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Special article

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Affiliations: *J.L.S. Donadio* is with the Department of Food and Experimental Nutrition, Faculty of Pharmaceutical Sciences and the Food Research Center (FoRC), CEPID-FAPESP, Research Innovation and Dissemination Centers, São Paulo Research Foundation, University of São Paulo, São Paulo, Brazil. *G.B.S. Duarte* and *S.M.F. Cozzolino* are with the Department of Food and Experimental Nutrition, Faculty of Pharmaceutical Sciences, University of São Paulo, São Paulo, Brazil. *P Borel* is with the C2VN, INRAE, INSERM, Aix Marseille Univ, Marseille, France. *M.M. Rogero* is with the Department of Nutrition, School of Public Health, University of São Paulo and the Food Research Center (FoRC), CEPID-FAPESP, Research Innovation and Dissemination Centers, São Paulo Research Foundation, University of São Paulo, São Paulo, Brazil.

Correspondence: *Janaina L. S. Donadio*. Department of Food and Experimental Nutrition, Faculty of Pharmaceutical Sciences, University of São Paulo, Av. Prof Lineu Prestes, 580 CEP 05508-900 São Paulo, Brazil. Tel: + 55 11 2648-6187. (janainalombello@usp.br).

Abstract

Selenium (Se) is an essential micronutrient for human biology that executes its functions as the amino acid selenocysteine via selenoproteins, which have important functions, such as, antioxidant, immunomodulatory, thyroid metabolism and human fertility. Se nutritional status is assessed using the quantification of blood Se biomarkers influenced by several factors, including diet, age, gender, smoking status, alcohol consumption, health condition and genetic characteristics of individuals. 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 (H_2O_2) 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 T_4 into its active form T_3.[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 formation[21].

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 proteins[26]; (3) this population might have a specific gut microbiota profile due to their exposure to high Se that helps excrete the excess Se more rapidly[27]; (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

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

149 A reliable marker of Se intake must to be sensitive to changes in Se status and
150 reflect the current intake through food. It should be noted that plasma Se levels can
151 be used to predict Se intake if SeMet is mostly consumed by using a linear
152 regression equation ($Se_{in,\ \mu g/kg0.75/day} = 0.44 + 0.03 \times Se_{\ plasma,\ ng/mL}$).[24] Food
153 questionnaires can also measure Se intake; nevertheless, the available food
154 composition tables do not address the huge geographical variation of Se content in
155 soil.

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

162 Several factors, such as geographical location, gender, age, race, BMI, smoking
163 status and alcohol consumption, affect plasma Se concentrations. Studies have
164 found a reduction in plasma Se concentration with age,[36] as well as in protein
165 malnutrition,[37] chronic inflammation,[38] in smokers,[39,40] in obese individuals,[39,41] in
166 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 events[58] 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

plasma Se concentrations: GPx1 around 80–120 µg Se/L[61] and GPx3 around 70–90 µg Se/L.[62] In this context, both activities are useful biomarkers of Se status to assess a nutritional deficiency. GPx3 activity varies with age and gender, being lower in adults between the ages of 40 and 49 years and obese females compared to adults of other ages and obese males.[41]

SELENOP acts as the primary Se transporter to peripheral tissues, being the only selenoprotein that can contain as many as 10 residues of Sec and comprises 40–60% of total plasma Se.[4] While the measurement of plasma SELENOP concentration is considered the most conclusive biomarker of Se status, no reference values for it exist.[24,63,64] SELENOP reaches a plateau when plasma Se concentration is around 120 µg Se/L.[52,65] Factors such as ethnicity and BMI affected SELENOP concentrations, for example, SELENOP is reduced in African-Americans[42] and obese adults.[66]

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

THE CHOICE OF SE BIOMARKERS DEPENDS ON THE SE STATUS OF THE POPULATION

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 absorved.[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 Project[72] 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 lipoxygenase 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 indcate 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 cancer[92] and colorectal cancer compare 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

317 genotype.[95] In addition, rs7579 was associated with a higher than average risk of
318 developing prostate cancer.[96]. Moreover, the presence of the rare allele A for rs7579
319 was associated with an increase in *SELENOP* mRNA expression[82,86] and higher than
320 average cholesterol levels after supplementation with Brazil nuts[97], while the
321 presence of the rare allele A for rs3877899 was associated with an increase in
322 *SELENOP* mRNA expression[82] and with lower levels of cholesterol after
323 supplementation with Brazil nuts.[97]

