

# The role of selected microelements: selenium, zinc, chromium and iron in immune system

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## Abstract

*The immune response is the process of recognition of potentially harmful agents by specialized cells of the immune system. It is expressed as cellular and humoral immunity. A number of nutrients have the ability to modulate immune response through the production of antibodies or cytokines (e.g. zinc, selenium, chromium). Moreover the elements are required for immune cells proliferation or activation (e.g. iron). The elements are also required for functioning of enzymes involved in antioxidant system (e.g. selenium) of the immune cells. It has been shown, that nutrient supplementation may enhance but may also suppress immune function.*

**Key words:** selenium, zinc, chromium, iron, immune system.

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## Introduction

The immune response is the process of recognition of potentially harmful agents by specialized cells of the immune system. It is expressed as cellular and humoral immunity [1]. Microorganisms such as viruses, bacteria, fungi, protozoa and also tumor cells may be the harmful agents [2]. The human microbial defense system can be viewed as consisting of 3 levels: anatomic and physiologic barriers, innate immunity and adaptive immunity. Anatomic and physiologic barriers provide first line of defense against microorganisms. These barriers include: intact skin, vigorous mucociliary clearance mechanisms, low stomach pH, lysozyme in tears, saliva and other secretions [3]. Adaptive aspects of the immune system include cell- and humoral-mediated immunity [2, 4, 5]. At first, the innate immunity is involved after the infection. When components of this type of immunity are not able to clear the infection, adaptive immune response components become involved [5]. Moreover, innate immunity plays a central role in activating the subsequent adaptive immune response [3].

Elements can give adverse effects. On the one hand, they can be expected to increase the production of reactive oxygen species (ROS). They can initiate lipid peroxidation

and cellular damage. Immune cells are particularly sensitive to oxidative stress, because their membranes contain high concentrations of polyunsaturated fatty acids which are very susceptible to peroxidation and, when stimulated, they produce large amounts of ROS. On the other hand, trace elements are involved in the antioxidant system and the deficiency of any of them may depress immunity. Moreover, the elements are required for functioning of enzymes involved in antioxidant system [6].

## Selenium

Selenium (Se) is a naturally occurring element found in soil, rocks and water. It is also a product of volcanic activity [7]. Selenium is a universal trace element for animals and humans which is important for many cellular processes [8]. It has been shown to regulate many intracellular functions by being a chemical component of selenoproteins. These are selenium-dependent enzymes such as glutathione peroxidase (cGPx) and thioredoxin reductase (TR). Selenium is also contained as selenomethionine and/or Se-methylselenocysteine in wheat and yeast [9]. Currently, more than 30 selenoproteins have been described, most of which are involved in enzyme activity and meta-

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bolic regulation of oxidative processes in animal or bacterial cells [10].

Selenium enhances the ability of lymphocytes to respond to the IL-2 by increasing the expression of IL-2 receptors on these cells. Enhancement of these interactions leads to increased numbers of lymphocytes, cytotoxicity of killer cells and antibody production by B cells [11]. Moreover, Pei *et al.* [12] have discovered that selenium pretreatment significantly inhibited IL-6 secretion in LPS-stimulated human PC3 cells.

It has been shown that selenium deficiency affects blood levels of IgG, IgM and IgA as well as T cell function. Moreover, the activity and life span of neutrophils, macrophages and lymphocytes diminishes, perhaps, because of a decrease in the activity of GSH-PX [10, 13]. In cows selenium deficiency has reduced the ability of blood and milk neutrophils to kill bacteria [14]. Chemotactic migration of neutrophils was also reduced by selenium deficiency in goats. However, *in vitro* addition of Se to bovine neutrophils and macrophages has enhanced their migration [14]. Investigations performed by other authors confirmed that neutrophils from Se supplemented cows show greater phagocytic and bactericide activities against *Staphylococcus aureus* and *Candida albicans*. Moreover, the increase of production of leukotriens was observed [10]. Cao *et al.* [15] suggest that selenium affects cell-mediated immunity in dairy cows. Peripheral blood lymphocytes isolated from Se-deficient animals have exhibited a reduced response to mitogen stimulation (ConA). Moreover these lymphocytes have produced less products of arachidonic acid, especially 5-hydroxyeicosatetraenic and leukotriene B<sub>4</sub>.

