1 **Special article**

2 **The influence of nutrigenetics on biomarkers of selenium nutritional status**

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9
10 **Abstract**

11 Selenium (Se) is an essential micronutrient for human biology that executes its
12 functions as the amino acid selenocysteine via selenoproteins, which have important
13 functions, such as, antioxidant, immunomodulatory, thyroid metabolism and human
14 fertility. Se nutritional status is assessed using the quantification of blood Se
15 biomarkers influenced by several factors, including diet, age, gender, smoking status,
16 alcohol consumption, health condition and genetic characteristics of individuals.
17 Nutrigenetic studies have identified single nucleotide polymorphisms (SNPs) in

selenoproteins that might clarify the high variability in values reported for biomarkers of Se nutritional status in different populations and the response of these biomarkers to Se supplementation with either organic or inorganic forms of Se. This review aims to (1) define the basic aspects of Se biology, (2) describe the current most commonly used biomarkers of Se nutritional status and, (3) provide a state of the art of associations observed between functional SNPs in selenoproteins and biomarkers of Se status in healthy populations.

Keywords: single nucleotide polymorphisms, selenoproteins, glutathione peroxidase, selenoprotein P.

INTRODUCTION

The essentiality of the trace element selenium (Se) to human health was first reported in 1978 when its presence was discovered in the antioxidant erythrocyte enzyme glutathione peroxidase.¹ Previous reviews on this topic have described this discovery in detail.²⁻⁴ After recognizing its important functions for human health, several studies have aimed to monitor the Se nutritional status of populations worldwide.^{3,5,6} However, the controversial data of epidemiological and intervention studies have demonstrated not only differences in the Se intake of populations from different regions, but also different individual responses. In this context, the influence of genetic variations in genes related to Se metabolism must be considered to understand this scenario.⁷

Following the conclusion of the Human Genome Project (HGP) and the advances in technology, numerous genetic variations in the human DNA sequence

have been described.⁸ Concerning Se metabolism, the identification of several functional single nucleotide polymorphisms (SNPs) in selenoproteins has raised the hypothesis that these SNPs could modify the biomarkers of Se status and modulate its beneficial effect on the development of chronic diseases.⁷ In this context, the nutrigenetic research field provides a better understanding of selenoprotein metabolism and its biological function in humans, which could help researchers to understand the data on Se status in different populations and the variable interindividual response to Se dietary interventions. Investigating how the presence of SNPs in selenoprotein genes modifies the biomarkers of Se status is crucial for a better assessment of Se nutritional status and a future revision of Se dietary recommendations according to the genetic characteristics of different populations or individuals.

This review aims to (1) define the basic aspects of Se metabolism, function, food sources, and nutritional recommendations; (2) describe the current most commonly used biomarkers of Se nutritional status; and (3) provide a state of the art of associations observed between functional SNPs in selenoproteins and biomarkers of Se nutritional status in healthy populations.

METHODS

The search for articles was conducted using the PubMed database available at www.ncbi.nlm.nih.gov/pubmed, and the terms “selenium”, “nutrigenetics” and the specific SNPs “pro198leu,” “rs1050450,” “rs713041,” “rs3877899,” “rs7579,” “rs5845,” and “rs34713741.” These SNPs were selected based on the literature search. The inclusion criteria were as follows: studies conducted with healthy populations, both genders or only males or females, an evaluation of one or more SNPs in

selenoprotein genes, and a quantification of biomarkers of Se nutritional status. The studies included were observational, longitudinal, and randomized clinical trials. Those conducted with a population with chronic diseases such as cancer, cardiovascular disease, and diabetes and without the quantification of biomarkers of Se nutritional status were excluded.

BASIC ASPECTS OF SE BIOLOGY: FUNCTION, FOOD SOURCES, AND DIETARY RECOMMENDATIONS

Se is an essential trace element for human health with its biological role directly related to the functions of selenoproteins and Se metabolites. Unlike other minerals that interact with proteins as cofactors, Se is inserted into mammalian selenoproteins as the 21st amino acid, selenocysteine (Sec). In mammals, 25 selenoprotein genes have been identified, while only half of them have been functionally characterized.^{9,10} Sec is generally located in the active site of the enzymes by using a mechanism that involves the recoding of the stop codon UGA during translation. The incorporation of Sec into proteins occurs in the 3'UTR in the Sec incorporation sequence (SECIS) region.¹¹ Most selenoproteins are involved in biological processes that concern the control of the redox state and antioxidant function.^{10,12}

One of the well established functions of selenoproteins is the redox activity mainly attributed to five members of the glutathione peroxidase (GPx) family and three isoforms of thioredoxin reductases (TXNRD) and deiodinases (DIO). They act in the reduction of hydrogen peroxide (H₂O₂) and phospholipid hydroperoxides, decreasing the overall oxidative damage to cell membranes, biomolecules, DNA, and mitochondria.¹⁰ Se is also important for modulating the inflammatory response since

it attenuates the activation of the nuclear factor (NF)-kB pathway;^{13,14} protection against toxic heavy metals, such as mercury and methyl mercury;¹⁵ and thyroid function due to the action of deiodinases in the conversion of T₄ into its active form T₃.^{16,17} Moreover, Se is critical for neurological function as it protects the brain against oxidative damage,^{18,19} as well as male fertility and reproduction through the role of GPX4 as an antioxidant in the early phase of spermatogenesis, which guarantees the functional and structural integrity of spermatozoa.^{20,21} In the later phase, GPX4 located in the mitochondria is essential to the sperm capsule formation²¹.

