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Review

The critical role of selenium in pathologies: an updated review

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Abstract: Selenium is an essential microelement required for a number of biological functions. Selenium – and more specifically the amino acid selenocysteine – is present in at least 25 human selenoproteins involved in a wide variety of essential biological functions, ranging from the regulation of Reactive Oxygen Species (ROS) concentration to the biosynthesis of hormones. These processes also play a central role in preventing and modulating the clinical outcome of several diseases, including cancer, diabetes, Alzheimer's disease, mental disorders, cardiovascular disorders, fertility impairments, inflammation, and infections (among which SARS-CoV-2). Over the past years, a number of studies focusing on the relationship between selenium and such pathologies have been reported. Generally, an adequate selenium nutritional state – and in some cases selenium supplementation – have been related with improved prognostic outcome and with reduced risk to develop several diseases. The results of recent studies focusing on this topic are summarized and discussed in this review, with particular emphasis to advances achieved in the last decade.

Keywords: selenium; antioxidants; ebselen; GPx; TrxR; inflammation; cancer; covid-19; fertility; gender medicine.

Citation: Barchielli, G.; Capperucci, A.; Tanini, D. The critical role of selenium in pathologies: an uodated review. *Antioxidants* **2021**, *10*, x. https://doi.org/10.3390/xxxxx
Academic Editor: Firstname Lastname

Received: date
Accepted: date
Published: date

1. Introduction

Selenium effects on human health are mainly related to the biological role of selenoproteins, even though some specific effects of different selenium-containing compounds have been described. Glutathione peroxidases (GPxs) and thioredoxin reductases (TrxRs) are involved in the protection against oxidative stress, the main cause of the onset and progression of several pathologies. Furthermore, other selenoproteins influence pivotal biological functions such as Ca2+ signalling, spermatogenesis or brain activity [1-3]. An adequate selenium intake may reduce the risk of developing cancer, au- toimmune diseases, sub-fertility, or mortality risk in severe illness, although some pathologies are due to specific selenoproteins genotypes [4]. However, the possibility of null or toxic rather than beneficial effects of selenium supplementation on human organism has been recently discussed [5-7]. Vinceti and Jablonska warn against the still not investigated effects of an excessive intake of selenium that may result specifically unsafe for the redox homeostasis, with severe effects on the epigenetic regulation of DNA or the gut microbiota. For this reason they even suggest a revision of the WHO RDAs for selenium [5].

While considering these issues, there is a general agreement about the multiple positive roles of selenium on human health, and a general U-shaped non-linear relationship between selenium status and beneficial effects has been suggested. Overall, subjects with low selenium levels at baseline could benefit from supplementation; on the contrary those with an adequate or high status might be negatively affected [8]. In this scenario, the study of selenium-containing small molecules has also received considerable attention. Indeed, a broad range of organoselenium compounds have been demonstrated to possess remarkable biological properties. For example, the benzoselenazole

derivative ebselen – arguably the most studied selenium-containing small molecule – exhibited a wide array of valuable biological functions. Over the past years, the synthesis and the study of synthetic or semi-synthetic selenium-containing derivatives attracted a steadily growing interest amongst organic chemists, medicinal chemists, and biologists [9-17]

Here we reported the main literature results about the relationship between selenium and some of the most important present-days diseases, considering the milestones of research about this topics, with a focus on the most recent results.

2. Cancer

A great interest about cancer chemoprevention by selenium dates back the late 1960s. In 1966 Shamberger and Rudolph showed that sodium selenide (Na_2Se_2) greatly reduced tumour formation in an induced mouse skin tumour model [18]. The anticancer role of selenium was also empirically speculated on the basis of the inverse relationship existing between cancer mortality rates and selenium contents in blood and forage crop in the United States [19,20].

Since 1970, numerous epidemiological selenium supplementation studies and clinical trials supported the "Selenium−cancer hypothesis" linking a low selenium intake with a higher incidence of cancer. The 1996 study led by Clark and Combs on a population of 1312 patients was considered the zenith of this research field, showing that supplementation with 200μg/day of selenium in the form of selenized yeast significantly reduced colon, prostate, and lung cancers in a multicentre, double-blind, randomized, placebo-controlled cancer prevention trial. The selenium supplementation was also showed to significantly reduce the total cancer mortality over a 10 year time period [21]. Since from the first studies, cancer patients showed lower pre-diagnostic serum selenium levels than controls; selenium-treatment reduced tumour yield in animal models [22].

Selenium exerts its chemo-preventive effect primarily by maintaining the correct redox homeostasis and an error-free protein folding, mainly through selenoproteins such as glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs) and selenoprotein P (SelP), that prevent DNA oxidative mutagenic stress [23]. Other functions include the modulation of gene expression, the redox and hormonal regulation of metabolism, and a role in DNA repairing and cell-signalling pathways. Selenoproteins act at different pivotal levels: they inhibit cell proliferation, stimulate apoptosis, and reduce metastasis arresting the cell cycle in the G1 phase, via the redox modification of protein-thiols, and methionine mimicry in critical proteins (Figure 1) [24-26]. Beyond selenoproteins, different metabolites act at different stages for tumour prevention. Methylselenol, generated in the body from inorganic or organic seleno-compounds, is arguably one of the most important among such metabolites [23,24]. Other active selenium metabolites include: i)selenodiglutathione (GS-Se-SG), the reductive metabolite of oxidized inorganic salts (selenite, selenate); ii)selenomethionine (SeMet), a methionine analogue that is the main form of selenium in food; iii) hydrogen selenide (H_2Se), the common intermediate of the reductive pathway and the catabolism of seleno-amino acids; iv) methylated metabolites of selenide such as CH_3SeH (methylselenol), $(CH_3)_3Se^+$ (trimethylselenonium), CH_3SeCys (methylseleno-cyeteine) and CH_3SeO_2H (methylseleninic acid).

Selenolates can be involved in killing cancer cells by the production of superoxide, that drives the cancer cell towards an irrecoverable oxidative status and then to the apoptosis. Selenite and methaneseleninic acid, common forms of selenium in biology, can both oxidize thiol groups of enzymes, leading cancer cells toward apoptosis [27].

Notably, genetics, gender, and modifiable behaviours modulate the impact of selenoproteins allelic variants on carcinogenesis. Particularly, the interaction between genetic factors and the dietary selenium intake seems to be effective in determining cancer risk and outcome, via the metabolism of pivotal selenoproteins such as SelP, SelF, GPx4, and

GPx1 [28]. Some polymorphisms may be associated with the increase of aggressive prostate cancer, breast cancer and colorectal cancer [23].