It has been shown that selenium deficiency has been implicated in accelerated disease progression and poorer survival among by HIV infected population [16].

## Zinc

Zinc (Zn) is an essential trace element for human nutrition. It is a component of more than 300 enzymes from six classes [17]. Zinc is also involved in DNA replication, RNA transcription, signal transduction, enzymatic catalysis, redox regulation, cell proliferation, cell differentiation and apoptosis [17, 18]. Zinc plays a crucial part in normal development, differentiation and function of cells belonging to both, innate and acquired immunity, especially for T lymphocytes. Zn<sup>2+</sup> is required for the thymic development, production of naive T lymphocytes, clonal expansion, TH1/TH2 differentiation and normal T lymphocyte function [17, 19]. Moreover, Zn is crucial for normal development of neutrophils, natural-killer cells and macrophages and B-cells [19]. Zinc deficiency affects phagocytosis, intracellular killing and cytokine production [19, 20]. It is also involved in gene expression of anti-inflammatory cytokines: IL-2, IL-12, IFN- $\alpha$  and increments of proinflammatory cytokine IL-4 [19, 21]. Zinc deficiency decreased IL-2 pro-

duction and, subsequently IL-1 production by mononuclear cells and decreased NK cells cytotoxicity [1]. The correlation between zinc concentration and the function of cells innate immunity is shown in Table 1 [20].

There is a lot of data in the literature showing the influence of zinc on viral replication and infection of cells on the one hand, and the immune system (cytokine production) and modulation of the activity of immune cells on the other hand [17]. It has been shown that zinc prevents replication of rhinoviruses *in vitro* by inhibiting the formation of viral capsid proteins and virus 3C protease. Moreover, zinc could interact with the binding of the rhinovirus to the intercellular adhesion molecule (ICAM-1), i.e. zinc ions bind to the negatively charged regions at the carboxyl termini of the rhinovirus coat protein or may protect or stabilize the cell membrane. Several *in vitro* studies indicate that zinc supplementation decreases in the incidence of gastrointestinal disturbances, body weight loss and mild anemia in patients with chronic hepatitis C. Moreover, zinc *in vitro* induces the production of IFN- $\alpha$  and IFN- $\alpha$ . The combination therapy with zinc and IFN- $\alpha$  was more effective than the therapy with IFN- $\alpha$  alone against HCV. Zinc may be able to inhibit viral replication of herpes simplex virus and rhinovirus *in vitro* at concentration of 100  $\mu$ g/ml [17].

## Chromium III

Chromium is an element commonly occurring in nature in trivalent (Cr III) and hexavalent (Cr VI) forms [22]. Chromium VI is widely used in industrial chemicals, whereas chromium III is used as a micronutrient and nutritional supplement [23]. Chromium is essential for proper insulin functioning and it is required for normal protein, fat and carbohydrate metabolism [24]. The signs and symptoms of chromium deficiency in mammals are as follows: impaired glucose tolerance, elevated circulating insulin, glycosuria, fasting hyperglycemia, impaired growth, elevated circulating cholesterol and triglyceride concentrations, decreased insulin receptor number and impaired humoral immune response [25]. The potentially effects of chromium on immunity are presented on Fig. 1.

The relationship between microelements and cytokine production *in vitro* and *in vivo* has attracted the attention of several investigators. It has been shown that incubation of macrophages with chromium leads to the release of TNF- $\alpha$  and PGE<sub>2</sub>, but not IL-1 $\alpha$  and IL-6 [26, 27]. Other authors have found a higher release of IL-6 and IL-1 $\alpha$  from J744 cell line, lymphocytes, monocytes and human synoviocytes [28-30]. Our investigations have shown the increase of IL-1 $\alpha$  concentration and decrease of IL-6 concentration after incubation of mouse fibroblasts with chromium chloride [31].