In foods, Se can be presented as either organic (Sec and selenomethionine [SeMet], Se- methyl-selenocysteine [SeMCys], and γ -glutamyl-Se-methyl-selenocysteine) or inorganic forms (selenate). The inorganic form selenite is found in supplements. In a normal physiological condition with an adequate intake, most organic and inorganic forms are well absorbed (~70 - 90%), except for selenite, which has an absorption no greater than 60%.⁴ Se concentration in foods varies worldwide according to Se content and bioavailability in the soil and the capacity of plants to accumulate Se.^{22,23} This geographical pattern of variation has a direct impact on the Se nutritional status of global populations, with the lowest values found in Eastern Europe, and the highest in Venezuela, the United States and Canada. China has regions of deficiency and toxicity.^{15,24} While seafood, meat, grains, eggs, and cereals are excellent sources of Se, Brazil nuts have the highest concentration.⁶ The Brazil nut tree (*Bertholletia excelsa*), a native species from South America, is found mainly in the Brazilian Amazon region, which has a Se-rich soil that influences the high Se content in the nuts and the Se status of the population.^{23,25} Nevertheless, for this population, the higher intake that reflects plasma Se concentrations that could

reach 900 µg/L, with a median of 135 µg/L, is not toxic.²⁶ Some factors that could explain the lack of selenosis in this population are as follows: (1) the population might have adapted to a higher than average Se status through metabolic mechanisms; (2) the high Se content might be protective against Hg exposure since plasma selenoprotein P can bind Hg and reduce its bioavailability to target proteins²⁶; (3) this population might have a specific gut microbiota profile due to their exposure to high Se that helps excrete the excess Se more rapidly²⁷; (4) they might have polymorphisms in genes that regulate Se metabolism and excretion.²⁷ The Brazil nut tree is considered a secondary accumulator tree that can accumulate about 100 to 1,000 mg/Se/g⁻¹ of dry weight in their seeds. The organic forms of Se (C-Se-C species) are predominantly present in this nut, which includes SeMet (the main Se compound), SeMCys, and Se-lanthionine.²⁸ However, the Se content in nuts varies according to the region of the Amazon rainforest where the Brazil nut tree was planted.²⁹ Studies have shown the Se concentration of one Brazil nut from the Brazilian Amazon rainforest can vary from 290 to 1,261 µg.^{19,30–33}

The dietary intake recommendation values proposed by the Food and Nutrition Board of the Institute of Medicine (IOM) were based on the intake needed to maximize plasma GPX3 activity.³⁴ The values of the estimated average requirement (EAR), the recommended dietary allowance (RDA), tolerable upper intake level (UL), no observed adverse effect level (NOAEL), and lowest observed adverse effect level (LOAEL) for children, adults, pregnancy, and lactation are summarized in **Table 1**.

BIOMARKERS OF SE NUTRITIONAL STATUS

The evaluation of Se nutritional status remains a matter of debate since the distribution of this mineral into selenoproteins depends on several factors, such as

the hierarchy system of incorporation, bioavailability from food sources, dietary intake, health state, and the presence of genetic polymorphisms in selenoproteins.⁴ Overall, Se status involves Se dietary intake, Se content in tissues, Se function, and excretion.²⁴ The current most commonly used biomarkers are 1) total Se concentration in whole blood, plasma, serum, erythrocytes, or urine; 2) GPx activity in plasma (GPx3), erythrocytes (GPx1), and whole blood (total GPx); and 3) plasma selenoprotein P (SELENOP) levels.²⁴

A reliable marker of Se intake must to be sensitive to changes in Se status and reflect the current intake through food. It should be noted that plasma Se levels can be used to predict Se intake if SeMet is mostly consumed by using a linear regression equation ($\text{Se}_{\text{in}}, \mu\text{g/kg}0.75/\text{day} = 0.44 + 0.03 \times \text{Se}_{\text{plasma}}, \text{ng/mL}$).²⁴ Food questionnaires can also measure Se intake; nevertheless, the available food composition tables do not address the huge geographical variation of Se content in soil.

After absorption, Se can be found in tissues, such as whole blood, erythrocyte, and plasma. In humans, whole blood Se is not the best biomarker option because it does not reflect its biological function, executed through selenoproteins activity. The evaluation of specific selenoproteins can thus provide a more precise diagnostic of Se status.^{4,35} Erythrocyte Se represents a long-term evaluation of Se status since the half-life of these cells is about 120 days.⁴

Several factors, such as geographical location, gender, age, race, BMI, smoking status and alcohol consumption, affect plasma Se concentrations. Studies have found a reduction in plasma Se concentration with age,³⁶ as well as in protein malnutrition,³⁷ chronic inflammation,³⁸ in smokers,^{39,40} in obese individuals,^{39,41} in African Americans,⁴² and in daily alcohol consumers.³⁶ Red wine consumers had

higher than average plasma Se levels in the SU.VI.MAX study conducted in France.³⁹

The measurement of selenoproteins activity, involved mostly with redox control, is the best option when evaluating Se status because this biomarker reflects Se function. It is important to note that Se have biological effects that do not occur through the selenoproteins.⁴³ In a xenograft model of prostate cancer, Se-methylselenocysteine and methylseleninic acid inhibited tumor growth while selenite and SeMet did not.⁴⁴ The direct biomarkers are GPx1 and GPx3 activities and plasma SELENOP concentration.²⁴ GPx1 activity is a suitable biomarker in cases of low Se status (plasma concentration < 60 µg/L) since the activity of this enzyme cannot reach its maximal level in that range of Se concentration and can be assessed in erythrocytes using spectrophotometry.⁴⁵ This biomarker is also effective and sensitive for evaluating Se supplementation due to its rapid response observed in a period of one to two weeks, depending on the baseline Se status and the chemical form of Se administrated.^{24,35} The response of the biomarkers to different chemical forms of Se has been reviewed extensively elsewhere and is not addressed in this article.^{46–52} GPx1 activity has been found to vary with gender and age, being higher in females than males^{53–57} and females under 55 years than males and females over 55 years.⁵⁸ GPx1 activity was reduced in smokers,^{56,58,59} in patients with cardiovascular events⁵⁸ and in patients with asthma.⁶⁰

GPx3 is an extracellular isoform that the kidney produces by and is responsible for around 10 - 25% of total plasma Se. The measurements of plasma GPx3 activity and/or concentration can be both used as Se biomarkers and they usually correlate with total plasma Se concentration.^{4,24} Regarding the two GPx activities, it is essential to highlight that they reach a maximal activity at different

192 plasma Se concentrations: GPx1 around 80–120 µg Se/L⁶¹ and GPx3 around 70–90
193 µg Se/L.⁶² In this context, both activities are useful biomarkers of Se status to assess
194 a nutritional deficiency. GPx3 activity varies with age and gender, being lower in
195 adults between the ages of 40 and 49 years and obese females compared to adults
196 of other ages and obese males.⁴¹

