)	AI (M/F)
EFSA 2014[2]			70/70
IOM 2000[33]	45/45	55/55	
WHO 2004[34]	27/20*	34/26	
UK 1991[35]		75/60†	
D-A-CH 2015[16]			70/60
NNR 2012[36]	35/30	60/50	
AESAN 2019[37]		70/55	
ANSES 2021[38]			70/70
SINU 2014[39]		55/55	
HCNL 2018[40]			70/70
NRVANZ 2006[41]	60/50	70/60	
CNS 2013[42]	50/50	60/60	
JAPAN 2020[43]	25/20	30/25	

AR, average requirement (intake that meets the needs of 50% of the population); EAR, estimated average requirement (intake that meets the needs of 50% of the population); PRI, population reference intake (intake that meets the needs of 97·5% of the population); RDA, RDA (intake that meets the needs of 97·5% of the population); RNI, reference nutrient intake (intake that meets the needs of 97·5% of the population); AI, adequate intake (intake that meets or exceeds the needs of 100% of the population); M, males; F, females; EFSA, European Food Safety Authority, Institute of Medicine; UK, Department of Health; D-A-C-H, Department of Health, German, Austrian and Swiss Nutrition Societies; NNR, Nordic Nutrition Recommendations; AESAN, Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition; ANSES, Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the 'Updating of the French Dietary Reference Values for Vitamins and Minerals'; SINU, Società Italiana di Nutrizione Umana; LARN, Livelli di assunzione di riferimento di nutrienti e energia per la popolazione italiana – IV revision. SICS, Milan; HCNL, National Council of the Netherlands. Dietary Reference Values for Vitamins and Minerals for Adults Health Council of the Netherlands, The Hague; NRVANZ, Nutrient Reference Values for Australia and New Zealand. Australian Government. Department of Health and Ageing. National Health and Medical Research Council; CNS, Chinese Dietary Reference Intake summary, People's Medical Publishing House; JAPAN, Dietary Reference Intakes for Japanese.
* The average requirement was calculated using a reference weight of 65 kg for men and 55 kg for women and average selenium normative requirements of 0·42 and 0·37 kg/d for men and women respectively[34].
† Lower reference nutrient intake (LRNI), the intake below which the needs of 97·5% of adult men and women are not met, is 40 μg/d.

Consequences of a lower selenium status on susceptibility to infection

Selenium deficiency in the host has been shown in animal models to affect the viral genome and exacerbates virulence and progression of viral infections. In the early 1930s an endemic cardiomyopathy termed Keshan disease[3] was described in Heilongjiang province, Northeast China, where severe selenium deficiency is

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Table 3. Randomised controlled trials on selenium supplementation and immune function

Country	Intervention	Impact of Se supplementation on immune function
Finland[20]	Se-yeast and Se-rich wheat flour (200 μg/d)	Little or no effect
UK[21]	Sodium selenite (50, 100 μg/d)	Cellular immunity augmented, no effect on humoral immunity
UK[22]	Se-yeast (50, 100, 200 μg/d) Se-enriched onions (50 μg/d)	Positive and negative effects (depending on dose and form) on cellular immunity, no effect on humoral immunity
USA[23]	High-Se (297 μg/d) or low-Se (13 μg/d) diet	Positive effect on B-lymphocytes and T-cell function
USA[24]	Se-yeast (300 μg/d)	No effect on immune function, low Se group had higher numbers of NK cells and T-lymphocytes
USA[25]	Sodium selenite (200 μg/d)	No change in Se status, no conclusions about the effect of Se can be drawn
USA[26]	Sodium selenite (200 μg/d)	Increased expression of high affinity IL-2 receptor on surface of activated lymphocytes
USA[27]	Se-yeast (400 μg/d)	Short-term increased NK cell cytotoxicity, increase in CD4+ T cells
Belgium[28]	Se-yeast (100 μg/d)	Increased T-lymphocyte response to pokeweed mitogen