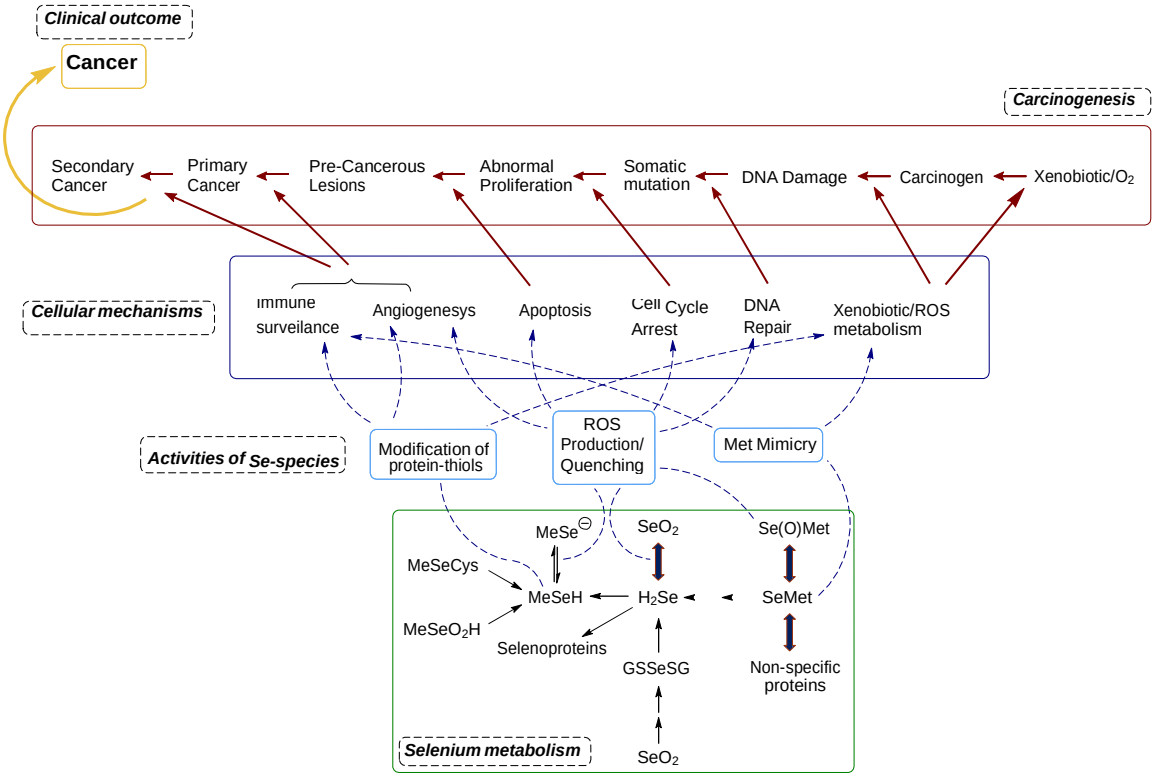

Figure 1. The multiple-stage action of selenium on cancer-related pathways.

Thus, selenium-deficient individuals and those with allelic variants of certain selenoproteins show an increased cancer risk. On the other hand, while GPx2 seems to act preventively at the very early stages of cancer or when carcinogenesis is driven by an inflammatory state, when the cancer cell is already initiated GPx2 seems to support the cell proliferation and the tumour grow, also enabling the metastatic floating cells a better survival [29].

Several randomized controlled trials have been conducted over years in humans to determine the efficacy of selenium in reducing cancer risk, showing conflicting results [22,30]. In the first studies the administration of selenium-enriched table salt proved to be effective against primary liver cancer [31,32] and selenium-containing multiagent supplements were effective against esophageal cancer [33,34], precancerous oral lesions [35, 36], non-melanoma skin cancer [21, 37] and prostate cancer [38,39].

Later researches showed contrasting evidence, as reported by Rayman [2] and other authors [1] that provided a comprehensive discussion of the main results on this topic up to 2012 and 2014 respectively. More recent studies highlighted that low selenium concentration in plasma was associated with 4 to 5 fold increased risk of prostate cancer, in a case-control study that included 318 patients [40]. However this result is in contrast both with evidence from the previous SELECT study [37, 41, 42] and with the results of a 2020 review of randomized controlled trials [43]. Some authors had suggested that divergent results could be primary due to the different specific cancer type considered, as well as to the selenium form and to the initial plasma selenium levels of the participants in the trials [27]. Consistently, a 2018 review of 37 studies conducted in different geographical areas on different cancer types confirmed that selenium supplementation may be protective against cancer but with different effects according to the specific tumour [44].

Selenium optimal doses and physiological status correspond to an antioxidant activity that can be exploited for cancer treatment. For example selenium nanoparticles could be administrated in a very narrow range of concentration in order to avoid potential pro-oxidant effects caused by supra-nutritional doses of selenium [45]. This was also highlighted by Vinceti *et al.*, who recently concluded that the exposure to su- pra-nutritional levels of organic selenium could be related to an increased cancer risk [46]. Vernia *et al.* [47] highlighted the potential benefit deriving from the dietary intake of some microelements, including Se, on colorectal cancer. Furthermore, a very recent meta-analysis on 18 case-control studies investigated the relationship between selenium levels in human tissue and breast cancer risk, highlighting a negative correlation [48]. In this context, a similar study [49] focused on breast cancer in obese patients, showing that decreased levels of selenoproteins in the adipose tissue of obese subjects resulted in an inflammatory state that may progress to cancer.

With reference to thyroid cancer, according to a very recent study [50] the link between selenium and thyroid cancer is inconclusive, because it is still unclear whether low selenium levels are a predisposing factor or a consequence. This is consistent with the results of previous works [51,52] that had already highlighted a poorly significant or no significant effect of selenium supplementation in thyroid cancer and thus the impossibility to establish a cause-effect relationship.

Very recently some experimental studies conducted using HeLa cells (a human cervical carcinoma cell line which contains HPV18 DNA) and mouse models of cervical cancer, either induced by HeLa cell transplantation, MCA (3-methylcholanthrene) exposition or human papillomavirus (HPV) exposition were also reported. Notably, HPV exposition-induced cellular cervical cancer model seems to be the most reliable mimic of the in vivo carcinogenesis process. The results highlighted an anticancer role of selenium nanoparticles (Se-NPs) against HPV and chemical carcinogen agents. Se-NPs enhance the targeting of specific drugs against cancer cells, increasing their effectivity at low doses. Most importantly, Se-NPs were shown to be non-toxic to non-cancer cells [53]. In fact, pivotal differences exist in the oxidative metabolism between tumours and normal tissues. This may represent the target for novel small therapeutic molecules, including selenium-containing derivatives, that simultaneously behave as pro-oxidant in neoplastic cells and antioxidant in healthy cells [26].

COS-Se, a non-toxic conjugated molecule of chitosan oligosaccharide (COS) and selenium recently displayed great potential as a functional food ingredient in cancer prevention. COS-Se inhibited proliferation and metastasis of human gastric cancer cells SGC-7901 with non-toxic effects on the normal fibroblast L-929 in vitro. A supplementation with this molecule could significantly repress the growth of gastric adenocarcinoma through reducing levels of CD34 protein, vascular endothelial growth factor, and matrix metalloproteinase-9. Moreover, a COS-Se treatment could effectively elevate phagocytosis and increase the secretion of anti-inflammatory cytokines. Further experiments showed that COS-Se exhibited immune-enhancing effects in mice models [54].

Novel seleno-derivatives drugs may also be used as alternative potential therapeutic strategy against glioblastoma, the most aggressive primary brain cancer in adults [55]. Additional studies are needed in order to understand the interplay of all the processes described above with individual metabolic differences and to confirm the relationship between selenium concentrations and cancer risk, determining the benefits from increased selenium intake. Particularly, the different tumour stage and the patients characteristics such as sex, age and selenium at baseline need to be taken into account [29].

3. Inflammatory states

Optimal levels of selenoproteins may be clinically beneficial in inflammatory disorders, especially when they have high peroxidase activity. In fact, oxidative stress from reactive oxygen and nitrogen species (ROS and RNS) results in different diseases where

inflammation underlies. Inflammation impairs healthy cells that thus evolve towards degeneration, with the onset of several clinical condition including cancers, atherosclerosis, diabetes, autoimmune disorder, rheumatoid arthritis, pancreatitis, asthma, and neurodegenerative disorders.

The multiple mechanisms underlying the anti-inflammatory role of selenium and their interrelations have been comprehensively discussed by Kaushal *et al.* [56]. Literature reported data focused on the potential role of selenoproteins against ROS and on the relationship between cellular redox state and the activation of cyclooxygenases (COX) and lipoxygenases (LOX). These enzymes are involved in the production of lipid mediators such as prostaglandins (PGs), thromboxanes (TXs), prostacyclins (PGI2), leukotrienes (LT) and oxidized fatty acids, that are well-known biomarkers of inflammation released from tissues and immune cells in response to stress, free radicals, and infections. Such molecules are also involved in the fine modulation of pivotal metabolic signalling pathways as well as in the conversion of pro-inflammatory macrophages M1 to anti-inflammatory macrophages M2 (Figure 2).