197 SELENOP acts as the primary Se transporter to peripheral tissues, being the
198 only selenoprotein that can contain as many as 10 residues of Sec and comprises
199 40–60% of total plasma Se.⁴ While the measurement of plasma SELENOP
200 concentration is considered the most conclusive biomarker of Se status, no reference
201 values for it exist.^{24,63,64} SELENOP reaches a plateau when plasma Se concentration
202 is around 120 µg Se/L.^{52,65} Factors such as ethnicity and BMI affected SELENOP
203 concentrations, for example, SELENOP is reduced in African-Americans⁴² and obese
204 adults.⁶⁶

205 Urinary Se is a marker of Se excretion associated with plasma Se
206 concentration and Se intake. Results from balance studies confirm that urinary Se
207 represents 50–60% of the total amount excreted; Se intake can therefore be
208 estimated as twice the urinary Se.³⁵ Hair and toenails are tissues that accumulate Se,
209 being markers of Se retention, and are thus more useful as markers of longer
210 exposure over the past six to 12 months.^{6,62,67} Nevertheless, hair samples must be
211 analyzed carefully due to possible contamination from by chemical products, such as
212 Se-containing shampoos.^{6,24}

214 **THE CHOICE OF SE BIOMARKERS DEPENDS ON THE SE STATUS OF THE** 215 **POPULATION**

216 The choice of a specific biomarker to evaluate Se status must consider

several factors, such as the health status of the individual, the specific biological function of selenoproteins, and the genetic polymorphisms.⁴ The use of different biomarkers is an adequate approach because it provides information related to Se nutritional status and the functionality of specific selenoproteins.²⁴ An ideal measurement of Se status must reflect the amount available for the functional activity of selenoproteins.³⁵ For instance, in populations with low plasma Se concentrations (< 60 µg/L), more options of biomarkers are available because selenoproteins do not reach their maximal activity. In this case, while plasma Se is an adequate option, so is erythrocyte GPx1 activity, plasma GPx3 activity, and plasma SELENOP concentration.⁶⁸

In individuals with adequate Se status and intake, the increase in Se biomarkers does not depend on chemical forms of Se since almost all inorganic and organic forms, including selenite in the presence of reduced glutathione (GSH), are rapidly absorbed.⁴ SeMet appears to be more bioavailable because it is being incorporated inespecifically into plasma proteins such as albumin. The raise in plasma Se due to the increase in SeMet is directly correlated with the increase in Se in albumin.²⁴ However, SeMet can raise plasma Se and SELENOP concentrations even in those individuals with adequate Se status.^{24,48,52,69} The increase in those two biomarkers is possible since its absorption occurs through a transcellular pathway that transporters mediate and the elimination of inorganic species is increased, while SeMet is retained and incorporated in an unspecific way into other proteins, such as serum albumin and hemoglobin. SeMCys can also be absorbed through the same process that SeMet contributes to the increased plasma Se.^{4,70} The consumption of Se as SeMet in individuals with adequate Se status can therefore be estimated using plasma Se concentrations as a biomarker.^{24,69} As to populations with

high Se exposure, the indicated biomarker is plasma Se concentration because all selenoproteins reach their plateau with a plasma Se concentration of 150 µg/L. The supplementation with 1,600 µg and 3,200 µg of Se yeast of individuals with baseline plasma Se concentration of 135 and 129 µg/L, respectively, was able to increase this biomarker.⁷¹

FUNCTIONAL SINGLE NUCLEOTIDE POLYMORPHISMS AFFECTING BIOMARKERS OF SE NUTRITIONAL STATUS

Evidence of the functional consequences of some single nucleotide polymorphisms in selenoproteins

After the conclusion of the HGP, several genetic variations were discovered. Within the five human DNA samples used for the entire HGP, more than 3 million SNPs with an average density of 1/1,250 bp were discovered.⁸ Other initiatives to map the entire diversity of the human genetic variation includes the International Hapmap Project⁷² and the 1000 Genomes Project Consortium.⁷³ The latter observed more than 85 million SNPs in a sample of 2,504 subjects with different ethnic backgrounds.⁷³

Different types of polymorphisms occur the human genome, including SNPs, short insertions/deletions (indels), and structural variants. By definition, a polymorphic locus in a chromosome is one in which the most common variant occurs in less than 99% of the population; in terms of the variant allele, the rarer allele must occur in more than 1% of the population.^{74,75} The substitution of a single nucleotide in the DNA sequence is the simplest and most common type of polymorphism, the SNP. In the nutritional genomics field, the most studied type of genetic variation is

the SNP. Polymorphisms located in intron were thought not to affect the structure of the final protein; however, this concept has changed because if the variation is located in an intron close to the splicing junction, it will change the entire open reading frame and, as a consequence, the entire sequence of aminoacids of the protein after the SNP.⁷⁶ It is worth noting that most SNPs have no biological effect for several reasons: they could be in exons and do not change the amino acid because the genetic code is degenerated, or even if they change the amino acid, this modification is not essential for the structure, stability, and function of the protein.^{76,77} Concerning genes that encode selenoproteins, the great challenge is therefore to discover SNPs that, alone or interacting with other SNPs, affect the expression or the activity of these proteins that modulate Se nutritional status.⁷⁷ Single nucleotide polymorphisms in at least 10 selenoprotein genes are believed to be associated with the variation of several biomarkers of Se status.²⁴

One of the most studied SNPs in selenoprotein genes is the Pro198Leu in the *GPX1* gene (rs1050450). It is a C > T substitution located in the coding region of the gene that changes the amino acid proline to leucine in position 198 of the protein.⁷⁸ Previous studies have demonstrated that the presence of the rare allele T was associated with a reduction in GPx1 activity^{59,79–84} and with a reduction in GPX1 mRNA expression.^{82,85,86} It is hypothesized that the change of the amino acid proline to leucine alters the secondary and tertiary structures of the protein, affecting its activity and stability.⁷⁹ Indeed, *in vitro* studies have confirmed a reduction in the thermostability of the enzyme-containing the leu variant.⁸⁷