common. Selenium supplementation contributed towards its eradication but there was also a reduction in incidence that was unrelated to selenium supplementation, and a seasonal trend, indicating that selenium deficiency was not the sole cause of Keshan disease. In the 1990s Beck *et al.*[7] undertook studies in animal models that demonstrated it had a dual aetiology, viz. a combination of selenium deficiency and an infectious cofactor, the single-stranded RNA virus Coxsackie virus B. Following on from this, it was demonstrated that a mild strain of influenza virus also exhibits increased virulence when given to selenium-deficient mice[14]. However, it should be noted that this finding has not been replicated in human subjects. Furthermore, it is possible that selenium exerts a direct antiviral activity through its toxic effects[15]. When the antiviral effects of three selenium compounds (selenite, selenate and selenomethionine) on Coxsackie virus B5 replication were examined, only selenite had an inhibitory activity, which the authors suggested was due to its toxicity following its interaction with thiols. This activity could be blocked by dithiothreitol, a sulphhydryl-protecting agent known to reverse several toxic effects of selenite, and zinc, another inhibitor of selenite toxicity, also counteracted the antiviral effect of selenite.

Public health nutrition: deriving dietary recommendations for selenium

Dietary reference values are the basis for setting dietary recommendations. Their derivation involves two key steps: (a) defining the average requirement and (b) estimating the upper safe level of chronic intake. Functional markers with a well-characterised dose–response relationship are generally used to derive dietary requirements. Biomarkers of selenium exposure include plasma and serum selenium concentration, GPX activity in plasma (GPX3), in erythrocytes (GPX1), in thrombocytes (GPX1) or in whole blood (GPX3 and GPX1), and plasma and serum SePP concentration. The derivation of most dietary reference values for selenium is based on the measurement of GPX activity in plasma, but in recent years, SePP concentration in plasma has been selected as the biomarker for determining the optimum intake of selenium[2]. There is some disparity in the dietary reference values for selenium set by different authorities (examples are shown in Table 2). This is partly due to the use of different endpoints since maximum GPX3 activity is achieved at lower intakes of selenium than are required to maximise SePP concentration[16,17]. In addition, there is no clear evidence that SePP needs to attain a plateau in order to achieve 'optimal' selenium status[18], and further research is required to link selenium intake/status to functional endpoints, including the impact of selenium status (biomarkers) on susceptibility to infection[3]. Currently, there are insufficient data on selenium and its physiological functions to estimate average requirements with a high degree of certainty, hence the decision by the European Food Safety Authority to derive an adequate intake rather than an average requirement[2].

In relation to public health policy in the UK, in 2013 the Scientific Advisory Committee on Nutrition published a position statement on selenium and health[19] which noted that results from randomised controlled trials (RCT), published to date, on selenium and response to viral challenge were inconsistent. They concluded that there was insufficient evidence to establish a cause–effect relationship between selenium intakes, at the levels studied, and human response to viral challenge. Since then, new statistical techniques for examining dose–response relationships have been developed, thus it would be timely to analyse all the available data to reach a conclusion about the effect of selenium on immune function.

Effects of selenium supplementation on markers of immune function

A number of RCT have been undertaken to examine the effects of selenium on immune function. We undertook a systematic search in PubMed/MEDLINE and Embase for experimental studies assessing the association between selenium status and infectious disease susceptibility. The search keyword terms were 'humans', 'selenium' or 'selenium supplementation', 'infectious disease', 'immune system' or 'immunity' and 'trial' or 'clinical

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trial'. We excluded non-experimental studies, case reports, reviews and commentaries.

Table 3 summarises the RCT on selenium supplementation and immune function, which are described in greater detail later. In the 1980s a study was undertaken in Finland because of concerns about the low intake (30 μg/d) of selenium in the population[20]. Healthy men aged 36–50 years with plasma selenium <70 μg/l were given 200 μg/d selenium as Se-yeast or toast made of Se-rich wheat flour or a placebo for 11 weeks. At the end of the supplementation period, plasma selenium concentrations were 74 μg/l in the placebo group and 169 μg/l in the group given selenium supplements. Immune function was measured *in vitro* by tests of lymphocyte and granulocyte function and activity. Antibody (IgA, IgG and IgM) formation was slightly higher in the selenium group, while plaque forming cells was lower or unaffected by the difference in selenium status as well as the proliferating response against mitogens such as phytohaemagglutinin and concanavalin A. Intracellular killing of *Staphylococcus aureus* by granulocytes was slightly lower in the placebo group than in the selenium group at the end of the supplementation period (77·2 compared to 85·2 %; $P < 0{\cdot}05$) but no other changes were observed. The authors concluded that the low-selenium status found in Finland has little, if any, influence on the immune functions measured in this study.