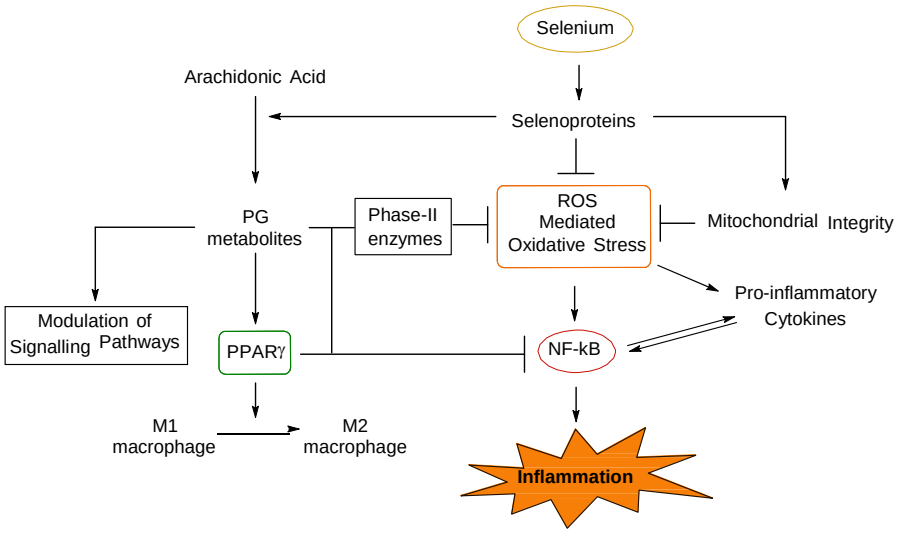

Figure 2. Selenium action on metabolic pathways of inflamation.

Selenium deficiency may cause a reduced GPx activity that indirectly regulates the expression of COX and LOX via the Mitogen-activated protein kinase (MAPK) pathway and Cyclooxygenases-2 (COX-2), by controlling the Nuclear Factor kap- pa-light-chain-enhancer of activated B cells (NF-kB), the "central mediator of immune and inflammatory responses". A number of naturally occurring dietary supplements and nutrients, including selenium, by suppressing such mediators may modulate low-grade inflammation [56] and support anti-inflammatory mechanisms.

High plasma levels of C-reactive protein (CRP), another common biomarker of inflammation, are associated with reduced serum selenium levels [57]. Low selenium levels may further trigger an increased ROS and RNS production up to the Systemic Inflammatory Response Syndrome (SIRS) and sepsis, with extensive tissue damage and organ failure [56,58]. Selenium supplementation reduced the mortality under these conditions [59].

Selenium-derivatives of Celecoxib (Figure 3), a well-known non-steroidal anti-inflammatory drug that selectively inhibits COX-2 activity, have been developed and tested in clinical trials for the prevention of colon cancer [60].These novel molecules act on inflammatory processes that are preliminary to carcinogenesis thus conjugating anti-inflammatory and chemo-preventive effects. Notably, such molecules can be used at extremely low doses, limiting the typical side effects [61].

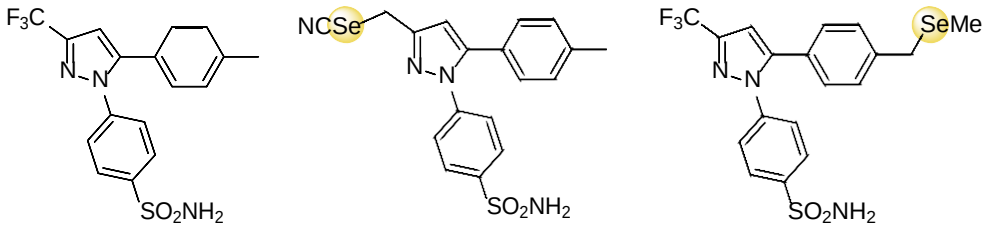

Figure 3. Structures of celecoxib (**I**), selenocelecoxib-2 (**II**), and selenocelecoxib-3 (**III**)

Recent epidemiological studies reported that a selenium deficiency in Inflammatory Bowel Diseases (IBDs) patients [8,62] was related to an increased severity of Crohn's disease and ulcerative colitis. Although IBDs have a multifactorial pathogenesis and different symptom, they share a common chronic inflammatory condition of the intestine. The high expression of the four GPx isoforms in the enterocytes of IBDs patients suggests a compensatory mechanism to reduce the high levels of free radicals produced by immune cells during the inflammatory process, mediated by the transcription factor Nrf2. If adequate levels of selenium are available, Nrf2 can enter the nucleus enhancing the expression of antioxidant genes, including GPxs and TrxRs. These selenoproteins contrast oxidative stress, attenuate inflammatory signalling pathways, and increase the population of anti-inflammatory M2 macrophages, helping patients to extend the remission phase [62].

The possible role of GPx in modulating the effect of inflammation in rheumatoid arthritis patients has been very recently investigated in a review of clinical and preclinical studies. In such a study the authors concluded that it is not clear whether selenium deficiency is a cause or a consequence of autoimmune inflammatory diseases [63]. Overall, the maintenance of an adequate redox homeostasis, also through the nutrients intake, seems to be helpful to prevent or relief the effects of inflammatory diseases.

4. Cardiovascular disease

Oxidative stress impairs the endothelial cells function contributing to the onset and progression of some cardiovascular diseases (CVD). Thus, an adequate intake of selenium may exert a potential preventive effect against non-infectious CVD. Selenium has already been recommended as a therapeutic measure in cardiovascular diseases to block IL-15-dependent epithelial damage and inflammation-linked complications [56]. However several epidemiological studies based on observational data and clinical trials aimed to clarify the relationship between selenium and cardiovascular health, without any conclusive response [1]. A general agreement ascribes the inconclusive results to differences in baseline selenium levels, to the influence of other co-supplemented antioxidants and to the different protocols (supplementation strategies and selenium species used) [64-68].

Experiments focusing on the role of selenium deficiency for cardiovascular diseases (without infectious origin) showed that the association between low selenium intake and cardiovascular pathologies might result from an increased oxidative stress and its consequences [64]. Already 80 years ago a low Se intake was related to a rapidly progressive cardiomyopathy, resulting in extensive fibrosis and degenerative changes, today named "Keshan disease" [64]. The onset of this myocarditis is known to be caused by a coxsackie virus, whose virulence is increased in condition of selenium deficiency and reduced GPx1protective activity [2]. Indeed, the redox active selenoproteins GPxs and TrxRs protect cardiovascular system by preventing or modulating the oxidative stress and the oxidative modification of lipids, reducing inflammation, limiting platelets aggregation,

and maintaining the correct vasoreactivity, that are all main risk factors for coronary and heart failure [2,69] (Figure 4).

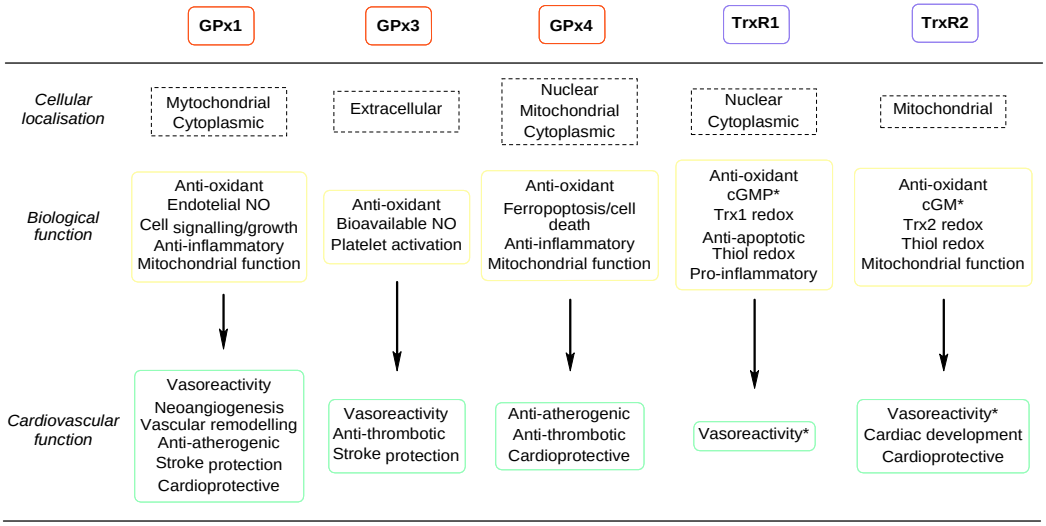

Figure 4. GPxs and TrxRs and their relationships with cardiovascular health. *It is unclear whether both TrxR1 and TRxR2 contributes to this function

Selenium supplementation proved to be effective in reducing the oxidative damage after cardiac ischemia-reperfusion, via an increased GPxs and TrxRs function [70]. Selenium supplements might thus help to maintain the general redox homeostasis and to reduce the risk of cardiovascular disease and associated mortality, as suggested by studies in human subjects. Further investigations are needed in order to better clarify the specific mechanisms of action of the involved selenoproteins.

