SELENIUM DEFICIENCY AS A RISK FACTOR FOR DEVELOPMENT OF ANEMIA

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Summary

Anemia is an important public health problem worldwide. Although iron (Fe) deficiency is considered the main factor in the pathogenesis of anemia, only 40-60% of anemia cases are responsive to Fe supplementation. Considerable data exist that other micronutrient deficiencies, such as selenium (Se), could be possible causes of anemia. The issue of Se deficiency as a risk factor for the development of anemia is of particular interest to our country since the Balkan region is known by a low Se content of soils. The aim of the study was to examine the contemporary conception of the influence of Se deficiency on the development of anemia by a review of the scientific literature. Most animal studies have shown a significant relation between Se deficiency and anemia, but one study indicates that there is no impact of Se deficiency on the hematological parameters. Associations of low serum Se with anemia have been found in a number of human studies including subjects of various age groups and pathological conditions. Three possible biological mechanisms have been suggested for the involvement of Se deficiency in the development of anemia: increased oxidative stress, modulation of inflammation through induction of interleukin-6, and increased expression of heme oxygenase-1. A more categorical clarification of the relationships between Se deficiency and development of anemia is needed with respect to appropriate trace element supplementation in cases of anemia with insufficient or absent therapeutic response to Fe treatment.

Key words: selenium deficiency, iron, anemia

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Introduction

Anemia still remains an important public health problem worldwide. Iron deficiency anemia (IDA) is one of the ten major risk factors contributing to the global burden of diseases [1]. The most affected by anemia groups are children under 5 years of age (global prevalence of anemia 42.6%) and women of reproductive age (overall prevalence of anemia 29.4%), especially during pregnancy (38.2%) [2].

Although deficiency of iron (Fe) is considered the main factor in the pathogenesis of anemia, only 40-60% of anemia cases are responsive to treatment with Fe-containing medications and a large proportion of anemia

does not respond to iron supplementation [3]. Considerable data exist that other micronutrient deficiencies, such as copper (Cu) and selenium (Se), could be possible causes of anemia. The mechanisms by which Se deficiency is implicated in the pathogenesis of anemia have not been well characterized. The issue of Se deficiency as a risk factor for development of anemia is of particular interest to our country since the Balkan region is known by a low Se content of soils [4]. Poor soil Se levels determine lower dietary intakes of Se through food and drinking water.

The alarming fact is that the mean serum Se concentration for Bulgarian population (45±6 μg/L) is lower compared to the Western European populations (70-120 μg/L) [5]. Results obtained by Lozanov et al. (2008) and Bivolarska (2014) have demonstrated the presence of Se deficiency in pregnant women living in some endemic regions of South Bulgaria - towns of Smolyan, Devin, Plovdiv, and Asenovgrad [6, 7]. A moderate Se deficiency has been found in school-age children from 7 to 10 years living in Smolyan endemic district [8].

Selenium is an essential trace element in all known forms of life. It is a cofactor of selenoproteins. The total number of known human selenoproteins is over 25, most of them with enzymatic activities. Selenoproteins are classified into 3 families: glutathione peroxidases (GPx), thioredoxin reductases (TrxR), and iodothyronine deiodinases (DIO). Selenoproteins participate in the defense against oxidative stress, muscle development and function, synthesis and metabolism of thyroid hormones. Selenoproteins enhance the apoptosis of cancer cells, improve the immune response against infectious diseases, suppress prostaglandin synthesis, and are involved in the normal sperm maturation and motility [9].

Selenoprotein expression is predominantly controlled by an adequate Se intake [10]. Selenium enters the body mainly by food [10, 11]. The major food sources of Se are Brazil nuts, organ meats, fish, poultry, and eggs. Good plant sources of Se are grains and vegetables grown on rich in Se soils, and sunflower seeds. It is worth noting that a diet containing 0.1 μg Se/g food is considered sufficient to support normal growth and reproductive performance in all mammalian species [11].

The most widely used biomarker for assessment of Se status is the plasma or serum concentration of Se [10]. In 1997, Rayman suggested a value of 100 ng Se/mL serum as a criterion of adequate Se intake [12]. Serum Se values above 100 μg/L are thought to be required for the optimal activity of GPx-1, a ubiquitously expressed cytosolic enzyme. Daniels (2004) has pointed out plasma Se concentration of 70-100 μg/L as a threshold level beyond which further Se supplementation will produce no detectable increase in plasma GPx activity [10].

As a cofactor of selenoproteins, Se acts in antioxidant and redox processes of the organism [9, 10], including erythropoiesis and erythrocyte functioning [13-15]. Mechanisms by which Se influences Fe metabolism, synthesis of hemoglobin (Hb) and erythropoiesis have not yet been completely elucidated.