324 The selenoprotein F (*SELENOF*), previously known as 15 kDa selenoprotein
325 (SEP15), has two functional polymorphisms located in the 3' UTR region (rs5845 and
326 rs5859) that are in linkage disequilibrium within the same haplotype, which means
327 that the presence of the rare allele for one SPN implicates the presence of the other
328 one. The first SNP is a G > A substitution at position 1,125 in the apical loop of the
329 SECIS element, and the second one is a C > T substitution at position 811.[98] The
330 variation in the apical loop (rs5845) might influence the efficiency of Sec
331 incorporation into proteins.[99] In vitro studies have verified that the TA haplotype was
332 less responsive to sodium selenite supplementation in NIH 3T3 mouse fibroblasts[99]
333 and mesothelioma cells than the GC haplotype.[100] In addition, the polymorphism
334 rs5845 was associated with a higher risk of lung cancer in plasma Se concentrations
335 below 60 µg/L,[101] an increased risk of colorectal cancer,[102] lower scores for verbal
336 learning memory[103] and a higher histological tumor grade in patients who have
337 undergone radical prostatectomy compared to individuals with the normal
338 genotype.[104]

339 Selenoprotein S (*SELENOS*), located in the endoplasmatic reticulum (ER), is
340 associated with the protection of the ER from the stress that by misfolded proteins
341 cause[105] and with the control of the inflammatory response.[106,107] A substitution C > T

342 occurs in the promoter region of the *SELENOS* gene (rs34713741) that has been
343 associated with an increased risk of rectal,[102] colorectal,[93] and gastric cancer[108] as
344 well as ischemic stroke.[109] Another relevant polymorphism is the rs28665122, located
345 in the promoter region of the *SELENOS* gene, also known as -105G/A. This SNP has
346 been correlated with plasma IL-1, IL-6, and TNF-α levels[106], an increased
347 susceptibility to Hashimoto´s Thyroiditis[110], preeclampsia in Norwegian women[107]
348 and an increased risk of gastric cancer.[111]
349
350 ***Plasma Se***
351 Plasma Se is a short-term biomarker that reflects the current nutritional status
352 of this mineral.[24,112] Since this biomarker is widely used to evaluate Se status and
353 responds to dietary intake, genetic variations that affect plasma Se should be
354 investigated as they can influence the assessment of Se nutritional status.
355 Lower plasma Se concentrations were associated with four SNPs in different
356 selenoproteins (rs1050450 [*GPX1*], rs3877899 and rs7579 [*SELENOP*] and
357 rs3471374 [*SELENOS*) and higher plasma Se with one SNP (rs7579 [*SELENOP*]). In
358 a study conducted with 261 adults from the United States with a mean age of 50
359 years, lower plasma Se concentrations were observed in subjects with the rare TT
360 genotype for the SNP in the antioxidant enzyme GPX1 Pro198Leu (rs1050450).[66] In
361 a Polish supplementation trial that included 95 adults with a mean age of 35 years
362 who were administred 200 μg of SeMet a day for six months, the coding SNP in the
363 *SELENOP* gene (rs3877899) was associated with lower plasma Se only at baseline
364 in individuals with the rare genotype AA.[113] In the SU.BRA.NUT trial, the association
365 of SNPs in selenoproteins with biomarkers of Se status was evaluated in 130 adults
366 after the supplementation with one unit of Brazil nut (~300–400 μg/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 ($\Delta 1_{\text{[8 weeks nuts – baseline]}}$) 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 nuts[86]. A reduction in GPx1 activity was also associated with rs5845 in the *SELENOF* gene in the SU.BRA.NUT trial during the washout period[32] 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 ($\Delta 1_{\text{[8 weeks nuts – baseline]}}$) 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