Iodothyronine deiodinase 1 (DIO1) also plays a role in cardiovascular health: a change in circulating lipoproteins occurs in case of hypothyroidism, with an increase of the atherogenic features. An adequate activity of DIO1 seems to be important for the homeostasis of lipid metabolism [1]. A meta-analysis of 25 observational studies that measured blood or toenail selenium concentrations (14 prospective cohorts, 11 case-control studies) and 6 randomized trials of selenium supplementation [71] had already found a statistically significant moderate inverse correlation between total selenium concentration and coronary heart disease (CHD) risk. People with lower selenium concentrations were found to have a higher risk of CHD, especially in populations with low selenium intake. Increased selenium levels corresponded to a lower incidence of CHD, in particular in subjects with low dietary Se-intake. On the other hand, in subjects who already had an adequate Se-intake, overexposure could cause cardiovascular damage.

A 2017 review and meta-analysis of randomized controlled trials evaluated the effect of selenium supplementation on CHD mortality, blood lipid profile, serum C-reactive protein (CRP), and the level of GPx. This study considered 16 place- bo-controlled and double blinded trials for a total of total of 43998 participants. Selenium supplementation decreased serum CRP and increased the GPx level, thus suggesting a positive effect on reducing the oxidative stress and inflammation that can exacerbate CHD. However, selenium supplementation was not enough for ameliorating the haematic lipid profile or reducing the mortality [72].

With reference to the effects of selenium on haematic lipid profile, the mechanism underlying this connection remains partially unclear [73]. Although selenium may play a crucial role in lipid peroxidation and lipoprotein metabolism, this topic needs to be further investigated [68].

Early data from the French multicenter trial SU.VI.MAX showed no significant impact on ischemic cardiovascular disease incidence from selenium supplementation. Intriguingly, increased triglyceride and lowered HDL-cholesterol levels were found among men but not in women [73-75]. A post interventional study on the same cohort during a 5-year follow-up showed that the total cholesterol and non–HDL cholesterol plasma levels were lower compared with the placebo group [76].

A randomized trial on the UK PRECISE cohort showed a significant reduction of total and non-HDL plasma cholesterol after a supplementation of low and medium doses of selenium. On the other hand, high supplementation increased the HDL-cholesterol, and the total/HDL cholesterol ratio decreased progressively with increasing selenium doses [77].

The BIOSTAT - CHF observational study on 2516 subjects with heart failure showed a strong association between selenium deficiency (<70μg/L in plasma) and mortality or hospitalization, reduced exercise tolerance and poorer quality of life [66].

On the other hand, the cross-sectional analysis on the random Kardiovize urban cohort, including 894 subjects, found no significant association between selenium intake (considered within a composite dietary antioxidant index) and the Carotid intima-media thickness (cIMT). Selenium levels negatively correlated with other cardiovascular risk factors such as Waist to Hip ratio (WHR), body fat mass, (BFM), and total cholesterol/HDL ratio, and positively correlated with HDL-cholesterol. Intriguingly, such association was more significant in women. However , in this context it is worth mentioning that the specific contribution of the different dietary antioxidants to the overall results were difficult to assess [78].

In the NHANES study on 2903 participants, the ones with higher serum selenium levels showed lower rates of general and CVD mortality. The best protective effects were on subjects with a lower cardiovascular risk. Furthermore, while serum selenium was significantly associated with overall mortality in both genders, the relationship with CVD mortality was significant only among females [65].

Lower levels of serum selenium were found in 32 hospitalized patients with chronic heart failure (CHF) with respect to the healthy controls. Additionally, selenium levels showed a significant reverse relationship with left ventricular volume and pulmonary artery pressure [79].

A very recent case–control study investigated the possible association between plasma selenium levels and first stroke risk. A non-linear negative association between baseline plasma selenium levels and stroke risks was found in males but not in females [80]. Similarly a very recent study investigated the relationship between trace elements, including selenium, and aortic valve sclerosis (AVSc), the thickening and calcification of the aortic valve described as the late outcome of a long-lasting inflammatory process. The patients group showed lower serum selenium concentrations compared with the healthy control group [81]. This appears to be consistent with the protection against ROS and RNS that some trace elements, including selenium, normally provide.

Despite the positive results reported above, several observational studies failed in finding statistically significant relationship between selenium concentrations and risk of heart disease or cardiac death. Remarkably association between higher selenium concentrations and globally increased risk of CVD were also found [2,67,82]. In this context, a recent meta-analysis of 16 observational studies and 16 random control trials showed no significant effects of selenium supplementation on cardiovascular events on the considered cohorts. However, a possible inverse and U-shaped correlation between selenium levels and CVD risk was suggested [83]. These findings are in line with results emerged from a comprehensive 2012 review [2]. The general conclusion of studies reported to date is that no further advantages derive by supplementing selenium beyond a certain plasma concentration. Therefore, these results generally do not support the use of selenium supplements for preventing heart disease, particularly in healthy people who already obtain sufficient selenium from food. Additional specific clinical trials are needed

354 to better understand the contributions of selenium from food and dietary supplements to
355 cardiovascular health, in particular for subjects that are Se-deficient.

356 **5. Thyroid disease**

357 Selenium concentration is higher in the thyroid gland than in any other organ in the
358 body. Together with iodine selenium plays an important role in thyroid hormone syn-
359 thesis and metabolism. An inverse association between serum selenium concentrations
360 and thyroid volume, risk of goitre, and risk of thyroid tissue damage was found in people
361 with mild iodine deficiency. However, these results were statistically significant only in
362 women.

363 A study identified a missense mutation of the SECIS-binding protein 2 (SBP2) gene
364 to be responsible for some issues in thyroid function. These dysfunctions cannot be
365 solved through selenium supplementation and they may be due to the decreased activity
366 of iodothyronine deiodinase 2 (DIO2) and to the lack of expression of iodothyronine de-
367 iodinase 1 (DIO1) and iodothyronine deiodinase 3 (DIO3) [84,85].

368 In other endocrine disorders, altered levels of iodothyronine deiodinase (DIO) may be
369 due to a not adequate intake of selenium through the diet: for example, the combination
370 of insufficient selenium and iodine intake seems to be the cause of the endemic myxe-
371 dematous cretinism [86]. Furthermore, a moderate selenium deficiency may be associ-
372 ated with autoimmune thyroiditis. Population with an adequate iodine status but low
373 selenium status are prone to increased prevalence of thyroid disease including Hash-
374 imoto's autoimmune thyroiditis (AIT) [87]. Several interventional studies over the past
375 few years have demonstrated a variable decrease of thyroid-peroxidase antibodies
376 (TPOAb) in patients with AIT or Grave's diseases supplemented with selenium in the
377 form of selenomethionine, selenites or selenated yeasts [56,87]. As recently reviewed by
378 Winther *et al.* other beneficial effects, such as reduced fatigue or reduced pro-
379 inflammatory cytokines, were in some case achieved [87]. Similarly, Ying Zuo *et al.*
380 analysed the results of 17 trials reporting the apparently beneficial effects of selenium
381 supplementation in patients with thyroid diseases, with decreased levels of FT3, FT4, and
382 TPOAb [88].

383 Hypothyroidism is a common occurrence during pregnancy or after childbirth
384 which can have negative consequences for the mother and the newborn. In this context,
385 different selenomethionine supplementation randomized control trials in pregnant
386 women with hypothyroidism and subclinical hypothyroidism were compared [89]. Se-
387 lenium supplementation proved to be effective in decreasing the incidence of moderate
388 to advanced postpartum thyroiditis. Micronutrients deficiency is a common occurrence
389 during pregnancy, that can impairs the correct foetal growth. A very recent prospective
390 cohort study on 1931 pregnant women showed that maternal selenium status during
391 pregnancy appears to be non-linearly associated with thyroid function and low thyroid
392 function with low birth weight [90].