Our aim is to examine the contemporary conception of the influence of Se deficiency on the development of anemia by a review of the scientific literature.

Materials and Methods

A review of the world scientific literature was conducted. Data were gathered through the databases Google Scholar and PubMed for the time period from January 1980 to April 2017 by using the keywords: "selenium deficiency", "iron", and "anemia".

Experimental studies on the relationship between selenium deficiency and development of anemia in animals

The role of Se deficiency as a factor contributing to the development of anemia has been extensively studied in animal subjects. Several research groups have found that there is a significant relation between dietary Se deficiency and development of anemia in mice, rats and cattle [13, 15-17]. Anemia has been associated with enhanced susceptibility of erythrocytes to hemolysis and the presence of Heinz bodies, which is indicative of increased oxidation of Hb to methemoglobin (metHb) and denaturation of its globin subunits. Se supplementation has been shown to prevent hemolysis and formation

of Heinz bodies, elevate the values of Hb concentration and hematocrit (Hct), and correct the anemia. As opposed to these findings, Hu et al. (1984) have not observed any impact of the long-term Se deficiency on the hematological parameters in rats. No alterations have been found regarding the erythrocyte count, Hb concentration, Hct, and the osmotic resistance of erythrocytes. Likewise, results of the same study indicate that Se supplementation produces no significant effect on the examined hematological parameters [18].

Studies on the relationship between low serum levels of selenium and development of anemia in humans

Associations of low serum Se concentrations with anemia have been found in a number of human studies including subjects of various age groups: children of primary school age from 6 to 9 years [3, 19]; adolescent girls from 11 to 17 years of age [20]; adults aged 65 years and over [21-23]. Statistically significant relationships between low serum Se and development of anemia have also been observed in different pathological conditions, such as chronic kidney disease [24] and pulmonary tuberculosis [25]. Contrary to these results, studies in patients with IDA and control subjects have shown no relation between the serum Se level and Hb concentration [26, 27]. Comparative analysis of results between the studies investigating the relationship of low serum Se concentrations with anemia is presented in Table 1.

Interactions between selenium and iron

In order to gain insight into the mechanisms by which Se deficiency leads to development of anemia, particular attention should be paid on the interactions between Se and Fe. Results of studies on the relationships between serum Se concentrations and laboratory parameters characterizing Fe metabolism are inconsistent. Significantly lower serum levels of Se have been described in subjects with IDA compared to controls [26-29]. On the contrary, in young women with prelatent iron deficiency without

manifest anemia, serum concentrations of Se have not been found to differ significantly from those of controls [30]. No relationship has been observed between serum concentrations of Se and parameters assessing different aspects of iron metabolism, such as serum levels of ferritin, Fe, and TIBC, in both subjects with normal Fe status and patients with IDA [26, 27, 31].

Of particular interest are findings from interventional studies investigating the interactions between these two essential trace elements. Results of studies examining the effects of Se supplementation on body Fe status are contradictory. Morris et al. (1984) have reported a positive influence of Se supplementation on Hb concentration and Hct in cattle [16]. Conversely, studies by other research groups have not shown significant impact of Se supplementation on the values of Hb concentration, Hct, and serum ferritin [18, 31].

Interventional studies assessing the effects of Fe supplementation on body Se status also provide conflicting results. Some authors have reported for negative effects of supplementary Fe on the status of Se reflected by plasma Se concentration and serum GPx activity [31, 32]. Findings by other authors indicate that Fe supplementation has not impact on serum Se and GPx concentrations [30].

Influence of selenium on synthesis of hemoglobin and erythropoiesis

Findings from a number of studies indicate that Se stimulates synthesis of Hb and is essential for the processes of erythropoiesis. Oster et al. (1988) have found positive correlations of the cellular Se content of erythrocytes with the erythrocyte count, Hb concentration, and Hct [33]. Consistent with these results, Se supplementation has been found to induce a striking reticulocyte response [33] and to elevate the values of Hb concentration and Hct [16]. The significance of Se for the erythropoiesis is supported by the high levels of GPx present in plasma and erythrocytes [15].

