The role of selenium in critical illness: Basic science and clinical implications

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Abstract

Over the last century, our understanding of selenium has progressed considerably and we have come to recognize it as an essential component or cofactor of enzymes throughout metabolism, such as glutathione peroxidase (GPx), thioredoxine reductase and iodine deiodinase. GPx acts against hydrogen peroxide and lipid peroxidation and is an important line of defense against free radicals; thioredoxine reductase is involved in nucleus redox status; and iodine deiodinase is involved in thyroid hormone metabolism, which is frequently impaired in critically ill patients. Selenium also has an anticarcinogenic effect that is thought to be induced by the production of methyselenol, a selenometabolite that affects gene expression and modifies cell cycling and immune function. We review current knowledge concerning clinically relevant selenoproteins, discuss the potential role of these compounds in health and disease, review the epidemiology of selenium deficiency and its clinical implications with a special emphasis on critically ill patients and discuss the role of selenium supplementation in critical care settings.

Key words: Organ dysfunction, reactive oxygen species, sepsis, trace elements

Introduction

The essential trace element selenium was discovered in 1817 by the Swedish physician and chemist Jöns Jakob Berzelius[1] and was named after Sêlenê, the goddess of the moon. Only two selenium containing amino acids have been detected in proteins: Selenomethionine and selenocysteine.[2] The physiological role of selenomethionine-containing proteins remains unclear.[3,4] However, selenocysteine is incorporated into proteins to form selenoproteins, which are involved in a variety of physiological functions.[1]

Over the last century, our understanding of selenium has progressed considerably and we have come to recognize it as an essential component or cofactor of enzymes throughout metabolism, such as glutathione peroxidase (GPx), thioredoxine reductase and iodine deiodinase.[5,6] GPx acts against hydrogen peroxide and lipid peroxidation and is an important line of defense against free radicals; thioredoxine reductase is involved in nucleus redox status; and iodine deiodinase is involved in thyroid hormone metabolism, which is frequently impaired in critically ill patients. Selenium also has an anticarcinogenic effect[7] that is thought to be induced by the production of methyselenol, a selenometabolite that affects gene expression and modifies cell cycling and immune function.[8]

In the following sections, we will review the current knowledge concerning clinically relevant selenoproteins, discuss the potential role of these compounds in health and disease, review the epidemiology of selenium

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deficiency and its clinical implications with a special emphasis on critically ill patients and discuss the role of selenium supplementation in critical care settings.

Historical Perspective

In 1916, Gassmann et al.,[9] speculated on the biological importance of selenium as a component of bones and teeth of healthy individuals. Selenium's reputation fell, however, when field research showed that selenium poisoning was the leading cause of "alkali" and "blind staggers" diseases,[10] threatening livestock in large farming communities. In addition, laboratory studies declared selenium to be a potential carcinogen.[11] Some decades later, Klaus Schwarz[12] provided strong evidence for a beneficial and essential role of selenium-containing (still not well defined) factor 3 against liver necrosis.[13] In the same era, Patterson and co-workers independently published a study in 1957 showing that selenium supplements prevented exudative diathesis in poultry.[14] In 1973, Turner and Stadtman[15] established that bacterial glycine reductase (EC 1.21.4.2) was a selenoprotein. Glutathione peroxidase was the first specific (that is genetically coded) mammalian selenoprotein to be discovered. In 1984,[16] Günzler et al., discovered the amino acid sequence of GPx. This subsequently led to the establishment of selenocysteine as the 21st proteinogenic amino acid.[17] In fact, the number of identified prokaryotic selenoproteins has increased by more than 100 to a total now of approximately 310.[18]