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

455

456 ***Plasma Selenoprotein P***

457 Plasma SELENOP concentration is considered one of the best biomarkers of
458 short-term Se status and intake.[62] Three SNPs have been associated with a
459 reduction in plasma SELENOP concentration: two on its gene (rs3877899 and
460 rs7579) and one in the *SELENOF* gene (rs5845). In the SELGEN trial, heterozygote
461 females for rs3877899 had lower plasma SELENOP concentrations than GA males.[41]
462 In healthy Americans, GA adults for rs7579 had lower plasma SELENOP than GG
463 and GA genotypes.[66] In the SU.BRA.NUT trial, T-carriers for rs5845 (SELENOF*)* had
464 a lower variation of plasma SELENOP concentration during the washout period ($\Delta 2$
465 $_{\text{[washout - nuts]}}$), which indicates that this biomarker dropped after Se withdrawal, being
466 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).

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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]

528 *Table 2* **Observational studies evaluating the effects of functional SNPs on biomarkers of Se status in healthy subjects.**
529

Country	Population	Plasma Se (µg/L)	SNP	Genotype % and MAF (allele)	Main results	Reference
Sweden	214 adults, age and BMI n.i	n.i	*GPX1* 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	*GPX1* 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	*GPX1* 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	*GPX1* rs1050450 (C > T)	48/ 48/ 4 MAF (T): 0.28	↑ GPx1 activity in females with CC genotype	Donadio et al. (2016)[54]
			GPX1 rs8179169 (G > C)	29/ 70/ 0 MAF (C): 0.35	↓ erythrocyte Se in GC genotype ↑ GPx1 activity in females with GC genotype	
			GPX4 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	*GPX1* 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	*GPX1* 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	*GPX4* 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	*GPX1* 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	*GPX1* 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	Karunasinghe et al. (2012)[40]
			GPX4 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	
			SELENOP 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	
			SELENOF 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	*GPX4* 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]
			SELENOP 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	*GPX1* 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]
			GPX4 rs713041 (C > T)	28/ 52/ 20 MAF (T): 0.46	↔ Se biomarkers with genotypes (plasma Se, GPx3, SELENOP, buccal Se and urinary Se)	
			SELENOP rs3877899 (G > A)	58/ 45/ 16 MAF (A): 0.23	↔ Se biomarkers with genotypes (plasma Se, GPx3, SELENOP, buccal Se and urinary Se)	
			SELENOP 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)	
			SELENOF rs5845 (G > A) 1125G>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)	

↔ 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/m^2), 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, SELENOF: 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	*GPX1* 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]
				SELENOP 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	*GPX1* 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]
				GPX4 rs713041 (C>T)	33/ 51/ 16 MAF (T): 0.30	↔ Se biomarkers with genotypes at baseline and after supplementation	
				SELENOP 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	
				SELENOP 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	*GPX4* rs713041	55/nd/ 45 MAF (T): nd	↓ GPx4 activity during washout in TT genotype	Méplan 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	2008)[41,90]
				SELENOP rs3877899 (G>A) Ala235Thr	53/ 53/ 7 MAF (A): 0.20	↓ GPX4 activity in females GA vs males GG ↓ lower SELENOP in females GA vs males GA ↑ higher SELENOP in females GG vs males GG	
				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	
				SELENOF 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
SELENOP rs3877899 (G>A) Ala235Thr	58/ 38/ 4 MAF (A): 0.23	↔ Se biomarkers with genotypes at baseline and after supplementation
SELENOP rs7579 (G>A)	44/ 44/ 12 MAF (A): 0.34	↔ Se biomarkers with genotypes at baseline and after supplementation
SELENOF rs5845 (G>A) 1125G>A	65/ 31/ 4 MAF (A): 0.19	↔ Se biomarkers with genotypes at baseline and after supplementation

↔ no association, ↑ increased, ↓ decreased. *: statistically different at $p< 0.05$.
BMI: body mass index (kg/m^2), F: females, GPx: Glutathione Peroxidase enzyme, GPX: Glutathione Peroxidase gene, M: males, MAF: minor allele frequency, nd: not determined, n.i: not informed, Se: selenium, SELENOP: Plasma Selenoprotein P, SELENOF: Selenoprotein F (former Selenoprotein 15kDa), SELENOP: Selenoprotein P, SELENOS: Selenoprotein S, suppl: supplementation, wks: weeks. Studies are ordered according to baseline plasma Se concentration.

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