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Review Article

Selenium in Critical Ill Patients, The Ongoing Discussion

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Abstract

Selenium (Se) is an essential trace element to human health. Its capacity to act, through selenoproteins, both as an antioxidant and antiinflammatory agent, provides it with a particular interest in clinical nutrition. In critical care patient, oxidative stress is a characteristic pathogenic event which usually is accompanied of Systemic Inflammatory Response Syndrome (SIRS). Because of this, pharmaconutrition with Se has been considered as a possible key point in the patient's treatment and recovery. However, due to the narrow therapeutic window, there is no consensus on Se use. The aim of this review was to summarize the current opinion about Se and its supplementation in Intensive Care Units (ICUs) as pharmaconutrient, being a potential biomarker in clinical patient outcome.

Keywords: Selenium, Critical Care Patient; Pharmaconutrition; Systemic Inflammatory Response Syndrome (SIRS); Sepsis; Biomarker

Abbreviations

Selenium (Se); Systemic Inflammatory Response Syndrome (SIRS); Intensive Care Units (ICUs)

Introduction

Despite the existence of a large heterogeneity in the Intensive Care Unit (ICU) population, the response to tissue injury usually leads to inflammatory processes and organ failures in the most cases, with an increased oxidative stress and reduction of antioxidative defenses. The increased production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) and antioxidant depletion are accompanied by other biochemical and metabolic alterations. In addition, an increased oxidative stress is associated with poor outcome in these patients. On the other hand, micronutrient may suffer a deficiency, redistribution or both in critically ill patients for several reasons, such as increased catabolism and urinary excretion. Because of this, the supplementation in critical illness still remains controversial [1-5].

An adequate trace element status in critical ill patients is considered to be of particular importance [6]. Namely, Se is involved in key processes for this population, such as immune response [7,8] or protection against the oxidation through Glutathione Peroxidase (GPx) [4]. It has been hypothesized that the requirement of Se might be increased during severe oxidative stress like sepsis or patients with SIRS which present low Se levels and diminished GPx activities [9].

Se is an essential trace element described in the genetic code as the 21st amino acid, Selenocysteine (SeCys), which acts as an active center of 25 different selenoproteins in humans. The nutritional functions of Se are achieved by these selenoproteins which present a wide variety of tissue functions and distributions [10-12]. Based on the function, there are two main groups of selenoproteins: the first ones are oxidoreductases, such as GPx, Thioredoxinreductases (TrxR) or iodothyroninedeiodinases (DIO), being antioxidant enzymes; the second group is composed by selenoproteins that facilitate Se transport, as Selenoprotein P (SePP), and selenoprotein biosynthesis and reticulum homeostasis [13,14]. Through these selenoproteins, Se plays a key role *in vivo* antioxidant pathway with an effect on regulating gene expression because of combined effects on redox balance and methylation status. Moreover, low Se concentrations are related to thyroid hormone disturbances [15] and impairment in immune system, which apparently represents one of most Se-sensitive target tissue [16].

Selenium requirements, the controversy

Dietary intake of Se by food is related with the kind of soil they are grown upon [15]. That is the main reason why Se intake varies hugely worldwide, ranging from deficient 7-30 μg Se/day in certain regions of China) to high amounts (100-200 μg Se/day in most areas of North America and Japan) [11,17]. In Europe, the intake of Se is also variable, though the risk of excessive intake in Europe is considered relatively low [18]. Furthermore, Europeans are considered sub-optimally supplied with Se and it has been suggested to increase the intake [19,20].

According to the World Health Organization (WHO) the tolerable upper intake level of Se has been defined as 400 μg Se/day, being from 55 to 70 μg Se/day the recommendations for the majority of Health Bodies [14]. Daily Se intakes of ≤15 μg, are related with Se deficiency and Keshan Disease as clinical condition, and <30 μg are considered harmful to health [14,21].