Important Human Selenoproteins

GPx was the first mammalian selenoprotein to be identified.[19] The GPx family includes seven isoenzymes in humans, of which GPx5 and GPx7 are not selenoenzymes.[20,21] Apparently all the GPx share the same catalytic mechanism involving a strictly conserved triad formed by selenocysteine, tryptophan and glutamine.[22,23] GPx play an important role in the body's antioxidative armory. GPx reduce and thereby detoxify different types of peroxidases to their respective alcohols at the expense of (typically) glutathione. GPx1 is abundant in liver and erythrocytes, with its concentration being dependent on the nutritional selenium status.[1,24] However, the vast majority of H_2O_2 formed in erythrocytes is not detoxified by GPx but by catalase.[25] GPx2 is conserved under conditions of adequate selenium supply,[26,27] and some authors suggest that it is the first line of defense against ingested hydroperoxides.[22,28,29]

However, regulatory functions have also been suggested and it may be involved in apoptosis and proliferation.[30] GPx3 is present mainly in plasma[31] and its expression is induced by hypoxia.[32] GPx3 may have a regulatory function but this issue is not fully resolved. GPx4 exhibits the broadest substrate specificity and can even reduce phospholipid hydroperoxidase, even when integrated in membranes and may play a role as a universal antioxidant in the protection of biomembranes.[33,34] GPx4 is also involved in redox signaling and regulatory processes, such as inhibition of lipoxygenase and apoptosis,[22,35] and is required for sperm maturation.[36]

The major selenoprotein in plasma is selenoprotein P (SelP). SelP provides more than 50% of the total plasma selenium.[37] It is transcribed in many tissues, yet the majority of the plasma SelP is secreted by the liver and presumably enters target cells via a receptor-mediated mechanism.[38] SelP is an established marker for nutritional (liver) selenium status[39,40] and its primary function is storage and transport of selenium.[41-43] Nutritional selenium is delivered to the liver and used for SelP synthesis, which is toxologically - in contrast to most low molecular weight selenium compounds - rather inert. SelP is then secreted into the plasma and delivered to target tissues where SelP is transported intracellularly via receptor-mediated mechanisms. Within the cells, SelP and subsequently selenocysteine are degraded to liberate selenium, which is recycled for the synthesis of novel selenoproteins.

Selenium is also incorporated in the classical thioredoxin system, which is formed by thiorodoxin reductase (TrxR; $TrxS_2 + NADPH + H+ \rightarrow Trx(SH)2 + NADP+$) and its associate substrate, the redox active protein, thioredoxin (Trx). Trx is reduced at the expense of NADPH. Reduced thioredoxin is reoxidized to provide reducing equivalents to various target molecules such as ribonucleotide reductase.[44] The thioredoxin system is involved in a myriad of cellular and intracellular processes. Thioredoxin reductase 1 (TrxR1) is a ubiquitous cytoplasmic housekeeping enzyme. It is capable of inducing apoptosis if the enzyme does not contain selonocysteine or if this residue is blocked, e.g. by chemotherapeutic agents.[45]

Another important human selenoprotein is deiodinase (DIO), which cleaves specific iodine carbon bonds in thyroid hormones, thereby regulating their enzyme

activity. Three types of thyroid DIO exist; types 1, 2, 3 have all been found to be selenoproteins. The thyroid gland has the highest per gram selenium content[46] as DIO and GPx and normal thyroid function depends on the two trace elements, iodine and selenium. Diminished DIO-1 levels are frequently encountered in low-T3 syndrome (accompanied by elevated levels of rT3), a clinical condition occasionally seen in critically ill patients, indicating the pivotal role of DIO-1 in the production of plasma T3 and in rT3 degeneration.

Other selenoproteins have been identified over the last two decades, the functions of which have not yet been fully characterized [Table 1].

Etiology of Selenium Deficiency

Selenium enters the food chain through plants, which take it up from the soil. Selenium deficiency has, therefore, been identified in parts of the world noted for their low soil content of selenium, such as volcanic regions.[47] Acid soil and complexation, frequently with iron and aluminum, also reduce the uptake of selenium by plants, as occurs in many parts of Europe[47] [Figure 1]. At low or fairly low, selenium intake, serum or plasma selenium is well correlated with erythrocyte GPx activity.[47] At higher intakes, GPx activity reaches a plateau.[47] Serum or plasma selenium, being readily accessible, is therefore a useful marker of selenium status in populations with low levels of intake. However, levels of selenium intake that saturate the activity of plasma GPx, while satisfying the enzymatic or antioxidant role of selenium, are insufficient to optimize the immune response and reduce cancer risk.