Moreover, the investigations performed by Bhagat *et al.* [32] have shown that IFN- $\gamma$  mRNA expression of post immunization of NDV in animals, which received chromi-

um, was higher than control animals. The investigations provided by Burton *et al.* [33] have shown that chromium caused increase of IL-2, IFN and TNF- $\alpha$  production by cows' lymphocytes *in vivo*. Myers *et al.* [34] investigations have shown that chromium picolinate in treated swines have very high IL-6 levels when compared with the control group. Similar results were obtained by other authors. It has been shown that chromium-treated swine have very high IL-6 levels in plasma. Moreover, peripheral blood mononuclear cells from chromium picolinate treated animals produce more IL-2 than from control groups [35]. Our investigations have shown that chromium chloride caused the statistically significant increase of IL- $\alpha$  concentration and no changes in IL-6 concentration after the intraperitoneal injection of 1 mg and 10 mg Cr per body weight as chromium chloride [36].

Investigations provided by Burton *et al.* [37] have shown the decrease of leucocytes blastogenesis. That is confirmed by Kegley's *et al.* [38] investigations. Moreover, investigations performed by these authors have shown that chromium chloride and chromium picolinate caused the decrease of IgG and IgM serum concentration in calves. However, the investigations provided by van de Ligt *et al.* have shown no effect of chromium on IgG and IgM concentration in gilts' milk [39]. The investigations performed by Chang X *et al.* [40, 41] have shown that chromium caused a decrease of IgM concentration, but no differences in IgG and IgA was observed. The investigations performed by these authors have also shown no effect of chromium on lymphocytes blastogenesis. The proliferation of both T and B cells was inhibited by chromium after intraperitoneal injection in mice [35]. These investigations are in contrast with our investigations which have shown that intraperitoneally injection of 1 mg and 10 mg Cr per body weight, as chromium chloride, have no effect on metabolic activity of proliferative response of the lymphocytes [36].

## Iron

Iron is an essential growth factor for the proliferation and differentiation of all living cells [42]. It is also a central regulator of immune cell proliferation and functioning. All lymphocyte subsets (B and T lymphocytes and Natural killer cells) are dependent on transferrin/transferring receptor mediated iron uptake. The blockade of this pathway

leads to diminished proliferation and differentiation of these cells. It has been shown that lymphocytes B are less sensitive to changes in iron homeostasis than lymphocytes T. Moreover, in malignant B lymphocytes a non-transferrin iron uptake mechanism has been described. The major role, in this pathway, plays a divalent metal transporter DMT-1. Apart from these mechanisms all lymphocyte subtypes express receptors for H-ferritin, which is involved in the iron turnover by lymphocytes, as well as macrophages. The proliferation of lymphocytes is regulated also by iron-binding protein – Lactoferrin [42].

The relationship between microelements and cytokine production has attracted the attention of several investigators. It has been shown that exposure of human astrocytoma cells to IL-1 $\beta$  increases ferritin synthesis. Investigations performed by Bergman *et al.* [43] have shown that peripheral blood mononuclear cells (PBMC) incubated with iron secreted significantly lower amounts of IL-1 $\beta$  than control cells. Moreover, iron had no effect on IL-6 release by these cells. The investigations performed by Bergman *et al.* [44] are in agreement with our investigations which have shown the decrease of IL-1 $\alpha$  production and no changes in IL-6 release after iron chloride injection in mice.

Moreover, the influence on IL-1 $\alpha$  and IL-6 production *in vitro* was determined. The present study has shown that iron chloride increases IL-1 $\alpha$  concentration and decreases IL-6 concentration secreted into the cell culture supernatant by mouse embryo fibroblasts [45]. Investigations performed by other authors have found a higher release of IL-6 from mouse epidermal JB6 cells induced by Fe<sup>3+</sup> when compared with control cells [46]. The investigations performed by Bergman *et al.* are in contrast with our investigations. They have shown that peripheral blood mononuclear cells (PBMC) incubated with 50 and 100  $\mu$ g% iron have secreted significantly lower amounts of IL-1 $\beta$  than control cells. Moreover, iron at concentrations of 50, 100 and 200  $\mu$ g% had no effect on IL-6 release from these cells [47]. These discrepancies may be explained by the different cell models. Thus, these problems still demand a lot of investigation.