All selenoproteins are sensitive to the overall Se intake depending on biological functions and specific tissue [22]. The reference values have been based on the intake required to achieve maximal GPx activity. Nowadays, these values are being assessed using SePP maximal levels as a suitable status biomarker for [18]. Thus, the German, Austrian and Swiss Nutrition Societies, using the reference body weights and the saturation of SePP as criterion, have estimated a value for Se intake of 70 μg/day for men and 60 μg/day for women [19].

In critical illness, it has been observed a profoundly low Se plasma concentration in ICU on admission [23,24]. The dose–response curves of Se provide it with a theoretical risk of toxicity which could

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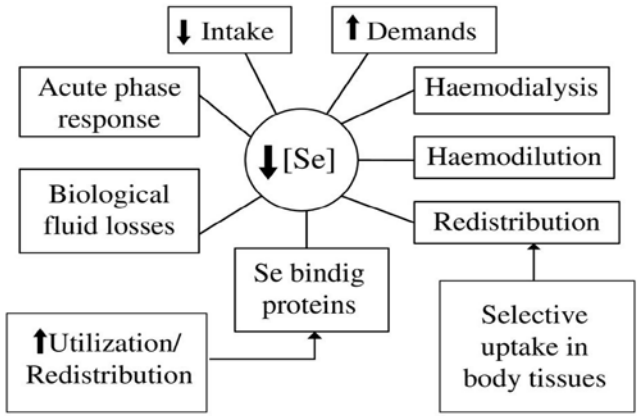

Figure 1: Possible multifactorial causes of low Se plasma concentrations in ICU patients [7,20,31].

appear at high levels and prolonged supplementation. However, the published toxicity data of Se refer to chronic intakes and not to short-term of Se supply in the ICU [25]. Nowadays, there is no optimum dose of Selenium established for nutritional support in ICU and the efficacy of high doses still remains controversial [10].

Selenium deficiency, the consequences

Due to the wide range of pleiotropic effects of Se in human health, its deficiency can lead to several physiological disorders, which usually takes years to develop. One of the most well-known pathologies associated to Se deficiency is a cardiomyopathy occurring in a region of China with poor Se soil, the Keshan disease. Many pathophysiological conditions are related to low Se intake such as defects in the immune response to viral infection, myalgias, myositis, the development of cancer, arthritis, asthma, cardiovascular diseases, hemolysis, anemia associated with aging, among others [13, 26-28].

In particular, an inappropriate Se status could be crucial for the recovery of critical patient. Stimulated proteolytic pathways, oxidative stress, mitochondrial dysfunction, and SIRS are important components of critical illness [7,10,29,30]. The role of selenoproteins, as efficient ROS scavengers, in maintaining redox homeostasis is expected to be critical [26]. The expression of these antioxidant selenoproteins falls with the increased accumulation of oxidized proteins [13]. Indeed, decreased serum Se concentration and GPx activity are inversely correlated to clinical outcomes [10].

Aetiology of low plasma Se concentrations in ICU patients: A key point

In most cases, a decline in plasma Se levels after ICU admission has been observed and these concentrations tend to maintain low during stay. This fact is associated with more tissue damage, the presence of infection or organ failure, and increased mortality [20]. Moreover, SIRS and MODS have been related with the early decrease of Se and GPx concentrations [1]. However, it is not clear if low plasma Se levels mean real deficiency because of the not well-known underlying mechanism [10,20,31,32].

It has been hypothesized a probable multifactorial aetiology of low plasma Se levels in ICU patients (Figure 1), which includes reduced previous intake, reduced binding proteins (due to redistribution and/or increased utilization), haemodilution, acute phase response, increased demands, continuous renal replacement therapies, losses through biological fluids and Se redistribution (selective uptake by tissues) [7,20,31].

More than 90% oral Se is absorbed, the majority is incorporated into glycoproteins (being the liver the major source of secretion) and it is excreted mainly in the urine [6,12]. In plasma, Se is bound to SePP (around 50-60%), to albumin (10%) or with GPx (20-40%) [7,10,32]. The concentrations of these proteins fall during SIRS and therefore the interpretation of plasma Se remains problematical [32].