Current understanding for the essential role of selenoproteins in erythropoiesis is provided by the studies of Kaushal et al. These authors have demonstrated that adequate cellular Se status

Table 1. Comparative analysis of results between studies investigating the relationship of low serum Se concentrations with anemia

Author /Year	Design	Setting	Health status	Number of patients (n)	Demographic characteristics Age (years)*	Sex Female (%)	Anemia (%)†	Serum/plasma Se (µmol/L)	Se deficiency (%)‡	Relationship of Se deficiency with anemia §§
Van Nhien et al. (2008) [3]	Cross-sectional	Bac Ninh province, Vietnam	free from chronic and acute illness and congenital abnormality	292	7.78±0.8 (range 6-9)	52	45.2	0.773±0.172	75.6	$p<0.05$
Rashid & Ghaznavi (2015) [19]	Cross-sectional	Nishtar Town Lahore, Pakistan	free from any acute or chronic illness	150	7.56±1.2 (range 6-9)	45.4	36.7	0.489±0.022	48	$p<0.01$
Van Nhien et al. (2009) [20]	Cross-sectional	Duy Tien district, Ha Nam province, Vietnam	free from chronic and acute illnesses and congenital abnormalities	245	14.1±2.1 (range 11-17)	100	20.4	1.36±0.432	15.9	$p<0.0001$
Bates et al. (2002) [21]	Cross-sectional	mainland Britain 1. subjects living in the community 2. subjects living in institutions	NA††	total 1134 free-living 883 living in institutions 251	≥65	NA	NA	0.90 (0.50-1.36)‡‡ significantly higher in free-living people than in those living in institutions	NA	$p<0.05$
Semba et al. (2006) [22]	Cross-sectional	Baltimore (MD), USA subjects living in the community	stratified by group: 1. non-anemic 2. anemic significantly higher proportion of subjects from gr. 2 had diabetes mellitus, cardiovascular disease, positive cytomegalovirus serostatus, and elevated serum IL-6 compared to gr. 1 (p<0.05)	total 632 gr. 1 543 gr. 2 89	range 70-79 mean=74.1 mean=74.6	100	14.1	1.55 (1.52-1.57)‡‡ 1.42 (1.37-1.47) p<0.0001	NA	$p=0.002$
Semba et al. (2009) [23]	Cross-sectional	USA non-institutionalized adults	stratified by group: 1. non-anemic 2. anemic significantly higher proportion of subjects from gr. 2 had osteoarthritis, diabetes and renal disease compared to gr. 1 (p<0.05)	total 2092 gr. 1 1822 gr. 2 270	≥65 73.6±0.2 75.2±0.6	55.4 58.2 48.1	12.9	1.60 (1.59-1.61)‡‡ 1.51 (1.47-1.56) p=0.0003	NA	$p=0.03$

Study	Design	Setting	Subjects	Group	N	Age			Se concentration / outcome	%	p-value
Hampel et al. (1985) [24]	Case-control	NA	dialysis patients healthy controls	NA	NA	NA	NA	NA	significantly lower in dialysis patients than in controls	NA	p<0.05 for dialysis group
Van Lettow et al. (2005) [25]	Cross-sectional	Zomba district, Malawi	purposive sampling of adults with pulmonary tuberculosis stratified by group:	total	500	NA	54.6	NA			p=0.001 for moderate to severe anemia
			1. HIV-negative	gr. 1	130	mean=32		76.9			
			a) no anemia §§	gr. 1a	30	32±10	33.3		0.729±0.23	73.3	
			b) mild to moderate anemia†††	gr. 1b	81	32±12	49.4		0.639±0.25	85.2	
			c) moderate to severe anemia‡‡‡	gr. 1c	19	30±11	47.4		0.554±0.22 p=0.01	94.7 p=0.04	
			2. HIV-positive	gr. 2	370	mean=34		88.4 p=0.002			
			a) no anemia	gr. 2a	43	32±8	65.1		0.724±0.22	79.1	
			b) mild to moderate anemia	gr. 2b	216	34±9	52.8		0.633±0.20	90.3	
			c) moderate to severe anemia	gr. 2c	111	34±8	64.9		0.513±0.20 p=0.001	94.6 p=0.006	
Yetgin et al. (1992) [26]	Case-control	Turkey	patients with IDA control subjects	total	80	children	NA	50	significantly lower in the patient group (p<0.001)	NA	p>0.05
				IDA gr.	40						
				controls	40						
Gürgöze et al. (2004) [27]	Case-control	Turkey	patients with IDA control subjects	total	104	range 1-8	NA	54		NA	p>0.05
				IDA gr.	56				0.426±0.104		
				controls	48				0.709±0.215 p<0.001		

*Values are presented as mean ± standard deviation unless otherwise indicated
†Defined as Hb concentrations below recommended thresholds for the respective sex and age group
‡Defined as serum Se concentration <0.89 μmol/L
§ Statistical significance is indicated by p<0.05
††NA – not available
‡‡Presented as mean (95% confidence interval)
§§Hb concentration ≥120 g/L for females and ≥130 g/L for males;
†††Hb concentration <120 g/L for females and <130 g/l for males, and ≥80 g/L for both sexes;
‡‡‡Hb concentration <80 g/L for both sexes

regulates oxidative stress-dependent expression and activation of two transcription factors in erythroid cells, hypoxia-inducible factor (HIF)-1α and Forkhead box O3 transcription factor (FoxO3a) [15, 34]. FoxO3a is known to be involved in the physiologic response to oxidative stress during erythropoiesis via induction of gene expression of antioxidant enzymes, including GPx-1, in erythroid precursors [35].