The investigations performed by Zhdanova *et al.* [48] on non-pregnant women with latent deficiency anemia have shown, that phagocytic index of phagocytes cells (mostly neutrophils and monocytes) increase when compared with control group. However, the investigations performed by Barkova *et al.* [49] have shown that phagocytic index (the

**Table 1.** Correlation between zinc concentration and cells of innate immunity [20]

Cell type	Zinc deficiency	Physiologic normal zinc level	High zinc dosage
Monocytes/macrophages	Decreased functions	Normal	> 30 $\mu$ mol/l: normal > 100 $\mu$ mol/l: direct inactivation
Neutrophil granulocytes	Decreased phagocytosis	Normal	> 100 $\mu$ mol/l: normal > 100 $\mu$ mol/l: direct chemotactic activity
Natural killer cells	Decreased cytotoxicity	Normal	Suppressed killing

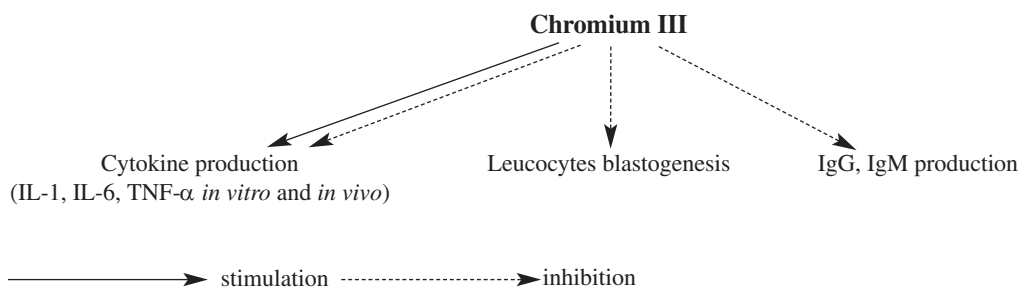


Fig. 1. Potentially effects of chromium on immunity

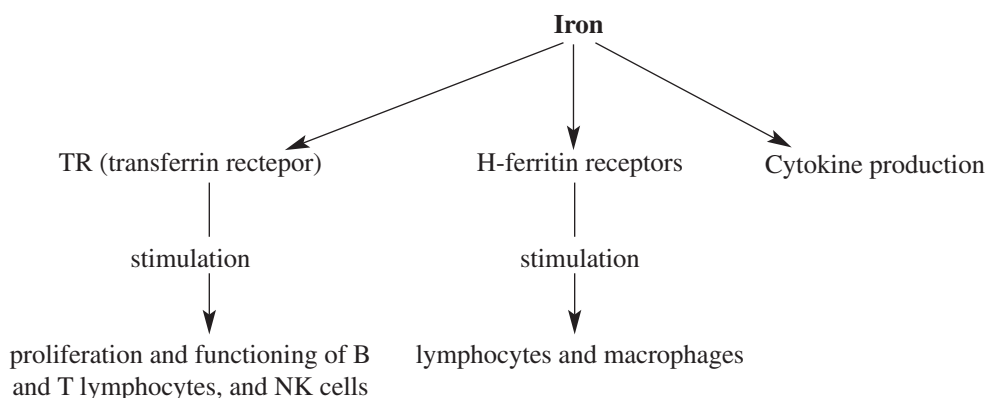


Fig. 2. Potentially effects of iron on immune cells

percentage of phagocytes cells) of monocytes obtained from breast-feeding women with iron deficiency anemia (IDA) and latent iron deficiency (LID) decreases when compared with control. That confirm Bergman’s *et al.* [50] investigations, which have shown, that percentage of phagocytosing neutrophils from IDA patients was lower as compared with the control group. The percentage of monocytes engaged in phagocytosis was similar in both groups and was not affected by addition of iron. That corresponds with our investigations, which have shown that iron have no effect on metabolic activity of phagocytosing cells. The potentially effects of iron on immune cells are presented on Fig. 2.

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