The concentration of selenium in plasma is about 80% of that in whole blood.[8]

Selenium concentrations in smokers,[48,49] chronically ill

Table 1: Selenoproteins and their biological functions

| Selenoprotein	Gene	Function
15 K Da selenoprotein (Sep 15)	1p31	May be involved in control of protein transport.
Deiodinase 1 (DIO 1)	1p32-p33	Production of plasma T3 and degradation of rT3.
Deiodinase 2 (DIO 2)	4q24.2-q24.3	Dominant form in the brain, responsible for 75% of local T3 production.
Deiodinase 3 (DIO 3)	14q32	Inactivation of T3 and T4.
Glutathione peroxidase 1 (GPx1, cGPx)	3p21.3	Reduction of peroxides to their respective alcohol. May serve as a selenium storage or buffer protein.
Glutathione peroxidase 2 (GPx2, GI-GPx)	14q23.3	Defense against ingested organic hydroperoxides. Might be involved in apoptosis and proliferation.
Glutathione peroxidase 3 (GPx3, P-GPx)	5q23.1	Not known
Glutathione peroxidase 4 (GPx4, PH-GPx)	19p13.3	Universal antioxidant in the protection of biomembranes. Reduce phospholipid hydroperoxide. Inhibit lipoxygenase and apoptosis. Required for sperm fertilization.
Glutathione peroxidase 5		Non-selenocysteine.
Glutathione peroxidase 7		
Glutathione peroxidase 6	6p22.1	May be involved in olfaction.
Selenoprotein H (Sel H)	11q12.1	Not known.
Selenoprotein I (Sel I)	2p23.3	Not known.
Selenoprotein K (Sel K)	3p21.31	Not known.
Selenoprotein M (Sel M)	22q12.2	Not known.
Selenoprotein N (Sel N)	1p36.13	May be involved in early embryonic development. May be involved in proliferation and regeneration of striated muscles.
Selenoprotein O	22q13.33	Not known.
Selenoprotein P (Sel P)	5q31	Plasma antioxidant and heavy metal antidote. Transport molecule Hepatic selenoprotein P seems to be an essential selenium source for most tissues.
Selenoprotein R (Sel R)	16p13.3	Protects brain against oxidative challenge.
Selenoprotein S (Sel S)	15q26.3	Involved in the retrotransport of misfolded luminal ER proteins to the cytosol for proteosome degradation.
Selenoprotein T (Sel T)	3q24	Not known
Selenoprotein V (Sel V)	19q13.13	Not known
Selenoprotein W (Sel W)	19q13.32	Its absence has been associated with white muscle disease in lambs. Potential function in redox metabolism.
Selenophosphate synthetase 2 (SPS 2)	16q11.1	Incorporates selenide to form monoselenophosphate.
Thioredoxin reductase 1 (Trx R1)	12q23-q24.1	Cellular redox regulation.
Thioredoxin reductase 2 (Trx R2)	22q11.21	Not known.
Thioredoxin glutathione reductase (TGR)	3p13-q13.33	Not known.
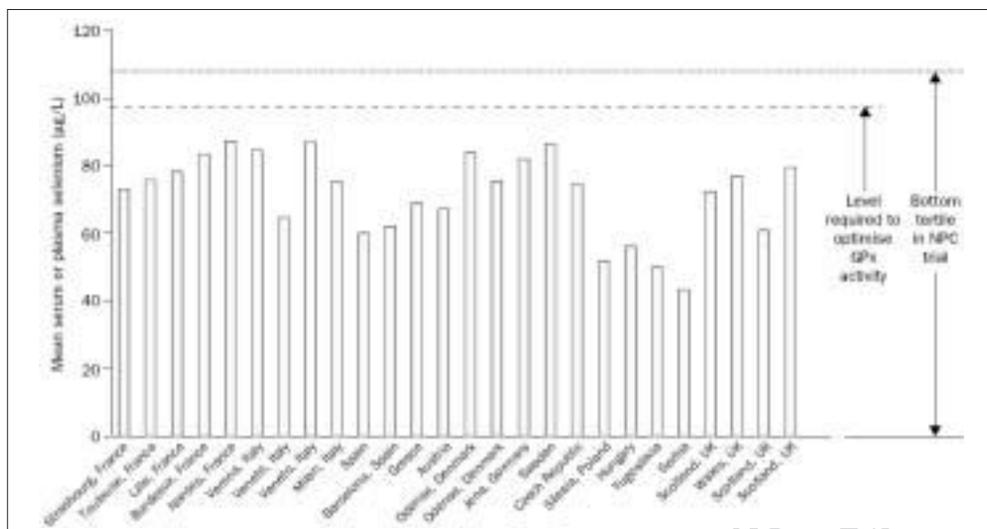
Figure 1: Mean concentrations, measured in 1990, of serum or plasma selenium in Europe compared with NPC trial levels and concentrations required for optimal plasma GPx activity. From[120] with permission