393 In this scenario, further research is needed to better understand whether selenium
394 supplements can effectively support the prevention or treatment of thyroid disease
395 [30,87] both in the general population and in pregnant women

396 **6. Fertility and reproduction**

397 Selenium deficiency causes impaired male fertility in livestock, laboratory animals,
398 and humans. Since the beginning it has been clear that while a moderate selenium defi-
399 ciency impairs sperm motility and morphology (up to the disconnections of head and
400 tail), a severe deficiency completely precludes spermatogenesis [91-93]. The very initial
401 studies with radio-marked ^{75}Se already s. owed that selenium is accumulated in testis and
402 epididymis into several proteins [94,95]. Recently, the high resolution X-ray fluorescence
403 microscope (XFM) allowed a more sensitive characterization of selenium delivery and

use in testis and sperm. These biochemical and histological data are completed by the results of quantitative analysis on biological samples via inductively coupled plasma mass spectrometry (ICP-MS) or atomic absorption spectroscopy (AAS) [93].

The main testis selenoproteins is the Glutathione peroxidase 4 (GPx4), that occurs for about 50% in the keratin-like mitochondrial capsule of spermatozoa and it is highly active in spermatids but inactivated in mature sperm [93,96]. GPx4 was found to reduce phospholipid hydroperoxides and H_2O_2 [1,97], that are involved in protamine sulfoxidation, fundamental for sperm concentration. On the other hand, phospholipid hydroperoxides and H_2O_2 also contribute to oxidative stress negatively affecting the structure and motility of spermatozoa. Thus, GPx4 reasonably performs an extremely fine modulator role for male fertility, protecting sperm cells from oxidative damage during maturation [93]. After reduction with GSH or other thiol reductants, GPx4 is restored in its active form. In addition to the mitochondrial form - mGPx4-, two other forms have been identified: the cytosolic form (cGPx4) [93] and the nucleus form (nGPx4) [98]. Initially it was unclear whether one of these forms in particular was responsible for the role of selenium in male reproduction or not. Specific studies [99,100] suggested that only the mitochondrial isoform is important for male reproduction. A genetic research on 73 men highlighted that GPx4 expression is decreased in about 10% of infertile men and about 35% of men with oligoastehenozoospermia, with significantly decreased sperm motility and spermatozoa concentration [101]. A different study [102] showed significantly lower GPx4 levels in sperm samples from 75 infertile men with respect to the controls. This was also correlated with spermatozoa viability, morphological integrity and forward motility.

An heterozygous mutation was identified in the SBP2 gene, leading to a lower expression of SBP2 in testis, with the arrest of spermatogenesis up to complete azoospermia.[93]. Further investigations also demonstrated that the liver-secreted SelP - the only mammalian selenoprotein with more than one selenocysteine - is an indispensable source of selenium for testis[93].where, as expected, it plays an antioxidant role. Notably, transgenic SelP-null mice were affected by male infertility [103].

Another testis-specific selenoprotein is thioredoxin-Glutathione reductase (TGR or TRxR3) which was suggested to participate in disulfide bond isomerisation during sperm maturation, thus directly affecting male fertility [104].

Additionally, selenoprotein V (SelV) showed testis-specific expression in rodents, where it was found to be locate especially in seminiferous tubules. Although its precise function in spermatogenesis still needs to be clarified, data about its structure, including a thioredoxin-like fold and a conserved CxxU motif, allow to hypothesize a potential redox function. Very recently, SelV was showed to be protective against endoplasmic reticulum stress and oxidative injury induced by pro-oxidants. For these reasons it may be reasonable to hypothesize a protective antioxidant role on sperm [105].

A recent study by Salas-Huetos *et al.* [106] concluded that selenium supplementation in sub-fertile men with low selenium intake significantly increased the sperm quality parameters including sperm motility, semen volume, total sperm count and concentration, spermatozoa morphology, and increased the chance of conception.

Tellez Rojo *et al.* analysed the correlation between selenium intake and pubertal development in a population of 245 male subjects (from 10 to 18 years old). The study highlighted that a consumption of selenium below the RDA was associated with later pubertal development [107].

Nevertheless, also different evidences have emerged. In the Hawkes *et al.* intervention study 42 men were administrated with a high selenium yeast supplement but no effects were observed on the sperm quality parameters [108]. The MOXI multicenter, randomized clinical trial on 171 participants (including oligospermic and asthenospermic men), administrated a part of them with a multi-antioxidant formulation, including L-selenomethionine. Although the sperm concentration increased after the treatment with respect to the control group, no statistically significant differences were detected in the sperm morphology or motility or in the in vivo pregnancy rate. According to this

study, the combined antioxidant treatment did not improve semen parameters; however, the authors suggested that larger trials should be performed to confirm these findings [109]. Furthermore, considering the small number of studies available on this topic, random controlled trials on larger population should be carried out in order to determine whether selenium supplements could affect not only sperm parameters but also the success of fecundation.

The effect of selenium on female fertility has been reviewed by Rayman in 2012 [2]. However, very recent findings on mouse models [110] showed increased ovary levels of SelM mRNA when the animals were administrated with inorganic or organic selenium. Furthermore, the production of blastocysts from oocytes was significantly higher in the Se-supplemented mice. Thus, also on the basis of these novel results, the effect of selenium on fertility represents a research field that surely deserves to be further investigated.

7. Bone and skeleton health

In humans, reduced serum selenium concentrations are associated both with increased bone turnover and reduced bone mineral density with an higher risk of bone disease. Thus, selenium is an essential nutrient for bone health and its role may be linked to the action of specific selenoproteins that maintain the redox cellular balance, protecting bone from oxidative stress and regulating the proliferation and differentiation of bone cells. An appropriate dietary selenium intake may have a potential role in preventing the development of osteoporosis.

Selenoproteins mutations and low selenium plasma levels are typical of skeletal diseases such as the Kashin-Beck disorder and postmenopausal osteoporosis. Selenium levels were positively associated with the bone mass at femoral and trochanteric site and an adequate intake of selenium is inversely related to the risk of hip fragility fractures [111]. However, in this regard some authors suggested that it would be more adequate to evaluate the bone mineral density (BMD) instead of the hip fracture related to selenium levels, because the fracture might be due to different causes from osteoporosis. Additionally, smoking status, drinking status, physical activity level, nutritional supplements, diabetes, hypertension, fibre intake, and calcium intake should be considered together in these patients, because they are all preventing or risk factor for oxidative stress that directly influences the bone health [112].

A recent cross-sectional study analysed the correlation between the hair selenium level, which represents a reliable index to reflect long-term nutrition state, correlation and lumbar spine and femur BMD values in a population of adults. Individuals with lower hair selenium levels showed significantly lower BMDs with a greater increased risk of developing osteoporosis. The study suggests that measuring hair selenium levels may be an easy and quick strategy to be used with patients with osteopenia or osteoporosis in order to evaluate the most appropriate dietetic strategy [113].

In this context, previous studies already highlighted the association between selenium serum concentration and lumbar spine BMD in women in post-menopause who had osteopenia or osteoporosis [114]. Furthermore, a positive association between general lower serum selenium levels and osteoporosis was pointed out. Individuals with lower selenium levels also showed lower femoral neck and lumbar spine BMD values [115]. A recent study compared plasma selenoproteins and selenium levels with BMD values in healthy aging European men. Intriguingly, selenoproteins and selenium levels were positively associated with BMD values, independently from the thyroid function [116].

A negative correlation between dietary selenium intake and the prevalence of osteoporosis was also found out in the general middle-aged and older population in China. The BMD was detected at the phalanges with a compact digital RA system and the evidence extended both to men and women, showing a dose-response trend [112].

On the other hand, some authors observed that an elevated selenium intake might negatively affect BMD in postmenopausal female subjects, depending on the calcium intake levels at the same time [117].

Very recently a randomised, double-blind, placebo-controlled trial [118] was conducted on 120 postmenopausal women with osteopenia or osteoporosis. Half of them were administrated with 200μg/day of selenite. Urine N-terminal cross-linking telopeptide of type I collagen (NTx), a bone turnover marker associated with fracture risk, was measured and serum selenium and selenoproteins levels were also evaluated. While serum selenium and selenoprotein P increased from baseline at the end of the treatment, NTx did not change, when lower levels were expected. However, authors considered that NTx might be a not appropriate marker. With reference to the mechanism for selenium in maintaining the skeletal health, the selenium ROS-reducing role and a possible contrast function against the pro-resorptive osteoclasts were considered.