GPx4 is the only GPx isoform that can reduce phospholipid hydroperoxides in the cell membrane.⁸⁸ A substitution C > T is located in the 3'UTR (rs713041), the mRNA region important for Sec insertion. Experimental evidence, both *in vitro* and *in*

vivo, has demonstrated that this SNP has functional consequences. Levels of lymphocyte lipoyxygenase products were higher in individuals with the CC genotype than in those with the TT genotype, and the C allele was associated with a higher risk for colorectal cancer compared to the T allele.⁸⁹ In vitro studies have revealed that *GPX4* transcripts that contain the C allele indicate a better ability to bind proteins during translation, competing strongly with not only the transcripts that contain the T allele but also the *GPX1* transcripts. Under a limitation of Se supply, this better ability to bind proteins means that *GPX4* with the C allele have a preference for protein synthesis.⁹⁰ In human endothelial cells, the T allele was associated with higher than average levels of lipid hydroperoxides and was also more susceptible to oxidative stress.⁹¹ In addition, the rare T allele was associated with a higher risk for breast cancer⁹² and colorectal cancer compared to the C allele.⁹³

Two SNPs with functional consequences were described in the *SELENOP* gene that encodes the plasma SELENOP, the main plasma Se transporter for tissues and the brain. Both SNPs are G > A substitutions: one located in the coding region, predicted to change the amino acid alanine to threonine at position 235 (rs3877899), and the other located in the 3' UTR region, important for Sec insertion (rs7579).⁴¹ It is hypothesized that rs3877899 regulates SELENOP stability and uptake through the cells, and the rs7579 affects the synthesis of this selenoprotein.⁴¹ Plasma SELENOP has two isoforms, the 50 kDa and the 60 kDa, with the second one containing the Sec-rich domain.⁹⁴ The two SNPs in the *SELENOP* gene affect both isoforms. At baseline, individuals with the GA genotype for rs3877899 had a lower proportion of the SELENOP 60 kDa, with the Sec-rich domain. After Se supplementation with 200 µg of selenite for eight weeks, individuals with the AA genotype for rs7579 presented a lower proportion of SELENOP 60 kDa compared to individuals with the GG

genotype.⁹⁵ In addition, rs7579 was associated with a higher than average risk of developing prostate cancer.⁹⁶ Moreover, the presence of the rare allele A for rs7579 was associated with an increase in *SELENOP* mRNA expression^{82,86} and higher than average cholesterol levels after supplementation with Brazil nuts⁹⁷, while the presence of the rare allele A for rs3877899 was associated with an increase in *SELENOP* mRNA expression⁸² and with lower levels of cholesterol after supplementation with Brazil nuts.⁹⁷

The selenoprotein F (*SELENOF*), previously known as 15 kDa selenoprotein (SEP15), has two functional polymorphisms located in the 3' UTR region (rs5845 and rs5859) that are in linkage disequilibrium within the same haplotype, which means that the presence of the rare allele for one SPN implicates the presence of the other one. The first SNP is a G > A substitution at position 1,125 in the apical loop of the SECIS element, and the second one is a C > T substitution at position 811.⁹⁸ The variation in the apical loop (rs5845) might influence the efficiency of Sec incorporation into proteins.⁹⁹ In vitro studies have verified that the TA haplotype was less responsive to sodium selenite supplementation in NIH 3T3 mouse fibroblasts⁹⁹ and mesothelioma cells than the GC haplotype.¹⁰⁰ In addition, the polymorphism rs5845 was associated with a higher risk of lung cancer in plasma Se concentrations below 60 µg/L,¹⁰¹ an increased risk of colorectal cancer,¹⁰² lower scores for verbal learning memory¹⁰³ and a higher histological tumor grade in patients who have undergone radical prostatectomy compared to individuals with the normal genotype.¹⁰⁴

Selenoprotein S (*SELENOS*), located in the endoplasmatic reticulum (ER), is associated with the protection of the ER from the stress that by misfolded proteins cause¹⁰⁵ and with the control of the inflammatory response.^{106,107} A substitution C > T

occurs in the promoter region of the *SELENOS* gene (rs34713741) that has been associated with an increased risk of rectal,¹⁰² colorectal,⁹³ and gastric cancer¹⁰⁸ as well as ischemic stroke.¹⁰⁹ Another relevant polymorphism is the rs28665122, located in the promoter region of the *SELENOS* gene, also known as -105G/A. This SNP has been correlated with plasma IL-1, IL-6, and TNF- α levels¹⁰⁶, an increased susceptibility to Hashimoto's Thyroiditis¹¹⁰, preeclampsia in Norwegian women¹⁰⁷ and an increased risk of gastric cancer.¹¹¹

Plasma Se

Plasma Se is a short-term biomarker that reflects the current nutritional status of this mineral.^{24,112} Since this biomarker is widely used to evaluate Se status and responds to dietary intake, genetic variations that affect plasma Se should be investigated as they can influence the assessment of Se nutritional status.

Lower plasma Se concentrations were associated with four SNPs in different selenoproteins (rs1050450 [*GPX1*], rs3877899 and rs7579 [*SELENOP*] and rs3471374 [*SELENOS*) and higher plasma Se with one SNP (rs7579 [*SELENOP*]). In a study conducted with 261 adults from the United States with a mean age of 50 years, lower plasma Se concentrations were observed in subjects with the rare TT genotype for the SNP in the antioxidant enzyme GPX1 Pro198Leu (rs1050450).⁶⁶ In a Polish supplementation trial that included 95 adults with a mean age of 35 years who were administered 200 μ g of SeMet a day for six months, the coding SNP in the *SELENOP* gene (rs3877899) was associated with lower plasma Se only at baseline in individuals with the rare genotype AA.¹¹³ In the SU.BRA.NUT trial, the association of SNPs in selenoproteins with biomarkers of Se status was evaluated in 130 adults after the supplementation with one unit of Brazil nut (~300–400 μ g/Se) for eight

weeks following a washout period of eight weeks. Two SNPs were associated with lower plasma Se after only four weeks of Brazil nut intake: *SELENOP* gene (rs7579) and *SELENOS* gene (rs34713741).³² In the SELGEN trial, the association of SNPs in the *SELENOP* gene with biomarkers of Se status before and after supplementation was investigated in 75 healthy adults from England with a mean age of 40 years, who were supplemented with 200 µg of sodium selenite for six weeks following six weeks of washout. Overall, individuals with the rare genotype AA for the 3' UTR on *SELENOP* rs7579 had higher plasma Se concentrations after the intervention period and two weeks of washout compared to individuals with the GG genotype.⁴¹