persons,[50] the frail elderly,[51] children,[52] and pregnant and lactating women,[53,54] may be 25%-30% lower than those in adult control subjects.[55] The value of plasma selenium levels in defining selenium deficiency remains, however, uncertain. While studies on selenium status and human immunodeficiency virus (HIV) disease have used a criterion of deficiency of < 85 ug/L, there is evidence that higher plasma levels are needed for optimal biological function.[5] In addition, selenium supplementation increased immune function in a study population with mean selenium levels > 130 ug/L, implying that these levels did not optimize immune function.[56]

In clinical nutrition, factors such as excessive metabolic demand for a given nutrient, increased losses or reduced intakes can participate in deficiency states.[57,58] Severe selenium deficiency has been described in patients receiving selenium-deprived, long-term total parenteral or enteral nutrition.[59,60] Low selenium status is also commonly observed in hepatic diseases, such as alcoholic cirrhosis and primary biliary cirrhosis, nutritional deficiency such as kwashiorkor, inflammatory gastrointestinal diseases and cystic fibrosis.[61]

Selenium in Various Disease Processes

Selenium deficiency-related diseases were first identified in livestock animals.[13] The most prominent examples in humans are Keshan disease, a dilatative cardiomyopathy primarily affecting children[62] and Kashin Beck disease, a disabling chondronecrosis.[63-65] Significantly lower serum

selenium levels were also found in women who had either first-trimester or recurrent miscarriages.[66] Selenium is required for testosterone biosynthesis and the formation and the normal development of spermatozoa[67] and selenium supplementation significantly increased sperm motility.[67]

Numerous studies have suggested that deficiency of selenium is accompanied by loss of immunocompetence.[68] In addition, selenium supplementation, even in "selenium replete" individuals has marked immunostimulant effects, including an enhancement of the proliferation of activated T cells.[56] Moreover, activated T cells show upregulated selenophosphate synthetase activity,[69] directed at the synthesis of selenocysteine, the essential building block of selenoproteins. Immune dysfunction has been found to be secondary to the deficiency of selenium in HIV-infected patients and in persons with other diseases.[70] This dysfunction includes an impaired T cell response, decreased lymphocytes, including T cells, impaired phagocytic function and decreased immune cytotoxicity. Among HIV-infected pregnant women, low plasma selenuim levels were associated with increased risks of fetal death and HIV transmission through the intrapartum route.[71] Beck and colleagues have shown that in selenium deficient hosts, harmless viruses can become virulent.[72] If these findings were applicable to other RNA viruses, such as poliovirus, hepatitis, influenza and HIV, there would be considerable public health implications. In individuals infected with hepatitis (B or C), selenium also