Selenium clinical biomarkers. which ones?

The main drawback of plasma Se is the difficult interpretation of results in patients with SIRS [33]. Most reference values are based on GPx activity in plasma, and plasma Se is the most widely studied in critical illness, finding negative correlation with leucocyte count, serum C Reactive Protein (CRP), IL-6, fraction of reduced glutathione in whole blood, etc; and positive correlation with cholesterol, prealbumin, albumin (in some cases) and GPx activity [20,32,34-36]. Moreover, in patients with SIRS, plasma micronutrients concentrations have similar significant trends of decreasing as CRP concentrations increase [37]. Low prealbumin levels and CRP to prealbumin ratio, have been also considered, finding some associations but without conclusive results [34].

Nevertheless, currently, SePP concentration in plasma have been proposed as the most conclusive biomarker for determining the optimum supply of Se [19,24]. Selenoproteins represent the specific Se pool (SeCys incorporated specifically into proteins) [38] and SePP incorporates the majority of extracellular Se circulating in plasma [8]. Furthermore, SePP reflects short-term Se status better than other selenoproteins due to its half-life in plasma is of few hours. The main limitation is that selenoproteins expression do not increase with upper Se levels, and they cannot be used to detect a high or toxic Se doses [22].

On the other hand, erythrocyte Se has been proposed as biomarker in the presence of SIRS due to its levels are not affected by the acute response [33]. When Se deficiency develops the erythrocyte concentrations fall, and they increase on supplementation. In healthy population, erythrocyte Se is correlated closely with Se plasma concentrations and GPx activity [23].

In summary, the most efficient biomarker of Se status is expected to be a set of combined parameters, with a specific application attending to particular circumstances [22]. For example, GPx activity and SePP could identify the risk of nutritional deficiency and total Se levels give information about the non-specific Se pool [38].

The discussion on selenium support

Nutritional support in critical patient is a continuous discussion. Controversy still exists on timing of nutrition, enteral *vs* parenteral nutrition and nutrients requirements [29]. In particular, Se is no longer recommended [29,39] in spite of its potential as pharmaconutrient, being necessary to define the optimal mode of supplementation and posology [6,25].

One of the main difficulties is to determine whether the decreased Se levels (and Se status biomarkers) in critical patients are due to a

real deficiency or to a redistribution process. It has been observed a significant interaction between the magnitude of the inflammatory response and low plasma Se [31]. Because of this, there are different opinions about Se supplementation, from not stablished recommendation to 60 μg Se/day or ≥100 μg Se/day *via* parenteral nutrition if a deficiency exists by the American Society for Parenteral and Enteral Nutrition (ASPEN) [6,40].

In the literature, there are several randomized controlled trials where the administration of supra-physiological high-dose of Se has shown positive results. Furthermore, many systematic reviews and meta-analyses [10,25,41], found a significant reduction in mortality when it was administered intravenously as monotherapy. Nonetheless, other authors are not in favour of giving Se to these patients or of its beneficial effects in clinical outcomes [12,42]. The Cochrane Collaboration considers the evidence as low quality because of high risk of bias in most included trials [39]. In contrast, the supplementation with low dose of Se appears to have no effect on mortality [3]. Ultimately, a greater understanding of underlying processes is needed before the use of Se high doses systematically [10,34].

In summary, more pharmacokinetic studies are needed to determine the real Se status and requirements, the optimum well tolerated dose, timing, duration of therapy, monitoring parameters and method of administration (singly *vs* with other micronutrients, enteral *vs* parenteral, bolus *vs* continuous infusion, chemical form of Se, etc.), taking into account the heterogeneity in critical ill patients [7,10,25].

Conclusion

Nutritional support in the intensive care is complex and continues to be a challenge. Further investigations are needed to provide valid recommendations. Comprehension of Se biochemical pathways is essential to elucidate its preventing/therapeutic effect, to establish reliable biomarkers and to clarify the required doses in order to optimize patient's recovery.

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