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Selenium and selenoprotein P

Crucial selenium balance parameters

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Selenium is an essential trace mineral naturally occurring in the human diet. Its numerous functions in the body can be attributed to selenium-containing **selenoproteins**. For instance, selenium is crucial for the antioxidant protection of cells and the synthesis of thyroid hormones.

State: 10.09.2024

In Central European countries, the selenium supply is generally insufficient, leading to a high risk of selenium deficiency. This shortage primarily stems from the low selenium content in the soil. Compared to American soils, which are considered rich in selenium, soils in Central Europe contain notably low levels of this mineral. Moreover, selenium content in soils varies considerably, even within Germany. Consequently, plants grown in Central Europe tend to have limited selenium levels [1,2]. Although meat, fish, and nuts (especially Brazil nuts) exhibit significantly higher selenium content than other plant-based foods, achieving an adequate selenium supply remains challenging, even with a balanced diet. While the German, Swiss, and Austrian Nutrition Societies recommend an adequate daily intake of 30 to 70 µg of selenium for adults, studies suggest that an intake of around 100 µg per day is necessary to maximize glutathione peroxidase activity [1-5].

What are selenoproteins?

By definition, selenoproteins are proteins containing the amino acid selenocysteine. These proteins encompass glutathione peroxidases, iodothyronine deiodinases, thioredoxin reductases, as well as selenoprotein P [6]. Due to the biochemical properties of selenocysteine, selenoproteins can catalyze specific enzymatic reactions exceptionally effectively. These reactions include the synthesis and degradation of thyroid hormones, modulation of the immune system, and repair of protein and lipid oxidation products [6].

Selenoproteins	Funktion
Selenoprotein P	**Selenium transport and distribution to the target cells**
Glutathione peroxidase	Degradation of peroxides, moonlighting activity
Iodothyronine deiodases	Activation and inactivation of thyroid hormones
Thioredoxin reductases	Maintanance of cellular redox balance
Methionine sulfoxide reductase	Repair of oxidized methionine residues
Selenophosphate synthetase 2	Synthesis of selenocysteine
Other selenoproteins	Unknown functions

Tab. 1 ***Various selenoproteins and their respective functions.***

Das **Selenoprotein P** holds a unique status in the storage and transportation of selenium, delivering this essential mineral to target cells as a storage and transport protein. The synthesis of various other selenoproteins, such as iodothyronine deiodase in the thyroid gland or glutathione peroxidase in the kidneys, depends significantly on selenoprotein P.

Given the multifunctional roles of selenoproteins within the body, selenium deficiency is associated with diverse diseases and health concerns. These encompass **autoimmune diseases**, notably those impacting the thyroid gland, as well as cancer, **cardiovascular diseases**, and **reduced immunity** [7]. Selenium, in the form of glutathione peroxidase, acts as an antioxidant, safeguarding DNA from oxidative damage. Additionally, selenium plays a pivotal role in synthesizing and metabolizing thyroid hormones T3 and T4 via iodothyronine deiodases. Hence, selenium deficiency can contribute to hypothyroidism [8]. Moreover, selenium influences both humoral and cellular markers of immunity, stimulating NK cell activity and antibody production, especially IgG. Additionally, selenium possesses the ability to bind to heavy metals, facilitating their excretion. Consequently, exposure to heavy metals heightens selenium expenditure, leading to increased selenium requirements [2].

Apart from inadequate selenium intake, reduced gastrointestinal absorption due to persistent digestive issues or increased expenditure owing to malignant tumors can also lower selenium levels. Early manifestations of selenium deficiency may include muscular weakness, muscle wasting, or chronic inflammation. Given the role of selenoproteins, selenium deficiency can contribute to a wide array of medical conditions [2].