Table 2: Selenium supplementation studies in critically ill patients

Author	Supplementation	Patients	No. of patients	Results
Zimmerman et al.[117] 1997	1000 µg/day Na-selenite IV vs no selenium.	SIRS+organ failure	40	Se supplementation reduced mortality.
Forceville et al.[61] 1998	40 µg/day Na-selenite+11.2IU Vit E + 500 mg Vit C IV	Adult ICU patients	134	3-fold increase in morbidity and mortality in patients with low selenium concentrations. Efficacy of Se supplementation needs further investigation.
Berger et al.[116]1998	159 µg selenium+40.4 µmol copper +406 µmol zinc vs 32 µg selenium +20 µmol copper+100 µmol zinc	Major burn	20	Significant decrease in bronchopneumonia infection and shorter hospital stay with trace element supplementation.
Satio et al.[128] 1998	150 mg ebselen twice daily orally	Subarachnoid hemorrhage	286	Ebselen reduced brain damage and may be a promising neuroprotective agent.
Angstwurm et al.[118] 1999	535 µg/day Na-selenite (3 days), then 285 µg (3 days), then 155 µg (3 days) vs 35 µg/day IV	SIRS+APACHE>15	42	Se replacement seems to improve clinical outcome and reduce incidence of acute renal failure requiring hemodialysis.
Porter et al.[114] 1999	50 µg q6h selenium IV+400IU Vit E, 100 mg VitC, 8 gm N-acetylcysteine q6h orally 500 µg Na-selenite only IV	Surgical ICU trauma patients	18	Antioxidant supplementation was associated with fewer infectious complications and fewer organ dysfunctions.
Berger et al.[113] 2001	500 µg Na-selenite +150 mg α-tocopherol +13 mg zinc Placebo	Critically ill trauma patients	31	Earlier normalization of T4 and reverse T3 plasma levels with Se supplementation.
Berger et al.[128] 2002	380 µg selenium+ 59 µmol copper+574 µmol zinc vs placebo	Burn	17	Not estimable
Andrews et al.[128] 2004	Glutamine containing and non-glutamine containing parenteral nutrition with or without Na-selenite 500 µg/day IV	ICU patients requiring parenteral nutrition	500	Not available-personal communication
Angstwurm et al.[129] 2004	500 µg/day Na-selenite (3 days), 250 µg(3 days), 125 µg (3 days) IV	ICU patients with nonthyroidal illness	41	Se supplementation in patients with nonthyroidal illness improved morbidity.
Mishra et al.[127] 2006	474 µg/day Na-selenite (3 days), 316 µg (3 days), 158 µg (3 days), then 31.6 µg/day IV vs 31.6 µg/day from the beginning	Severe sepsis	40	Se supplementation did not reduce oxidative damage or requirement for renal replacement therapy
Angstwurm et al. 2007[126]	1000 µg/day Na-selenite IV vs placebo	Severe SIRS, sepsis and septic shock	249	Se supplementation reduced mortality in patients with severe sepsis and septic shock.

appears to be protective against the progression of the condition to liver cancer.[73,74] Baum et al., reported that the likelihood of death was increased about 20 times in selenium-deficient HIV patients compared with those with adequate selenium levels and that a low plasma selenium concentration is a more significant mortality risk than a low helper-T-cell count.[75]

Selenium deficiency has also been shown to be associated with several forms of cardiovascular disease.[76] Selenium deficiency has been associated with a higher incidence of myocardial infarction and increased mortality rates from cardiovascular disease.[76] In men with coronary artery disease, platelet agreeability is inversely related to selenium status.[76,77] Epidemiologic studies have, however, shown conflicting results.[76,78-80] The disparity between these studies may be explained, in part, by the status of other antioxidants such as vitamin E, which may compensate for the deficiency in selenium in protecting against atherosclerosis.[81] The protective role of selenium in cardiovascular disease may be mediated by counteraction of lipid oxidation by GPx and reduction in platelet aggregation.[82]