Erythrocyte Se

Erythrocyte Se concentration is a biomarker of Se status that reflects long-term Se intake.²⁴ Although it is a useful biomarker, it is not commonly used in studies that investigate the association of SNPs with biomarkers of Se status in healthy adults. Specifically for patients with systemic inflammatory response, erythrocyte Se is a better biomarker than plasma Se since the acute phase response does not affect it.¹¹⁴ Two studies have found this association. In the observational study, there was an association between the coding SNP rs8179169, a substitution G > C that changes the amino acid arginine to proline in position five of the protein (Arg5Pro) in the *GPX1* gene, and erythrocyte Se concentrations: lower concentrations were observed in individuals with the GC genotype.⁵⁴ In the SU.BRA.NUT trial, erythrocyte Se concentration was associated with two SNPs: rs713041 (*GPX4*) and rs34713741 (*SELENOS*). The 3'UTR SNP in *GPX4* gene rs713041 was associated with lower erythrocyte Se in T-carriers at baseline. Moreover, an increase in the variation ($\Delta 1_{[8 \text{ weeks nuts} - \text{baseline}]}$) of erythrocyte Se concentration in T-carriers for rs34713741

occurred in the *SELENOS* gene, which means that in these individuals, erythrocyte Se concentration was higher compared to the CC genotype after Se supplementation with Brazil nuts; the T-carriers were more responsive to Se supplementation.³²

Erythrocyte GPx1 activity

Erythrocyte GPx1 activity is a widely used biomarker of Se status and intake, especially in cases of suspected deficiency.²⁴ While several studies have evaluated the influence of SNPs in selenoprotein genes that can affect GPx1 activity, the most studied is the rs1050450 in the *GPX1* gene (Pro198Leu).^{32,40,54,56,113,115,116} However, SNPs in other selenoproteins have also been associated with alterations in GPx1 activity in healthy volunteers. These include rs713041 (*GPX4*),^{32,54,90} rs3877899, rs7579 (*SELENOP*)^{32,40} and rs5845 (*SELENOF*)³². Overall, the presence of the rare allele T or genotype TT for rs1050450 has been associated with lower GPx1 activity in seven studies (see **Table 2**).^{32,40,56,83,113,115,116} In three of these studies, a gender-SNP interaction was modulating GPx1 activity.^{54,56,83} Moreover, T-carriers for rs1050450 in the *GPX1* gene had a reduction in GPx1 mRNA expression after supplementation with Brazil nuts⁸⁶. A reduction in GPx1 activity was also associated with rs5845 in the *SELENOF* gene in the SU.BRA.NUT trial during the washout period³² and with rs3877899 in the *SELENOP* gene in adults from New Zealand.⁴⁰

The presence of the rare allele T for rs713041 (*GPX4*) was associated with both higher^{32,40} and lower than average GPx1 activity.⁹⁰ It is initially surprising that SNP in genes other than *GPX1* can affect GPx1 enzyme activity; nevertheless, the hierarchy of selenoprotein expression could explain this result. Indeed, selenoproteins compete with one another against components of the selenoprotein synthesis machinery and for available Se, as the amino acid Sec, during the

translation process.^{88,117} The differences in the 3' UTR region, where the Sec insertion occurs, are the main factor that drives this competition. Single nucleotide polymorphisms in this specific region of Sec insertion can therefore change the hierarchical order of selenoprotein expression.⁹¹ RNA-protein binding assays *in vitro* demonstrated that the C-variant for rs713041 in *GPX4* transcripts bind to protein more strongly than the T-variant and *GPX1* transcripts.⁹⁰ In addition, *GPX4* protein is ranked high in the hierarchy of selenoprotein expression, which indicates that it has a preference for protein synthesis when Se supply is scarce.¹¹⁷ Such evidence suggests that in individuals with the C allele for rs713041 in the *GPX4* gene, the synthesis of *GPX1* protein is expected to be lower because, during translation, the C transcript for *GPX4* can compete more strongly against the *GPX1* transcript for Se incorporation into *GPX4* protein, which means that Sec will be incorporated preferentially into *GPX4* protein rather than *GPX1*. By contrast, in individuals with the T allele for the *GPX4* SNP the opposite scenario occurs, changing the hierarchy: Sec will be directed to *GPX1* synthesis because the T-transcript is not strong enough to compete against *GPX1* during translation.^{90,91} In the SU.BRA.NUT trial, an increase in the variation ($\Delta 1$ [8 weeks nuts – baseline]) of erythrocyte Se concentration in A-carriers for rs7579 occurred in the *SELENOP* gene, which suggests that in these individuals, erythrocyte Se concentration was higher compared to the GG genotype after Se supplementation with Brazil nuts; A-carriers were more responsive to Se supplementation.³²

Plasma GPx3 activity

Studies conducted with healthy adults found an influence of genetic polymorphisms in selenoprotein genes on GPx3 activity, and overall, the presence of

the rare allele for rs7579 (*SELENOP*), rs713041 (*GPX4*), and rs5845 (*SELENOF*) was associated with a reduction in its activity. In the SELGEN trial, rs713041 (*GPX4*) and rs7579 (*SELENOP*) were associated with lower GPx3 activity after the supplementation and washout period.^{41,90} The same rationale for the influence of the SNP in rs713041 (*GPX4*) on GPx1 activity could be applied to explain the influence of SNPs in *SELENOP* and *SELENOF* on GPx3 activity. In the SU.BRA.NUT trial, rs5845 (*SELENOF*) was associated with lower variation in GPx3 activity after the intervention period ($\Delta 1_{[8 \text{ weeks nuts} - \text{baseline}]}$), which means that in T-carriers, the GPx3 activity was less responsive to Brazil nut supplementation compared to the CC genotype.³² In a study conducted with healthy pregnant women in the United Kingdom, A-carriers for rs3877899 (*SELENOP*) increased GPx3 activity after supplementation with Se-yeast; in the placebo group, the A-carriers were able to maintain their Se status measured by whole blood Se.¹¹⁸