As already suggested [113], selenium plays a pivotal skeletal maintenance role and possesses antioxidant defence activity in the bone microenvironment, mainly in the form of selenoproteins, that are the essential selenium transporter and are expressed both in bone-resorbing osteoclasts and in bone-forming osteoblasts.

Low selenium and selenoproteins levels correspond to increased intracellular ROS concentrations that, via different mechanisms, inhibit osteoblastic differentiation of bone marrow stromal cells, contributing to the onset of osteoporosis. Additionally, selenium is critical in cell cycle progression and cell proliferation; a selenium deficiency results in G2 cell cycle arrest. Furthermore, it has been postulated that interleukin-6 (IL-6) and some other cytokines play a significant role in the pathogenesis of osteoporosis. Selenium can delay the onset and progression of the disease by exerting an inhibitory action on IL-6 and cytokine activities. Finally, since a selenium deficiency may increase the level of thyroid hormones in the blood, thus accelerating bone loss and osteoporosis genesis, this element is also indirectly related to the skeletal health through this way [113].

8. HIV

Selenium is implicated in the inhibition of viral expression, and in the delay of the progression of AIDS in HIV-positive patients [119,120]. HIV/AIDS is a major health priority worldwide and the development of efficient antiretroviral therapy increased the number of people living with HIV. Nutrient deficits, however, may interfere with the effectiveness of antiretroviral therapy by weakening the immune system that is directly depending on selenium intake. This may be related not only to the role of selenium in immune functions, but also to its activity in modulating the viral expression. Furthermore, as stated above, selenium is involved in the protection against oxidative damage, that is associated both with the chronic infection and with the treatment [121]. Several studies highlighted that HIV infection is typically associated to increased ROS [121,122], with consequent decrease of the major antioxidant nutrients, including selenium [121,123,124].

Antiretrovirals drugs have also been associated with increased oxidative stress and damage [125], especially in human aortic endothelial cells [126,127] which may cause the long-term development of atherosclerosis and coronary heart disease as a side-effect [121]. Thus, supplementation of antioxidants, including selenium, may be an important part of the therapy against the side effect of the treatment.

In HIV-infected children and adults, selenium deficiency has been associated with advanced immune-deficiency [121], disease progression and mortality [128-130]. The significant HIV-related mortality in situations of selenium deficiency supported the importance of maintaining adequate selenium status in HIV infected patients.[129,131-133] The beneficial effects of selenium on immune system have been documented in animal [134] and in human supplementation studies [121]. Selenium status influences HIV dis-

ease progression modulating cytokines expression, interleukin-2 production and phagocytic neutrophils and macrophages ability to destroy antigens.

As stated above, the correct functionality of antioxidant systems also depends on selenium, which also affects the production of tumour necrosis factor-α (TNF-α). Plasma selenium levels were inversely associated with TNF type II receptors in HIV-positive patients [121]. Selenium supplementation in HIV-positive patients has shown benefits on biomarkers of disease progression, morbidity and mortality [121], reducing the viral replication and increasing the Glutathione peroxidase activity in latently HIV infected T-lymphocytes [135,136]. Furthermore, the glutathione peroxidase and thioredoxin reductase 1 activity in macrophages, normally decreased after HIV infection, resulted improved with selenium supplementation [137]. This was speculated to be linked to the activity of glutathione and thioredoxin systems [121]. Indeed, selenium supplementation increased the expression of GPx1 and TrxR1, and also inhibited HIV transcription and replication. This was probably due to the lower oxidative stress levels and decreased expression of the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and pro-inflammatory cytokines, which have a pivotal role in the HIV infection.

Several studies about selenium status and HIV progression observed a direct association between low plasma/serum selenium concentration or erythrocytes GPx1 activity, and a reduced count of CD4+ lymphocytes, with a greater HIV progression and mortality. An adequate selenium status in HIV patients may increase immune defences, thus improving general health and reducing the hospitalization for opportunistic infections [1]. In this context, some randomised controlled trials highlighted the benefits deriving from selenium supplementation in HIV patients, with a significant decrease in the hospital admissions [2].

In a 24-month double blinded, placebo controlled, randomized clinical trial on 300 Highly Active Anti-Retroviral Therapy (HAART) patients, the effect of selenium on the rate of CD4 glycoprotein decline, viral suppression, and morbidity were evaluated. The rate of CD4 decline was reduced by 43.8% in the subject that were administrated with 200μg of selenium a day, with overall beneficial for the immune system [138]. In this regard, another randomized, double-blind clinical trial involved 878 HIV-infected, HAART adult subjects. A daily supplement of 200μg selenium + vitamins significantly reduced the CD4 count decrease with respect to the placebo group, with a minor risk for the clinical manifestations of AIDS-related complications and death.

These results confirm the important role of selenium, even if administered along with a multivitamin, in the maintenance the immune system [139]. Specific trials on HIV-infected pregnant women show neither amelioration on the CD4+ cell count [133] nor decrease in the preterm delivery [140]. However this may be due to the poor baseline nutritional status of the considered patients.

9. COVID-19

The novel coronavirus SARS-CoV-2 (Severe Acute Respiratory Syd- rome-coronavirus-2), causing COVID-19, is by far the most dangerous coronavirus ever identified. It is responsible for a worldwide Pandemic situation whose severity surpassed the past acute respiratory syndrome coronavirus of 2003 (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) of 2012, which were limited to more restricted areas [141].

Despite the recent production of specific vaccines, the global threat deriving from COVID -19 to human health and economy persists, especially considering the diffusion of new variants to the original viral strain. Fast, reliable and safe measures for reducing infection risk, suppressing virulence development, strengthening the immune system, and supporting recovery are needed. Selenium may play a relevant role for most of these issues, having a wide range of protective functions, first of all a complex im- mune-modulator action mediated by specific selenoproteins [142,143].

Many studies have well-documented that selenium deficiency caused an increased host-susceptibility to RNA viral infections and more critical disease outcome up to mortality [143,144].

An analysis of very recent literature about the relationship between SARS-CoV-2 and trace elements provided direct evidence for an association between selenium and COVID-19. An adequate selenium intake is essential for resistance to viral infections, boosting the immune function and reducing inflammation that favors the onset of the infection. Observational studies showed that nutritive supplements administered at an early stage of the infection were important for enhancing the host resistance against RNA viral infections, such as COVID-19. In fact, selenium deficiency supports mutations, replication and virulence of RNA viruses. Selenium has a wide spectrum of pleiotropic effects in COVID-19 disease, restoring the host antioxidant capacity, reducing apoptosis and the effect of SARS-CoV-2 on endothelial cell damages as well as on platelet aggregation. Low selenium status is a common evidence in patients at risk to develop severe COVID-19-related syndrome, especially in vulnerable, obese and elderly patients. Selenium might thus represent a game changer in the global response to COVID-19 [143].

When SARS-CoV-2 virus enters the lung cells, it exploits the cell structures interfering with metabolic and physiologic process. Oxidative stress response arises from such activities and the budding of the virion from host cells further disrupts the cell membrane, causing cell lysis, an enhanced ROS production and the activation of inflammatory signalling pathways. The level of oxidative stress in COVID-19 can be linked with the severity of the disease itself (extension of tissue damage and hyperinflammation). The redox activity of selenium species, in particular low molecular selenium compounds such as methyl-selenol, dimethyl-selenides, (mostly achieved in human body by high selenium intake), selenium nanoparticles, and other selenium containing molecules can stop the viral life cycle by interrupting the replication and transcription. In particular, these processes are due to 3C-like protease (3CLpro) or Mpro (formally known as C30 Endopeptidase), the main SARS-CoV-2 protease that allows viral maturation within the host. Ebselen (Figure 5) was shown to directly inhibit Mpro activity, by covalently binding the sulfhydryl group of the Cys145 residue in the catalytic dyad [142,144].

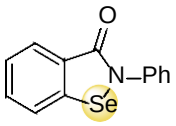

Figure 5. Ebselen

Papain-like protease (PLpro) is another enzyme that SARS-CoV-2 uses to antagonize the host's antiviral innate immune response. Ebselen was found to highly inhibite PLpro through a covalent binding with the sulfhydryl group of the Cys112 residue in the catalytic triad [142].