Selenium behaves both as an antioxidant and an anti-inflammatory agent. This is because selenium in its antioxidant role, notably as GPx, can: i. reduce hydrogen peroxide, lipid and phospholipid hydroperoxides, thereby damping the propagation of free radicals and reactive oxygen species (ROS); ii. reduce hydroperoxide intermediates in the cyclo-oxygenase and lipoxygenase pathways, diminishing the production of inflammatory prostaglandins and leukotrienes; and iii. modulate the respiratory burst, by removal of hydrogen peroxide and reducing superoxide production.[68] Any condition associated with increased oxidative stress or inflammation might be expected to be influenced by selenium levels, which may be the case in rheumatoid arthritis,[83,84] pancreatitis,[85] and asthma.[86,87]

Selenium has insulin-mimetic properties in vitro and in vivo,[88] probably by stimulating the tyrosine kinase involved in the distal signaling of the insulin signaling cascade.[89] When administered to streptozotocin-diabetic rats, selenium restores glycemic control and modifies the activity of a range of enzymes involved in hepatic glycolysis and gluconeogenesis. These changes are not linked to changes in insulin levels.[90-93] A combination of selenium

and iodine deficiency exacerbates hypothyroidism and may manifest itself as myxedema.[94] There is a higher incidence of thyroid tumors correlated with low levels of selenium.[95] Finally, patients with Alzheimer's disease have lower brain selenium levels compared with controls[96] and a low selenium status has been associated with a significantly increased incidence of negative mood states, such as depression and anxiety.[97]

Role of selenium in critical illness

In critical illness, ROS can be produced due to mitochondrial dysfunction[98] and impairment of the oxygen radical scavenger system of the body and a resulting increase in oxidant stress has been implicated in the evolution and maintenance of tissue injury in critically ill patients with multi-organ failure.[99,100] In addition, selenium deficiency may activate some pro-inflammatory genes because selenium inhibits many transcription factors, such as activator protein (AP)-1 or nuclear factor-kappa B (NF-κB), involved in the transcription of various inflammatory mediators (e.g. tumor necrosis factor [TNF]-alpha).[101] Selenium also plays an important role in regulating the arachidonic acid cascade by controlling the concentration of lipid peroxides,[102] as well as the biosynthesis of thromboxane A2 and pro-inflammatory lipoxygenase products.[103,104] Selenium deficiency may increase the thromboxane A2/prostacyclin ratio, thereby increasing vasoconstriction and blood coagulation.[105]

In a study of critically ill patients, plasma selenium concentrations remained low for > 2 weeks in patients with systemic inflammatory immune syndrome (SIRS) despite selenium supplementation.[61] However, there was a slight increase in plasma selenium concentrations in surviving SIRS patients, whereas plasma selenium concentrations decreased in non-surviving patients.[61] In patients after major trauma, Berger et al.,[105] showed that mean selenium levels were strongly decreased upon admission, reverting progressively to normal ranges after the first week following admission. The more severe the trauma, SIRS or sepsis, the larger the depletion of antioxidants appears to be.[106,107] The decrease in plasma selenium levels in critically ill patients is multi-factorial: initiation of the acute phase response,[24,108] hemodilution by resuscitation fluids and incompletely replaced biological fluid losses which contain large quantities of trace elements (mainly blood losses), are the main contributors.

These described observations are not mere epiphenomena as low endogenous stores of antioxidants are associated with an increase in free radical generation, augmentation of the systemic inflammatory response, subsequent cell injury, increased morbidity and even higher mortality in the critically ill.[109,110] Forceville *et al.*,[61] reported that plasma selenium measured on ICU admission, correlated inversely with APACHE II or SAPS II scores. Patients with SIRS had lower selenium concentrations than those without SIRS; selenium concentration was low in all patients with severe sepsis and septic shock and in those patients with ischemia-reperfusion from aortic cross-clamping. Low selenium values were associated with an increase in secondary complications and higher mortality rates.[61]