Plasma Selenoprotein P

Plasma SELENOP concentration is considered one of the best biomarkers of short-term Se status and intake.⁶² Three SNPs have been associated with a reduction in plasma SELENOP concentration: two on its gene (rs3877899 and rs7579) and one in the *SELENOF* gene (rs5845). In the SELGEN trial, heterozygote females for rs3877899 had lower plasma SELENOP concentrations than GA males.⁴¹ In healthy Americans, GA adults for rs7579 had lower plasma SELENOP than GG and GA genotypes.⁶⁶ In the SU.BRA.NUT trial, T-carriers for rs5845 (*SELENOF*) had a lower variation of plasma SELENOP concentration during the washout period ($\Delta 2_{[\text{washout} - \text{nuts}]}$), which indicates that this biomarker dropped after Se withdrawal, being more responsive to a reduction in Se availability.³² By contrast, the same two SNPs

on the *SELENOP* gene were associated with an increase in plasma SELENOP concentrations after Se supplementation. An SNP-gender interaction occurred after the supplementation: higher than average plasma SELENOP concentration was associated with the GG genotype for rs3877899 in women^{41,116} and with the GA genotype for rs7579 in men.⁴¹ In American adults, plasma SELENOP concentrations were lower in GA individuals compared to GG individuals for rs3877899.⁶⁶ Moreover, in A-carriers for rs7579, *SELENOP* mRNA expression was higher than in GG individuals before and after Brazil nut intake.⁸⁶

Conclusions

This review provided an overview of the effects of functional SNPs in selenoprotein genes on the most common biomarkers of Se nutritional status. Evidence demonstrates a significant reduction of GPX1 activity in the presence of the rare allele T for the coding SNP rs1050450 (*GPX1*). Concerning the other functional SNPs, insufficient evidence prevents stating that some genotypes can modulate one or more biomarkers of Se status.

As to the association between the reduction on GPX1 activity and the SNP rs1050450 in the *GPX1* gene, non-RCT and RCT interventions and observational studies with a baseline plasma Se below 100µg/L have confirmed this association; however, in populations with high Se status, such as that of the United States, this association has not been observed. One explanation is the saturation of selenoproteins activity or concentration with plasma Se above 120 µg/L. Even with a supplementation, populations with high Se status would not increase selenoprotein activity because they are already at their maximal and the presence of the SNP would not change this response.

Nutrigenetics studies have helped the great advances in Se biology of the past two decades years. The ultimate goal of a more personalized nutritional recommendation is closer to being realized than ever before. Nevertheless, more research in this area must be encouraged and be integrated with other omics tools (metabolomics, epigenomic, proteomic and transcriptomic) to better understand all the data provided so far. When strong evidence on the effects of some genotypes on biomarkers of Se status becomes available, it will likely be used to update the current dietary recommendation based on not only the regional particularities but also on the genetic characteristics of the population or even of individuals (personalized nutrition).

Acknowledgments

Author contributions. J.L.S.D. and G.B.S.D. wrote the manuscript with the supervision of M.M.R., P.B. and S.M.F.C. All authors read and approved the final manuscript.

Conflict of interest. The authors declare no conflict of interest.

Funding and support. This manuscript was funded by Brazilian grants from Sao Paulo Research Foundation to J.L.S.D. (Fundação de Amparo à Pesquisa do Estado de São Paulo - FAPESP process: 2011/17720-0, 2013/ 03224-0 and 2015/10146-8).

Table 1 Summary of Selenium dietary reference intake values

Life Stage Group	EAR (µg/day)	RDA (µg/day)	UL (µg/day)	NOAEL (µg/day)	LOAEL (µg/day)
Children and adolescents					
1 – 3 y	17	20	49	90	-
4 – 8 y	23	30	150	150	-
9 – 13 y	35	40	280	280	-
>14 y	45	55	400	800	900
Adults					
19 – 70 y	45	55	400	800	900
> 70 y	45	55	400	800	900
Pregnancy					
14 – 50 y	49	60	400	800	900
Lactation					
14 – 50 y	59	70	400	800	900

EAR = estimated average requirement; RDA = recommended dietary allowance, UL = tolerable upper intake level; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level.³⁴

Table 2 **Observational studies evaluating the effects of functional SNPs on biomarkers of Se status in healthy subjects.**

Country	Population	Plasma Se (µg/L)	SNP	Genotype % and MAF (allele)	Main results	Reference
Sweden	214 adults, age and BMI n.i	n.i	<i>GPX1</i> rs1050450 (C > T)	53/ 40/ 7 MAF (T): 0.27	↔ GPx1 activity with genotypes	Forsberg et al. (2000) ¹¹⁹
USA	115 Asians, 63 Caucasians, 20 Hispanics, 19 Others, adults, 17-21 y, BMI n.i, M= 102, F= 129	n.i	<i>GPX1</i> rs1050450 (C > T)	A: 86/ 11/ 3 C: 46/ 46/ 8 H: 60/ 35/ 5 O: 58/ 21/ 21	No effect of ethnicity on GPx1 activity ↓ GPx activity in males with TT genotype All: 13.16 U/g Hb. Males/females: 2.49/ 2.62 ^a , 2.60/ 2.65 ^a , 2.20/ 2.63* ^a (CC, CT, TT)	Bastaki et al. (2006) ⁸³
Brazil (North Region)	149 women, mean age 26 y, BMI= 22.9	49.7	<i>GPX1</i> rs1050450 (C > T)	58/ 35/ 7 MAF (T): 0.25	↔ Se biomarkers with genotypes	Rocha et al. (2016) ¹²⁰
Brazil (Southeast Region)	116 adults, mean age 28 y, BMI= 23.1, M= 44, F= 72	53.2	<i>GPX1</i> rs1050450 (C > T)	48/ 48/ 4 MAF (T): 0.28	↑ GPx1 activity in females with CC genotype	Donadio et al. (2016) ⁵⁴
			<i>GPX1</i> rs8179169 (G > C)	29/ 70/ 0 MAF (C): 0.35	↓ erythrocyte Se in GC genotype ↑ GPx1 activity in females with GC genotype	
			<i>GPX4</i> rs713041 (C > T)	39/ 45/ 16 MAF (T): 0.15	↑ GPx1 activity in females with CC genotype	
Brazil (Northeast Region)	343 adults, mean age 24y, BMI= 22.8, M= 145, F= 198,	54.0	<i>GPX1</i> rs1050450 (C > T)	52/ 39/ 9 MAF (T): 0.28	↓ GPx1 activity in T-carriers ↑ ORAC levels in T-carriers	Almondes et al. (2018) ¹¹⁵
Poland	405 adults, mean age 57 y, BMI n.i, M= 282, F=	54.4	<i>GPX1</i> rs1050450	48/ 42/ 10 MAF (T):	↓ correlation of GPx1 activity and Plasma Se in TT genotype	Jablonksa et al.