There is a significant body of research indicating that Se regulates biosynthesis and metabolism of heme [33, 36-38]. It has been found that Se induces expression of both the mitochondrial enzyme synthase of δ-aminolevulinic acid (δ-ALA) and the microsomal enzyme heme oxygenase-1. The latter is believed to be an indirect effect resulting from the increased production of "free" heme in the cell. Other enzymes involved in the biosynthesis of prostetic group of Hb, such as dehydratase of δ-ALA and ferrochelatase, have shown to be significantly inhibited by Se.

Mechanisms by which Se deficiency can contribute to the development of anemia

Three possible biological mechanisms have been suggested for the involvement of Se deficiency in the development of anemia: increased oxidative stress, modulation of inflammation through induction of the proinflammatory cytokine interleukin (IL)-6, and increased expression of heme oxygenase-1 [3, 19].

Se-deficiency-induced oxidative stress
Data from experimental studies [13, 15-17] have shown that anemia in Se deficiency is associated with increased lipid peroxidation, elevated levels of protein carbonyls and metHb in the erythrocytes, denaturation of Hb, increased number of Heinz bodies, and decreased osmotic resistance of erythrocytes. These findings suggest increased generation of reactive oxygen species and exposure of erythrocytes to high degree of oxidative stress.

Selenium is a cofactor of GPx catalyzing the reduction of hydrogen peroxide and different organic peroxides [9, 14]. Activity of cytosolic GPx-1, which is responsible for the protection of Hb in erythrocytes from oxidative stress, is diminished in Se deficiency [13, 15, 17, 18]. Increased lipid peroxidation of membrane lipids and denaturation of Hb can both contribute to hemolysis and reduced life-span of circulating erythrocytes. Moreover, recent study has shown that Se deficiency-induced anemia is associated with expansion of erythroid progenitors, but is not accompanied by an increased reticulocyte count. These results indicate inefficient erythropoiesis with defective erythroid differentiation and maturation in Se deficiency [15]. Taken together, data suggest that the development of anemia caused by Se deficiency results from an excessive destruction of circulating erythrocytes along with a lack of sufficient production of mature erythroid cells.

Induction of inflammation
It has also been shown that oxidative stress mediated by increased hydrogen peroxide and lipid peroxides stimulates synthesis of IL-6 [39]. This proinflammatory cytokine has proven to be the most important direct inducer of hepcidin expression [40]. The Fe-regulatory hormone hepcidin, identified at the beginning of the XXIth century by Krause et al. [41], is a peptide predominantly produced by the hepatocytes [42, 43]. Its mechanism of action involves binding and inactivation of the transmembrane Fe exporter ferroportin [44].

Hepcidin plays a key role in the regulation of Fe homeostasis [45]. It suppresses the intestinal absorption of Fe, its release from macrophages recycling senescent erythrocytes and, at least partially, from hepatocytes [43]. Stimulated synthesis of hepcidin in inflammation thus results in a decreased Fe supply to erythropoiesis.

Elevated serum levels of IL-6 have been found in older women with low serum Se concentrations [46]. Se deficiency can therefore be considered to be an important factor in the pathogenesis of anemia of chronic inflammation mediated by the hormone hepcidin.

Increased expression of heme oxygenase-1
Deficiency of Se leads to increased oxidative stress and production of IL-6, both of which induce expression of heme oxygenase-1 [47, 48]. This enzyme catalyzes the initial reaction

of heme catabolism in which heme is reduced to biliverdin, carbon monoxide (CO), and free Fe^{2+}.

Conclusions

Selenium deficiency has been associated with anemia in a number of studies involving animal and human subjects. At present, data of many studies support interactions between selenium and iron, although the exact underlying mechanisms by which selenium influences iron metabolism, synthesis of hemoglobin and erythropoiesis have not been fully established yet. One of the possible links between selenium and the homeostasis of iron is the peptide hepcidin. A more categorical clarification of the relationships between Se deficiency and development of anemia is needed with respect to appropriate trace element supplementation in cases of anemia with insufficient or absent therapeutic response to Fe treatment. Selenium supplementation could be considered in the strategies for treatment and control of anemia.

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