In the UK, according to the 2013 Scientific Advisory Committee on Nutrition report[19], the Total Diet Survey showed a downward trend in intakes of selenium between 1974 and 2000, probably due to the replacement of Canadian wheat with European wheat containing less selenium, and the UK was included in the list of countries considered to have low intakes of selenium. Two UK studies[21,22] reported the effects of selenium on immune function. In the first study[21] twenty-two adult men and women with plasma selenium concentrations <95 μg/l were recruited and given 50 or 100 μg selenium (as sodium selenite) or placebo daily for 15 weeks in a double-blind study. All subjects received an oral live attenuated poliomyelitis vaccine after 6 weeks. Selenium supplementation increased plasma selenium concentrations (from about 80 μg/l at baseline to 95 and 110 μg/l in the 50 and 100 μg groups respectively). In both supplemented groups there was an increased production of interferon and other cytokines (IL-2 and IL-10) and an earlier peak T-cell proliferation. The percentage change of T cytotoxic proliferation was similar in the 50 and 100 μg/d groups, total T cells and T-helper cells showed a dose–response relation with increasing selenium intake, especially in the 100 μg/d group. A similar increasing pattern could be noted for natural killer (NK) cell-mediated cytotoxicity. Conversely, humoral immune responses were reported as unaffected. In the second study[22] individuals with plasma selenium levels <110 μg/l were given capsules containing a placebo or Se-yeast (50, 100, 200 μg selenium/d) or Se-onion containing meals with either <1 μg Se/d or 50 μg Se/d. Influenza vaccine was administrated at week 10 and immune parameters were assessed until week 12. There was no effect on humoral immunity as measured with IgA and IgG1 and IgG2 titres, but a mixture of beneficial and detrimental effects on cellular immunity that depended on the form and dose of selenium. There was a dose-dependent increase in T-cell proliferation with selenium supplementation in both Se-yeast and Se-onion groups, but with no differences in the number of any cytotoxic cell subsets investigated, including CD8 cells and NK cells. Conversely, granzyme B content of CD8 cells was lower in the 200 μg/d Se-yeast group, but higher in the Se-onion group compared to their control groups. Finally, concentrations of IL-8, IL-10, interferon-γ and TNF-α were assessed showing a dose–response increase for IL-8 and IL-10 after flu vaccination in the Se-yeast group, and for IL-8 and interferon-γ in the Se-onion group. TNF-α showed however reduced levels in the Se-onion group compared to its control group.

Two RCT were undertaken in the USA[23,24], which is a country with generally higher selenium intakes than in the UK. Since diets high in selenium are mainly comprised of organic selenium, instead of using inorganic selenium supplements (as used in many of the other trials described in this review), the authors fed specially selected foods to volunteers in order to compare the effect of a low- and high-selenium diet on immune function. In the first study[23], eleven adult men, confined to a metabolic unit, were fed with diets that were low (13 μg/d) or high (297 μg/d) in selenium for 11 weeks. The only difference in the diets was the geographical origin of the rice and beef staples, which were obtained from regions with either very high or very low soil selenium; all other components of the diets were identical. Serum Ig, complement components and primary antibody responses to influenza vaccine were unchanged. However, antibody titres against diphtheria vaccine were 2·5-fold greater after reinoculation in the high-selenium group. Leucocyte counts decreased in the high-selenium group and increased in the low-selenium group, resulting primarily from changes in granulocytes, while lymphocytes increased in both the groups. In particular, the leucocyte subpopulation analysis noted a tendency for a higher increase in the high-selenium group for T suppressor, T cytotoxic and T-activated cells, not present in B and T cells. *In vitro* proliferation of peripheral lymphocytes in autologous serum in response to pokeweed mitogen was stimulated in the high-selenium group by day 45 and remained elevated throughout the study, whereas proliferation in the low-selenium group did not increase until day 100. Finally, no effect on delayed-type hypersensitivity skin responses to total diameter and number of indurations at 48 and 72 h was noted with none of the seven antigens tested (i.e. tuberculin purified-protein derivative, mumps, tetanus toxoid, candida, trichophyton, streptokinase streptase, coccidioidin). The authors concluded that the immune-enhancing properties of selenium in human subjects are the result, at least in part, of improved activation and proliferation of B-lymphocytes and perhaps enhanced T-cell function. Although the results support the conclusion about T-cells, the baseline *v.* final B-lymphocytes (CD19+) in low- and high-Se diets were: 222 *v.* 251 for low-Se and 307 *v.* 294 for high-Se (thousand/mm^3), which do not support the authors' conclusions. A weakness of the