Possible consequences of selenium deficiency

- Hypothyroidism
- Immunodeficiency
- Allergies
- Autoimmune diseases
- Increased oxidative stress
- Cardiomyopathies
- Increased tumor risk
- Gestational diabetes

Selenoprotein P

Selenoprotein P, a glycoprotein containing 10 selenocysteine residues, serves as the primary storage form of selenium in serum, constituting over 50 percent of the selenium found in serum [9]. Selenocysteine, the 21st amino acid encoded by the UGA codon in DNA, typically functions as a stop codon, resulting in the termination of the translation process. However, specific mRNA structures (such as the SECIS element) reinterpret this signal, allowing the incorporation of selenocysteines rather than termination. Functioning as a bioavailable transporter, selenoprotein P selectively delivers selenium to vital tissues, recognizing and delivering selenium to target cells [10]. This protein reaches its target cells through apolipoprotein E receptors or megalin. Like the apolipoprotein E receptor, megalin – a membrane receptor – facilitates the uptake of various substances into the cell [11]. Once within the cell, the protein undergoes degradation, releasing its stored selenium for the synthesis of other selenoproteins. A reserve of selenium is stored in the liver in the form of selenoprotein P and can be mobilized if the supply becomes insufficient [12]. Beyond its storage and transport roles, selenoprotein P also exhibits peroxidase-like functions by oxidizing phospholipid hydroperoxide. Consequently, it shields endothelial and other cells from oxidative damage [11].

The measurement of selenium in whole blood captures both the free selenium present in the serum and the selenium integrated into all blood cells. However, this measurement is unable to distinguish between the bioavailable and bound portions, indicating only the total selenium status. While intracellular selenium offers insight into the long-term supply situation, it does not reveal the bioavailability of circulating selenium since the supply to target cells depends on selenoprotein P. Focusing solely on free selenium in serum during diagnostics does not reflect the cell's selenium supply status. Even if serum selenium levels appear adequate, reduced selenoprotein P levels may indicate insufficient supply to the target cells. Therefore, a high measurement of selenium levels alone cannot ensure sufficient selenium supply to the target cells. Conversely, measuring selenoprotein P determines bioavailable selenium, making it the most suitable functional biomarker for assessing selenium supply. Selenoprotein P serum concentrations correlate with the severity of selenium deficiency, establishing it as a meaningful biomarker for evaluating selenium supply [9,10].

For a comprehensive and meaningful diagnosis, the most suitable approach involves determining selenium levels in whole blood combined with assessing selenoprotein P.

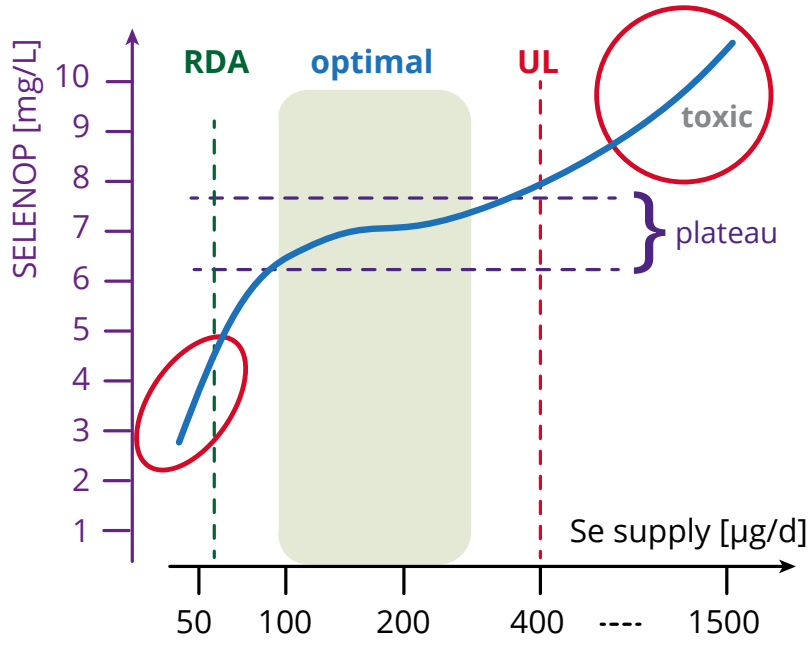

Fig. 1 *Relationship between selenium intake and selenoprotein P concentrations. Low levels of selenoprotein P indicate a selenium deficiency. When selenium intake falls within the optimal range, selenoprotein P concentrations stabilize, reaching a plateau. Within this range, an increase in selenium supply does not affect the concentration of selenoprotein P. Only when selenium intake surpasses the Upper Limit (UL) do selenoprotein P concentrations rise again. The red circles on the graph highlight critically low or toxic high selenium intake. RDA: Recommended Daily Allowance [10] Source: Schomburg and Lutz 2022*