Some authors suggested that the selenium protective action mechanism could also involve an increased resistance towards the virus induced cytokine release syndrome. Both selenoproteins and redox-active selenium species (such as ebselen and related GPx mimics) could be involved in slowing down virus-triggered oxidative stress, abnormal inflammatory responses and immune-system failure, thus improving the prognosis of SARS-CoV-2 infection.

The administration of antioxidant seleno-derivatives may indeed be pivotal in contrasting the onset or ameliorating the clinical course of COVID-19 infection [142,144]. A nutrition intervention with an adequate supplementation may be protective or coadjutant in COVID-19, especially in vulnerable groups of populations or high-risk areas, such as developing countries [141].

An association of mortality risk with selenium deficiency in COVID-19 patients has also been highlighted. Moghaddam *et al.* conducted a cross sectional study on 39 COVID-19 patients in a German hospital. The researchers found that selenium plasma levels were significantly higher in surviving with respect to non-surviving COVID-19 patients [145]. Furthermore, a significant, positive, linear association was found between the cure rate of Chinese patients with COVID-19 and regional selenium status [142].

As afore mentioned, selenium seems to play a role in COVID-19 disease aggressiveness and positive convalescence. Thus, supplementation could be considered in the most severe cases and in selenium-deficient patients. Although the causality mechanism is still unclear, preliminary observational studies also revealed that selenium status analysis in COVID-19 patients could provide useful diagnostic information, even if the causality mechanism is unknown. Intervention studies should be set in order to clarify the relationship between selenium and SARS-CoV-2 disease, and to define possible preventive measures or adjuvant treatments via selenium supplementation [145].

Heller *et al.* proposed a composite biomarker including Selenoprotein P and zinc as a reliable indicator of survival in COVID-19 and suggested that a personalized supplementation of selenium and/or zinc may support convalescence [146]. COVID-19-associated inflammation has been linked to a reduced expression of many selenoproteins, including glutathione peroxidase, thioredoxin reductase and those involved in controlling endoplasmic reticulum (ER) stress and the expression of interleukin-6 (IL-6) in SARS-CoV-2 infected cells. This is further accentuated in obese patients in which dietary selenium supplementation may help to alleviate the respiratory and inflammatory clinical symptoms [147].

Selenium also plays a role as a NF-kB inhibitor, with consequent im- mune-modulation and anti-inflammatory action [143]. The cytokine release has a nega- tive effect on COVID-19 and, especially in elder people, selenium deficiency is correlated with higher circulating inflammatory cytokines. On the other hand, selenium adequacy prevents excessive cytokine activation in infections and inflammatory models. In some cases high doses of selenium contributed to increase the adaptive immunity and moderate the release of inflammatory cytokines by the innate immune system [142].

A connection between more-than-adequate selenium intake/status and higher cure rate has been highlighted. Daily doses of 1 mg selenium (in the form of selenite) have already been used in sepsis and critical care applications. Preliminary results suggested that the use of selenium should be clinically tested, preferably in randomized controlled trials [142].

Selenite tetravalent cation (Se^{4+}) can be reduced to divalent cation (Se^{2+}), acting as an oxidant. This oxidizing capacity has important implications for its antiviral property. Selenite quickly reacts with sulfhydryl groups in the active site of viral protein disulfide isomerase (PDI), oxidizing and inactivating this enzyme according the reaction showed in Figure 6. In this way the viral hydrophobic spike cannot longer perform the exchange reaction with disulfide groups of cell membrane proteins, and consequently the virus cannot enter the healthy cell cytoplasm [148,149].

On the basis of these results, it seems reasonable to speculate that sodium selenite, a rather inexpensive and readily available molecule, could represent a potential agent for the prevention of viral infections including Coronavirus, according to the mechanism already suggested for other infections such as Ebola, Polio and Influenza virus [149]. Considering that the acute infection phase in COVID-19 is only few weeks long in typical cases, it may be reasonable to consider the same supra-nutritional selenium administration for such a short time, in order to have benefits in patients with moderate-to-severe symptoms, without toxicity risks. The whole potential of this strategy is a preliminary suggestion that would need to be tested clinically to be validated, preferably in a randomized, controlled trial in large cohorts [142,144].

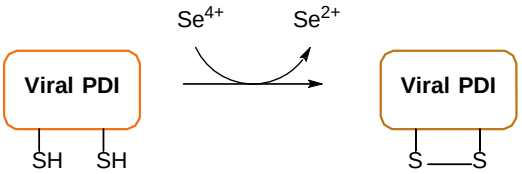

Figure 6. Se(IV)-promoted oxidation of thiol functions of viral protein disulfide isomerase (PDI).

10. Cognitive Decline and Alzheimer's disease

Serum selenium concentrations decline with age and low selenium concentrations might be associated with age-related declines in brain function, reasonably due to decreases in antioxidant activity [150,151]. In this context, studies in areas with low selenium content in soil, such as some regions of rural China, have demonstrated that lower dietary selenium is associated with poorer cognitive function [152].

Kesse-Guyot *et al.* analysed the data of 4447 participants aged 45 to 60 years from the French SU.VI.MAX. study. They reported that the administration of an antioxidant supplement including ascorbic acid, vitamin E, β-carotene, selenium, and zinc for approximately 8 years was associated with higher episodic memory and semantic fluency test scores. However, the independent contribution of selenium to the general observed effects cannot be determined. Kesse-Guyot *et al.* [153]. Similarly, the InCHIANTI cohort study involved 1012 participants aged 65 years or older, whose coordination performance were assessed. The lowers selenium levels were significantly associated with decreased performance in neurological tests [154]. In the French EVA cohort of 1166 people aged 60–70 years a significant increase in the risk of cognitive decline was recorded over 4 years in participants with low baseline plasma selenium [151]. Restoring correct levels of selenium in the body through the diet - via administration of a Brazilian nut per day, containing about 288 micrograms of selenium, for six months - improved the cognitive performance of patients [155].

A cross sectional study including 2016 participants with adequate selenium status provided the first evidence of a sex difference in the association between selenium status and cognitive performance in older adults. Particularly, a positive association between blood selenium concentration and cognitive performance was found in males but not in females [156].

Alzheimer's disease (AD) was described for the first time in 1906 and, despite years of studies, the aetiology of this disorder remains poorly understood. The disease is characterized by the production of extracellular amyloid plaques that spontaneously aggregate into oligomeric forms, and by the presence of intracellular neurofibrillary tangles, formed from aggregates of the protein tau within the large pyramidal neurons [157]. Alzheimer's disease current treatment is only mildly effective in maintaining cognitive function. Early research suggested that different forms of selenium may be effective in the prevention or the treatment of this disorder. Selenium, alone or combined with vitamin E, has been proposed for treating or preventing Alzheimer's disease, primarily because of its antioxidant properties [157]. Although the selenium concentration in the brain is not as high as in other organs, selenium is preferentially retained in this organ under conditions of low selenium intake and it is essential for proper brain function [158]. Owing to the high oxygen utilization and the abundance of oxidizable metals, brain is particularly reliant on antioxidant mechanisms that include several selenoproteins and seleno-compounds [157,159]. In this regards., Seleno-L–methionine was demonstrated to be protective against oxidative stress and against toxicity from β-amyloid in cell culture and in rodent model [157]. Sodium selenite can inhibit amyloid production by decreasing γ-secretase activity [157], while sodium selenate can reduce neurofibrillary tangle formation [160,161]. Recent researches have also suggested the importance of the seleno-

760 protein P (SelP). SelP knock-out had already been shown to increases neurotoxicity
761 caused by amyloid peptides [162]. Additionally, there are evidence about the role of se-
762 lenoprotein P as a signalling molecule associated to the neuronal mechanism of long-
763 lasting memories [157]. Thus, a potential role of SelP in the formation of amyloid
764 plaques and neurofibrillary tangles, as well as in the memory pathways, has been hy-
765 pothesized. In this regard, SelP may behave as a protective agent against AD-related
766 oxidative stress. [157,163].

767 Post-mortem studies on tissue from Alzheimer's patients highlighted that SelP,
768 normally increased in ageing brain, showed a particularly significant increase in amy-
769 loid-beta plaques, neurofibrillary reticles and cerebrospinal fluid. [163,164].