	123		(C > T)	0.31		(2009) ¹²¹
Scotland	66 adults, 20-60 y, gender and BMI not informed	67.6	<i>GPX4</i> rs713041 (C > T)	34/ 41/ 25 MAF (T): 0.45	↔ GPx4 activity with genotypes	Villette et al. (2002) ⁸⁹
Denmark	295 adults, mean age 34 y, BMI n.i, M=134, F= 161	83	<i>GPX1</i> rs1050450 (C > T)	33/ 33/ 34 MAF (T): 0.31	↓ GPx1 activity in females T-carriers	Malling et al. (2009) ⁵⁶
New Zealand	503 males, mean age 52 y, BMI= 26.7	111.6	<i>GPX1</i> rs1050450 (C > T)	48/ 44/ 8 MAF (T): 0.30	↓ correlation between GPx1 activity and serum Se in TT genotype ↑ correlation between GPx1 activity and serum Se in CT genotype ↑ correlation between DNA damage and serum Se in CC genotype	Karunasingh et al. (2012) ⁴⁰
			<i>GPX4</i> rs713041 (C > T)	31/ 48/ 21 MAF (T): 0.45	↑ correlation between Serum Se and GPx1 activity in CT genotype ↓ trend in DNA damage with increasing serum Se in TT genotype	
			<i>SELENOP</i> rs3877899 (G > A)	57/ 38/ 5 MAF (A): 0.25	↓ correlation between GPx1 activity and serum Se in GG genotype ↑ correlation between serum Se and TR activity in GG genotype	
			<i>SELENOP</i> rs5845 (G > A) 1125G>A	63/ 34/ 3 MAF (A): 0.20	↑ correlation between serum Se and GPx1 activity in CC genotype	
USA	195 adults, mean age 64 y, 82% males,	136.6	<i>GPX4</i> rs713041 (C > T)	27/ 48/ 24 MAF (T): 0.49	↔ Se biomarkers with genotypes (GPx1 activity, GPx3 activity, SELENOP, serum Se)	Takata et al. (2012) ¹²²
			<i>SELENOP</i> rs3877899 (G > A)	62/ 32/ 5 MAF (A): 0.21	↔ Se biomarkers with genotypes (GPx1 activity, GPx3 activity, SELENOP, serum Se)	

USA	261 adults, mean age 50 y, BMI= 27.4, M= 106, F= 155	142	<i>GPX1</i> rs1050450 (C > T)	46/ 43/ 11 MAF (T): 0.33	↓ plasma Se in TT genotype All: 142.0 ng/mL. 145.9/ 139.5/ 135.7* (CC/CT/TT)	Combs et al. (2012) ⁶⁶
			<i>GPX4</i> rs713041 (C > T)	28/ 52/ 20 MAF (T): 0.46	↔ Se biomarkers with genotypes (plasma Se, GPx3, SELENOP, buccal Se and urinary Se)	
			<i>SELENOP</i> rs3877899 (G > A)	58/ 45/ 16 MAF (A): 0.23	↔ Se biomarkers with genotypes (plasma Se, GPx3, SELENOP, buccal Se and urinary Se)	
			<i>SELENOP</i> rs7579 (G > A)	44/ 44/ 12 MAF (A): 0.34	↓ Plasma SELENOP in GA genotype All: 3.43 ng/mL 3.62/ 3.24* / 3.49 (GG/ GA / AA)	
			<i>SELENOP</i> rs5845 (G > A)	65/ 31/ 4 MAF (A): 0.19	↓ buccal Se in CT genotype All: 8.39 ng/mg prot 8.77/ 7.65* / 8.27 (GG/ GA / AA)	
			1125G>A			

↔ no association, ↑ increased, ↓ decreased. *: statistically different at p< 0.05. #: number of genotyped samples were smaller than the total N^a: mean log activity.

BMI: body mass index (kg/m²), F: females, GPx: Glutathione Peroxidase enzyme, GPX: Glutathione Peroxidase gene, M: males, MAF: minor allele frequency, nd: not determined, n.i: not informed, ORAC: oxygen radical absorbance capacity, measurement of antioxidant capacity in biological samples, Se: selenium, SELENOP: Plasma Selenoprotein P, SELENOP: Selenoprotein F (former Selenoprotein 15kDa), SELENOP: Selenoprotein P, SELENOS: Selenoprotein S, suppl: supplementation, wks: weeks. Studies are ordered according to plasma Se concentration

Table 3 Intervention trials (Non-RCT and RCT) evaluating the effects of functional SNPs on biomarkers of Se status in healthy adults.