Health Hazards of Selenium Deficiency

Given the crucial functions of selenoproteins, it's evident that selenium deficiency is linked to various diseases. For example, lower levels of selenium and selenoprotein P have been associated with an increased risk of mortality in patients with COVID-19 and severe trauma [13,14]. Moreover, maintaining an adequate selenium supply yields positive effects on disease risks and the prospects of recovery, including a reduced risk of coronary heart disease, heart attacks, and strokes [15].

Hashimoto's thyroiditis

A selenium deficiency can lead to hypothyroidism due to decreased activity of iodothyronine deiodinases. Additionally, inadequate selenium levels elevate the risk of Hashimoto's thyroiditis. Individuals with Hashimoto's thyroiditis often exhibit a higher prevalence of selenoprotein P autoantibodies compared to those without the condition [8]. These autoantibodies impede the uptake of selenium into thyroid cells, resulting in a deficiency within the thyroid. Selenium supplementation has shown potential in reducing thyroid-specific autoantibodies, thereby offering a beneficial impact on thyroid therapy [16].

Tumor Diseases

Maintaining an optimal supply of selenium can mitigate the risk of certain types of cancer and enhance the chances of recovery. Increased selenium intake demonstrates inhibitory effects on the initial stages of carcinogenesis. Elevated selenium levels have shown associations with a reduced risk of hepatocellular carcinoma and cholangiocarcinoma [17]. Moreover, colorectal cancer risk has been linked to selenium levels [18]. In breast cancer patients, lower serum selenium and selenoprotein P levels have been correlated with a poorer prognosis [19]. Additionally, patients exhibiting selenoprotein P autoantibodies have an increased risk of experiencing a less favourable disease prognosis [19].

Gestational Diabetes

Unfortunately, insufficient attention continues to be directed toward the preventive aspects of selenium status in gynecology. A study observed that deficiencies in selenoprotein P and other functional parameters of selenium status, such as glutathione peroxidase, contribute to increased insulin resistance and significantly elevate the risk of gestational diabetes. Decreased glutathione peroxidase activity is also linked to a higher risk of prolonged gestation [20].

Selenoprotein P autoantibodies

Autoantibodies target the body's own tissues. Selenoprotein P autoantibodies bind to selenoprotein P, compromising selenium transport and cellular uptake. Consequently, the cellular availability of selenium diminishes, leading to increased selenium requirements. Selenoprotein P autoantibodies are associated with a broad array of diseases. On one hand, in certain chronic fatigue syndrome (CFS) patients, they contribute to low T3 levels and ATP deficiency, exacerbating fatigue [8]. Conversely, these autoantibodies are more prevalent in patients with Hashimoto's thyroiditis and cancer [16,19]. Recent studies indicate a higher prevalence of autoantibodies in CFS patients, ranging from 10-16 % compared to healthy controls at 1-2 %. Additionally, breast cancer patients exhibit an increased prevalence of 7-8 % [8]. In cases where selenoprotein P is deficient despite adequate selenium supply, the presence of autoantibodies should be considered, particularly in patients with chronic fatigue and Hashimoto's thyroiditis.