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study design is the absence of a 'normal' selenium diet, making it impossible to draw conclusions as to whether it is the added selenium or the deficiency of selenium that is responsible for the observed differences in immune function. The second RCT undertaken by the same research group[24] was designed to investigate the effect of selenium on leucocytes (overall and subpopulation) and on delayed-type hypersensitivity skin responses (both total diameter and number of indurations at 48 and 72 h) to five infectious disease antigens (i.e. mumps, candida, trychophyton, tuberculin-purified protein and tetanus). Subjects were given 300 μg/d selenium as Se-yeast for 48 weeks. Selenium supplementation increased plasma selenium from 142(SD 19) to 228(SD 63) μg/l. Total induration from delayed-type hypersensitivity skin responses decreased by 57 % in the low-Se group, while it decreased approximately 20–25 % in the high-Se group; in particular, the response to all five specific antigens decreased from baseline in both low- and high-Se groups, but not for tetanus toxoid (unchanged in low-Se) and trychophyton (increased in high-Se) but did not change in the selenium-supplemented subjects. There was no effect on total lymphocyte, B-cell, T-cell, CD4+ or CD8+ cell counts. However, the number of IL-2 receptor expressing T-cells and IL-2 receptor expressing NK cells increased in the low-Se group during supplementation. The data suggest that selenium supplementation of healthy people may modulate the development of immuno-tolerance.

Two other RCT have been undertaken in the USA[25,26], which investigated the effect of 200 μg/d selenium as sodium selenite. One focused on the potential role of the immune system to inhibit tumourigenesis[25]. The authors reported an increase in the ability of an activated lymphocyte population to destroy a fixed number of Raji tumour cells in the group given sodium selenite. The cytotoxic efficiency of activated lymphocytes from the selenite and placebo groups remained the same but the number of lymphocytes required to destroy tumour cells decreased significantly in the selenium supplemented group, and there was a significant increase in the lytic activity of NK cells towards tumour cells. It is possible that selenium exerted a toxic/inhibitory/lytic effect against the tumour cells, making them more susceptible to the NK activity. However, a valid interpretation of the findings of this study is impossible because there were no changes in plasma selenium concentration after 8 weeks supplementation, suggesting either a compliance problem, particularly in the treatment group, or unblinding in relation to selenium supplementation. No conclusions can therefore be drawn about the effects of selenium *per se*. The other sodium selenite trial in the USA[26] reported only a small increase in plasma selenium after 8 weeks supplementation, indicating that the population, also residing in New York as in the previous study, was virtually selenium replete or that the selenite supplements had low bioavailability. In addition, the placebo group also showed an increase in plasma selenium levels at the end of the trial, suggesting a possible increase in selenium intake in addition to the trial intervention. They reported an augmentation of the ability of peripheral blood lymphocytes to respond to stimulation with phytohaemagglutinin or alloantigen and to express high affinity IL-2 receptors on their surface. This trial indicates that selenium supplementation can modulate T-lymphocyte-mediated immune responses that depend on signals generated by the interaction of IL-2 with IL-2 receptor.

In order to investigate the possible effect of selenium on immune function that could have implications in cancer prevention, very high doses of selenium (400 μg/d) as Se-yeast, together with β-carotene, were given for 6 months to healthy non-smoking free-living American adults aged 57–84 years[27]. The mean baseline plasma concentration of the placebo group was, by chance, significantly higher than the other groups, and the percentage change in plasma selenium as a result of supplementation was zero at 3 months and only 10 % at 6 months which suggests a compliance issue. As with the other USA RCT, the baseline values for plasma selenium concentrations were relatively high. The authors reported that selenium did not affect total leucocyte levels. Conversely, it enhanced immune function (NK cell cytotoxicity) and phenotypic expression of T-cell subsets but the increased NK cell cytotoxicity only lasted for a short time and was not sustained throughout the 6 months of supplementation. They also noted that selenium supplementation increased the percentage of total T cells in lymphocytes after 6 months of supplementation due to increases in CD4+ (T-helper/inducer) cells. However, drawing conclusions about the impact of selenium supplementation is impossible given the fact that the plasma selenium concentrations were higher in the control than the treatment group.