Study design/ Country	Intervention	Population	Plasma Se (µg/L) before/after	SNPs	Genotypes % and MAF (allele)	Main results	References
Non-RCT Intervention trial/ Poland	Supplementation with 200 µg Se yeast a day for six wks + six wks of washout	95 adults, mean age 35 y, BMI= 23.8, M= 43, F= 52	62.6/ 93.8	<i>GPX1</i> rs1050450 (C>T) Pro198Leu	41/ 37/ 22 MAF (T): 0.41	↓ GPx1 activity in TT genotype ↔ plasma Se and SELENOP with genotypes	Jablonska et al. (2015) ¹¹³
				<i>SELENOP</i> rs3877899 (G>A) Ala235Thr	48/ 31/ 21 MAF (A): 0.36	↓ plasma Se in AA genotype at baseline All: 62.6 µg/L. 66.3/ 68.9/ 52.0* (GG/GA/ AA)	
RCT/ Denmark	Supplementation with 1,000 g of raw fish and mussel (50 µg Se/day) for 26 wks	94 adults, mean age 61 y, BMI= 26.3, M= 28, F= 21 (from intervention group only)	84.7/ n.i	<i>GPX1</i> rs1050450 (C>T) Pro198Leu	47/ 45/ 8 MAF (T): 0.30	↓ GPx1 activity in T-carriers at baseline for intervention group ↔ whole blood Se and SELENOP with genotypes	Kopp et al. (2018) ¹¹⁶
				<i>GPX4</i> rs713041 (C>T)	33/ 51/ 16 MAF (T): 0.30	↔ Se biomarkers with genotypes at baseline and after supplementation	
				<i>SELENOP</i> rs3877899 (G>A) Ala235Thr	61/ 37/ 2 MAF (A): 0.19	↑ higher SELENOP and whole blood Se in GG compared to A-carriers at week 26 in the intervention group	
				<i>SELENOP</i> rs7579 (G>A)	49/ 45/ 6 MAF (A): 0.29	↔ Se biomarkers with genotypes at baseline and after supplementation	
Non-RCT Intervention	Supplementation with 100 µg sodium	40 adults, mean age 40y, BMI 68%	90.8/ 107.4	<i>GPX4</i> rs713041	55/nd/ 45 MAF (T): nd	↓ GPx4 activity during washout in TT genotype	Méplán et al (2007,

trial/ England	selenite for six wks and six wks of washout	<25, M= 16, F= 24		(C>T)		↓ GPx1 activity in females TT after 2 wks of washout ↓ GPx3 activity in TT genotype ↓ GPx4 activity in females GA vs males GG ↓ lower SELENOP in females GA vs males GA ↑ higher SELENOP in females GG vs males GG	2008) ^{41,90}
				SELENOP rs3877899 (G>A) Ala235Thr	53/ 53/ 7 MAF (A): 0.20		
				SELENOP rs7579 (G>A)	49/ 43/ 8 MAF (A): 0.29	↑ plasma Se in AA genotype (post suppl. and 2 wks of washout) ↑ SELENOP in males GA vs females GA after supplementation ↑ SELENOP in GA genotype with BMI <25 ↓ GPx3 activity in males AA (pre, post and 2 wks of washout)	
Non-RCT Intervention trial/ Brazil	Supplementation with one Brazil nut (400µg Se) a day for eight wks + eight wks of washout	130 adults, mean age 29y, BMI = 23.3, M= 32, F= 98	96.7/ 267	GPX1 rs1050450 (C>T) Pro198Leu	54/ 40/ 6 MAF (T): 0.26	↓ GPx1 activity in T-carriers	Donadio et al. (2018) ³²
				GPX4 rs713041 (C>T)	38/ 42/ 20 MAF (T): 0.40	↓ Erythrocyte Se in T-carriers at baseline ↑ GPx1 activity in T-carriers during washout period ↑ variation in GPx1 activity in females T-carriers after washout; values did not drop after Se withdrawal in females T-carriers	
				SELENOP rs3877899	54/ 36/ 10 MAF (A):	↓ plasma Se in A-carriers	

				(G>A) Ala235Thr	0.28		
				SELENOP rs7579 (G>A)	38/ 42/ 19 MAF (A): 0.40	↓ plasma Se in A-carriers after 4 wks of supplementation ↑ variation in GPx1 activity in A-carriers after supplementation: GPx1 activity was more responsive to Se supplementation in A-carriers	
				SELENOP rs5845 (G>A) 1125G>A	42/ 46/ 12 MAF (A): 0.35	↓ GPx1 activity in T-carriers during washout period ↓ variation in GPx3 activity in T-carriers after supplementation: GPx3 activity was less responsive to Se supplementation in T-carriers ↓ variation in SELENOP in T-carriers after washout: SELENOP was more responsive to changes in Se availability in T-carriers	
				SELENOS rs34713741 (C>T)	54/ 38/ 8 MAF (T): 0.27	↓ Plasma Se in T-carriers after four wks of supplementation ↑ variation in Erythrocyte Se in T-carriers after supplementation: Erythrocyte Se was more responsive to Se supplementation in T-carriers	
RCT/ USA	Supplementation with 0, 50, 100 or 200 µg of L-SeMet a day for 1y	243 adults, mean age 50 y, BMI = 27.4, M= 98, F= 145	142/ 291.6	GPX1 rs1050450 (C>T) Pro198Leu	46/ 43/ 11 MAF (T): 0.33	↓ plasma Se in TT genotype at baseline All: 142.0 µg/L. 145.9/ 139.5/ 135.7* (CC/CT/TT) ↑ Urinary Se in TT genotype after 3months of supplementation	Combs et al. (2012) ⁶⁹
				GPX4	28/ 52/ 20	↔ Se biomarkers with genotypes at	

rs713041 (C>T)	MAF (T): 0.46	baseline and after supplementation
<i>SELENOP</i> rs3877899 (G>A) Ala235Thr	58/ 38/ 4 MAF (A): 0.23	↔ Se biomarkers with genotypes at baseline and after supplementation
<i>SELENOP</i> rs7579 (G>A)	44/ 44/ 12 MAF (A): 0.34	↔ Se biomarkers with genotypes at baseline and after supplementation
<i>SELENOP</i> rs5845 (G>A) 1125G>A	65/ 31/ 4 MAF (A): 0.19	↔ Se biomarkers with genotypes at baseline and after supplementation

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544 ↔ no association, ↑ increased, ↓ decreased. *: statistically different at p< 0.05.

545 BMI: body mass index (kg/m²), F: females, GPx: Glutathione Peroxidase enzyme, GPX: Glutathione Peroxidase gene, M: males, MAF: minor
546 allele frequency, nd: not determined, n.i: not informed, Se: selenium, *SELENOP*: Plasma Selenoprotein P, *SELENOP*: Selenoprotein F (former
547 Selenoprotein 15kDa), *SELENOP*: Selenoprotein P, *SELENOS*: Selenoprotein S, suppl: supplementation, wks: weeks. Studies are ordered
548 according to baseline plasma Se concentration.

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