The negative correlation between plasma selenium concentrations and mortality has been shown by several studies. In a large longitudinal French study[111] in an elderly population, the baseline plasma selenium was higher in individuals who were alive at the end of the 9-year follow up period than in those who died. After adjustment for various potential confounding factors, the association between lower plasma selenium levels and mortality remained significant. Forceville *et al.*,[61] reported that the frequencies of ventilator-associated pneumonia and organ system failure and the mortality rate were three times higher in patients with low plasma selenium concentrations at the time of admission to the ICU than for other patients. We[112] recently reported that plasma selenium levels were less than the standard values for healthy subjects in 92% of critically ill patients admitted to a surgical ICU. There was a consistent decrease in plasma selenium concentrations during the ICU stay in all patients. Interestingly, there was a tight relation between plasma selenium and all components of organ dysfunction/failure as assessed by the maximum sequential organ failure assessment (SOFA) score during the ICU stay. Plasma selenium concentrations were inversely correlated with serum C-reactive protein (CRP), procalcitonin (PCT) and interleukin (IL)-6. Previous studies have shown not only an association between low selenium concentrations and early mortality but also unfavorable long term outcomes.

Selenium Supplementation in the Critically Ill

As selenium deficiency is commonly associated with critical illness and with poor outcome, the notion of selenium supplementation in such patients is appealing. Supplementation with selenium has been shown to improve antioxidant capacity, as demonstrated by increased GPx activity.[113] Several randomized controlled studies have investigated the possible effect of selenium supplementation on outcome.[113-118] However, most of these studies were performed on relatively small patient populations presenting with trauma, burns, sepsis or acute pancreatitis and thus are underpowered to detect a treatment effect on clinically important outcomes.[119]

The current recommended dietary intake of selenium in humans is between 55 and 75 µg per day.[120] These amounts are based on the selenium intake that maximally induces the activity of GPx in plasma and erythrocytes. Low molecular weight selenium compounds[121] are important for the beneficial effect of selenium.[122-124] This might suggest that higher doses of selenium supplementation than the currently recommended 55-75 µg per day should be used.[125] However, the narrow therapeutic window of selenium should be taken in account - selenocompounds are toxic and their therapeutic index is rather small.[1]

Angstwurm *et al.*,[118] demonstrated a reduction in the incidence of acute renal failure in patients suffering from SIRS who received supplemental selenium, even if their creatinine concentration was elevated at admission. Selenium supplementation has been associated with earlier normalization of thyroid profile in surgical ICU patients,[114] significant reduction in bronchpneumonia events and shorter hospital stays in burn patients,[116] and reduced mortality in septic patients[126] and patients with acute pancreatic necrosis.[115] However, the mortality benefit was not reproducible in another study[127] and another study could not find a significant effect regarding resolution of organ dysfunction, duration of intensive care unit (ICU) stay, incidence of mechanical ventilation, need for hemodialysis or vassopressor therapy or the incidence of acute respiratory distress syndrome (ARDS).[126]

In a meta-analysis of randomized controlled studies (n=7) in 186 patients, selenium supplementation (alone or in combination with other antioxidants) was associated with a trend towards a lower mortality (*P*=0.09), while non-selenium antioxidants were found to have no effect on mortality. Studies using high doses of selenium (500-1000 µg/day)[113,115,117,118] were associated with a trend

towards a lower mortality (P=0.1), whereas studies using lower selenium doses (<500 μg/day)[114,116] showed no effect on mortality. No effect was observed on infectious complications, suggesting that the mortality effect was mediated by some other mechanisms, perhaps related to improved organ function. In a recent prospective, randomized placebo controlled, multi-center trial by Angstwurm and colleagues, 249 patients with severe SIRS, sepsis and septic shock were randomized to receive selenium or placebo. Patients in the study group received 1000 μg sodium selenite for 14 days. The primary end point of 28-day mortality was significantly reduced to 42.4% in the treatment group compared to 56.7% in the placebo group. In predefined subgroup analyses, the mortality rate was significantly reduced in patients with septic shock with disseminated intravascular coagulopathy as well as in the most critically ill patients with APACHE III scores > 102 or more than three organ dysfunctions.[126]

Selenium supplementation in critical illness and other disease states is promising; however, large randomized multi-center studies are needed to confirm the beneficial effects of selenium supplementation in critically ill patients.

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