An RCT in elderly institutionalised men and women was undertaken in Belgium[28]. The authors highlighted the fact that elderly subjects may be prone to marginal selenium deficiency and are usually affected by moderate immune disturbances. The effect of 6 months supplementation with 100 μg/d selenium as Se-yeast on lymphocyte-proliferation responses to mitogens was investigated. In this trial, mean baseline plasma selenium concentration was relatively low (68 μg/l) and increased to 122 μg/l by the end of 2 months supplementation, at which point it reached a plateau. After 4 and 6 months of selenium supplementation the proliferative response to pokeweed mitogen increased significantly and reached the upper limit of the usual range for adults by the end of the trial, while no effects in both groups can be noted for other mitogens (phytohaemagglutinin and monoclonal anti-human T lymphocyte antibody-OKT3).

Selenium and coronavirus disease 2019: the evidence so far

The coronavirus disease 2019 (COVID-19) pandemic has severely affected the world's population in the past 2 years. Major efforts have been made to identify effective drugs or active substances that are involved in immune function for preventing and treating COVID-19, including trace elements such as selenium. There are a number of observational studies linking a lower Se status with

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COVID-19 prevalence or progression[29,30], but this type of evidence has substantial methodological limitations, arising from exposure misclassification and/or bias attributable to reverse causality. However, there is a systematic review[31] focusing on RCTs in which selenium supplementation was used to treat or prevent COVID-19. Searches were made in PubMed, Scopus and ClinicalTrials databases until 10 January 2022. There were no published trials but one on selenium and two on zinc and selenium are ongoing. One trial (NCT04869579), which had not started recruiting in April 2022, plans to give selenious acid (first day 2000 μg, following days 1000 μg) or placebo as treatment for 100 Texan adults with COVID-19 following a double-blind randomised design. Another trial (NCT04751669), which had not started recruiting in April 2022, plans to give a daily supplement containing 10 mg zinc and 110 μg selenium or placebo as treatment for COVID-19 in 300 Spanish adults in a double-blind randomised parallel trial design. A third trial (NCT04323228), which was at the recruitment stage in April 2022, is being carried out in Saudi Arabia. An oral daily supplement containing 15 μg selenium and 7·5 mg zinc or placebo will be given as treatment to forty individuals infected with COVID-19 using a double-blind randomised parallel design. When the results of these trials are published, it will be a little clearer as to whether or not selenium supplementation is justified for improving outcomes relating to COVID-19.

The impact of selenium status on the response to COVID-19 vaccination has recently been addressed in a prospective observational study[32]. Adult health care workers (*n* 126) were given two consecutive anti-severe acute respiratory syndrome-coronavirus 2 vaccinations, 3 weeks apart, and blood samples were collected at the time of the first vaccine, second vaccine and at 3 and 21 weeks after the second dose. Plasma selenium and SePP concentrations, GPX3 activity and the IgG response were measured. The humoral immune response was not related to any of the three selenium status biomarkers. In addition, self-reported supplemental selenium intake had no effect at any time point on the vaccination response. The tertiles for serum selenium concentration were: $Q1 < 70{\cdot}8$ μg/l, $Q2$ <82·7 μg/l and $Q3 > 82{\cdot}7$ μg/l, and for serum GPX3 activity they were: $Q1 < 215{\cdot}3$ (U/l), $Q2 < 248{\cdot}0$ (U/l) and $Q3 > 248{\cdot}0$ (U/l). No differences in immune response were noted across the tertiles, and although the cell-mediated vaccination response was not assessed, the absence of a humoral response agrees with earlier publications[21,22].

Conclusions

Evidence for a selenium-specific effect on immune function obtained from RCT is limited and varies according to the study design, immune function measures, form and dose of selenium and background selenium status of the trial participants. There is a consistent finding that selenium has little if any effect on humoral immunity, while the picture for cellular immunity is less clear and consistent. In some cases, NK cells and T-lymphocytes appear to respond positively to selenium supplementation, but it is not possible to draw conclusions about the relationship between selenium intake and immune function because of the limited and heterogeneous nature of the data, and the substantial risk of bias affecting some of these studies. Therefore, the uncertainties about the actual relation between selenium status and immune function limit the possibility of using immune function as an endpoint for deriving dietary reference values for this trace element. There is clearly a need for well-designed RCTs in human subjects to investigate the relationship between selenium and immune function, and for dose–response analysis to be used to obtain in-depth characterisation.

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Conflict of Interest

None.

Authorship

The authors have sole responsibility for all aspects of preparation of the present paper.

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