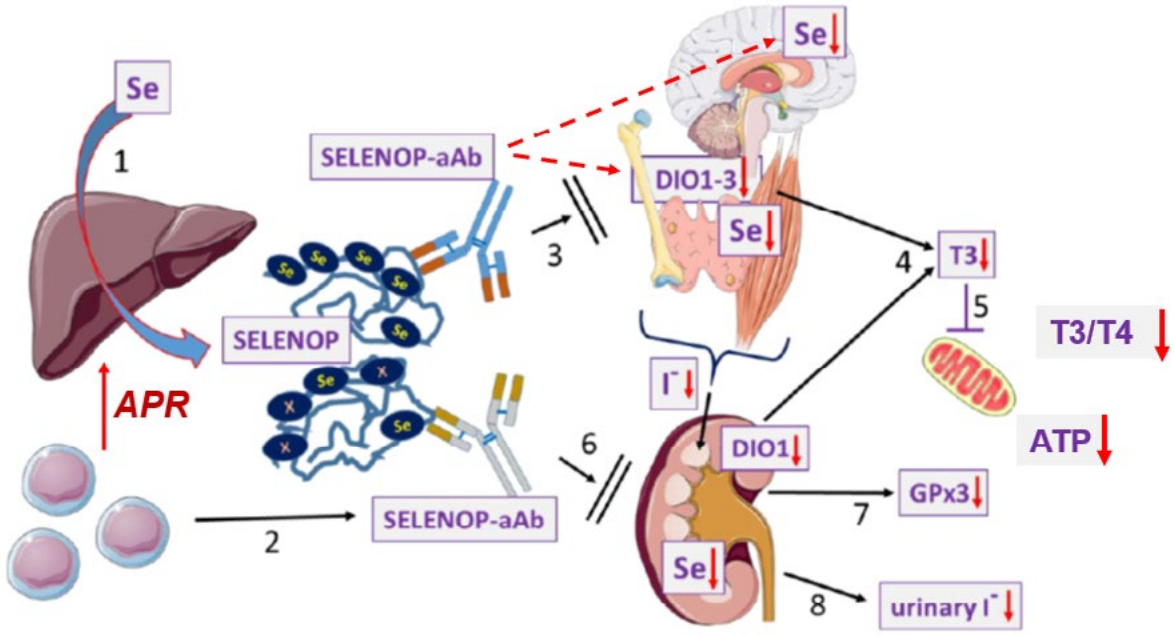

Fig. 2 *Overview of the effects of autoantibodies in chronic fatigue. Source: Schomburg Lutz 2022*

Selenium, acquired through dietary intake, undergoes absorption in the small intestine and then moves to the liver, where it gets integrates into selenoprotein P. Subsequently, selenoprotein P enters the bloodstream, facilitating selenium distribution to target cells. However, when autoantibodies are produced against selenoprotein P by activated plasma cells, selenium distribution to these cells is hindered. This limitation affects the supply of selenium to crucial organs, tissues, and cells, such as the thyroid gland, bone tissue, and the immune system. Given that the expression of selenoproteins relies on selenium availability, reduced selenium leads to decreased synthesis of iodothyronine deiodase 1-3 (DIO1-3) enzymes responsible for thyroid hormone production in the thyroid gland. Iodothyronine deiodases play a pivotal role in synthesizing thyroid hormones by converting T4 into T3 through iodine cleavage and activation of T4. A deficiency in these deiodases leads to reduced iodine conversion and concentration, resulting in hypothyroidism. Consequently, reduced mitochondrial activity and ATP production decline. This decline in mitochondrial activity contributes to symptoms associated with chronic fatigue. Moreover, decreased selenium concentrations also lower DIO1 production in the kidneys, where lesser deiodination of T4 occurs. This reduction in iodine release leads to decreased iodine levels in the urine. Supplementation of selenium, along with potentially T3, can ameliorate symptoms in individuals affected by chronic fatigue syndrome (CFS) [16].

A selenium deficiency poses a significant health risk. Numerous diseases are linked to the insufficiency of this vital trace mineral, underscoring the critical need to identify and address it promptly at an early stage.

These diseases are associated with a selenium deficiency:

- Colorectal tumors
- Liver and breast cancer
- Graves' disease
- Hashimoto's thyroiditis
- Gestational diabetes
- Heart attacks
- Cardiovascular disease
- COVID-19 mortality
- Chronic fatigue
- Long-COVID

☐ **E130 Selenium in whole blood**
Material: heparin whole blood

☐ **E132 Selenoprotein P**
Material: serum

☐ **E133 Selenium supply**
(Selenium in whole blood and selenoprotein P)
Material: serum, heparin whole blood

☐ **E134 Selenoprotein P autoantibodies**
Material: serum

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