770 Recent studies focused on the role of SelP in Se-delivery to neurons, antioxidant ac-
771 tivity, cytoskeleton assembly, chelation of redox-active metals (copper and iron), and in-
772 teraction with misfolded proteins (amyloid beta and tau protein). Furthermore, a possible
773 involvement in glial activation and brain cholesterol metabolism, related to signalling,
774 has been hypothesised. Future animal model and human-based studies are needed to
775 clarify these topics [165]. The exact mechanism that implicates SelP in Alzheimer's dis-
776 ease has to be further investigated and discussed.

777 With reference to the metal chelation role of selenium, which indirectly protects
778 brain from oxidative stress, recent investigation in in vitro models focused on the Aβ
779 aggregation process. Selenium nanoparticles stabilized with chitosan (Ch-SeNPs) inhib-
780 ited the metal-induced Aβ aggregation, also showing a significant disaggregation capac-
781 ity of Aβ fibrils, and reducing their length and width [166].

782 In Alzheimer's disease, oxidative damage of proteins, lipids, and nucleic acid is
783 particularly relevant in areas of amyloid plaques and in cells with neurofibrillary tangles
784 [167]. Several selenoproteins are important for the mitigation of oxidative stress also in
785 Alzheimer's brain; particularly GPx1, GPx4 and TrxR1 work synergically for the reduc-
786 tion of peroxides, free radicals, and oxidized biomolecules. Moreover, Gpx1 may act as a
787 neruromodulator, impacting on neurodegenerative and neuropsychiatric disorders (not
788 only AD but also PD, schizophrenia and bipolar disorders) as very recently discussed by
789 Sharma *et al.* [168]. Other selenoproteins such as SelP, SelW and the ER residents sele-
790 noproteins K, T, M have been suggested to play pivotal roles in the brain [169]. Seleno-
791 proteins in the brain may act as antioxidants using either glutathione or thioredoxin as
792 substrates. [157] Additionally selenoproteins could be involved in the regulation of ER-
793 Ca2+ flux and balance at the synaptic level and in the degradation of the uncorrected
794 folded protein [169].

795 Proper folding of proteins in the endoplasmic reticulum (ER) is essential for their
796 intended function, and errors in this process require a correction via the Endoplas-
797 mic-reticulum-associated protein degradation (ERAD) system. Early studies already
798 suggested an important role for ER stress in Alzheimer's disease, indicated by the pres-
799 ence of specific markers in Alzheimer's brain [157,170]. ER stress can be triggered by the
800 presence of extracellular amyloid β and, in turn, it can promote the formation of neuro-
801 fibrillary tangles [171]. In this context selenoprotein S has an important role in ERAD
802 and, therefore, a possible preventative role in neurofibrillary tangles formation [172]. On
803 the other hand, considering that calcium has important roles in neuronal signalling, sur-
804 vival, and cell death, loss of calcium regulation may be an important part of Alzheimer's
805 pathology [173,174]. A growing number of selenoproteins have been implicated in regu-
806 lating calcium flux from ER like selenoprotein M that, as previously reported, alters ER
807 calcium signalling in neurons and protects neurons from oxidative stress [175]. Fur-
808 thermore, selenoprotein N expression alters calcium signalling through the calci- um-
809 sensitive ryanodine ER receptors [157]. Selenoprotein T can also alter calcium release
810 from ER deposits in neuroendocrine cells in response to the Neuropeptide polyadenylate
811 cyclase-activating polypeptide (PACAP). Thus, the selenoprotein family appears to have
812 significant importance in ER calcium regulation and homeostasis [176]

Although the potential importance of selenium in AD, investigations about selenium levels in AD patients are very limited, because of the difficulties and variability in living environments and dietary states. This is probably also the main reason for the conflicting and inconsistent results up to date available [177]. A recent systematic review and meta-analysis of 14 studies [178] found a significantly lowered selenium status in AD patients' brains, with the lowest values in the temporal and hippocampal regions, that are pivotally involved in the memory processes. The decreased selenium levels in these areas may play an important role in the pathophysiology of AD.

Mouse model studies provided initial evidence about the beneficial role of selenium supplements in preventing AD and slowing down the progression of symptoms. Ebselen ameliorated memory impairment, hippocampal oxidative stress, apoptosis, and cell proliferation in a mouse model of induced Alzheimer's disease [179]. Selenomethionine restored the structural and functional plasticity of synapses in AD mice [180].

Normally AD patients show significantly lower selenium levels in plasma than healthy people; this may be related to the disease onset through the mechanism discussed above. A multiple linear regression analysis showed that frequent consumption of a nutritional pattern including bread, butter, coffee, cheese, and tinned fish may be associated with increased selenium concentration in the serum of patients with Alzheimer's disease. An adequate consumption of dietary antioxidants including selenium may be a preventive factor [181].

A very recent study on 40 AD patients in different clinical stages and 40 healthy controls found high selenium levels in nail and hair samples from AD patients. The authors hypothesised that the higher selenomethionine in nails and hairs corresponded to a lower selenocysteine concentration in the brain, thus explaining neurodegeneration as a consequence of the impairment of active selenium forms [177]. According Vinceti *et al.*, past case-control studies do not allow a reliable assess of the role of selenium exposure in AD aetiology since they considered data about peripheral selenium exposure (e.g. toenail, hair, serum or plasma levels) and not central nervous system indicator like cerebrospinal fluid [182]. In this regard Vinceti *et al.* recently performed a study focused on the analysis of cerebrospinal fluid (CSF). The results of this study showed that AD risk was inversely correlated with inorganic selenium species and with the organic form bound to selenoprotein P in the CSF. On the other hand, some previous studies had shown no significant differences in CSF and serum selenium levels between AD-patient and control groups [183,184,185].

11. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of pigmented dopaminergic neurons in the substantia nigra, and by the simultaneous presence of intraneuronal protein inclusions called "Lewy bodies". Dopaminergic neurons are particularly vulnerable to oxidative stress, mainly due to their accumulation of iron ions with advancing age. Oxidative stress has been described a major contributor to the development and progression of neurodegeneration at the cellular levels [186-190].

Oxidative stress, in fact, damages intracellular organelles, in particular the mitochondria, impairing neuronal energy metabolism and, as a consequence, neurotransmission and neuritogenesis. Mitochondrial dysfunction trigger apoptosis, calcium release, and opening of Mitochondrial permeability transition pore (mtPTP), leading to the death of neurons, including specific dopaminergic neurons. In turn, the imbalance of dopamine metabolism contribute to the ROS production. Dietary antioxidants, by interacting with ROS, have a significant role in the termination of oxidative chain reactions [190]. In this regard, the maintenance of an adequate antioxidant nutritional status may be a strategy in the prevention or slowing-down of PD.

The biological function of selenium is implemented through selenoproteins, which contain a selenocysteine residue in the active site. Selenium is particularly uptaken by the brain tissue, where it plays different functions, of which is of particular importance the antioxidant one. Selenium deficiency can be a risk factor for diseases associated with oxidative stress, including PD [191]. However, although these premises, it is difficult to state a cause-and-effect relationship between selenium and the pathophysiology of Parkinson's disease. Indeed, the general impairment of the motor system is associated with the overall malnutrition condition and therefore not only to selenium but also to other microelements deficiency that could affect the progression of the disease [192]. A number or recent studies in animal models have suggested that a selenium deficiency could contribute to a greater vulnerability to oxidative stress by dopaminergic neurons. In particular it was observed that a preparatory treatment based on selenium as hyposelenite, before the exposure to parkinsonian neurotoxins, could decrease dopamine depletion of the striated area in a dose-dependent way [193].

On the other hand, a very recent systematic review and meta-analysis of 56 case-control studies highlighted that selenium levels in serum or plasma of PD patients were similar to the controls data; additionally, cerebrospinal fluid (CSF) levels were considerably higher in PD patients [194]. These findings were confirmed also by a later meta-analysis of 11 studies by Zhang *et al.* [195].

According Adani *et al.*, a selenium overexposure in the central nervous system might even be a cause of PD onset rather than a protective factor. Notwithstanding the multiple beneficial properties of selenium for human body (antioxidant activity, regulation of Ca2+ channels, modulation of neurogenesis) it may also exert some adverse effects, especially in case of overexposure, that may lead to neurodegeneration, directly via alteration of mRNA expression of dopamine receptors [194].

As aforementioned for the case of AD (vide supra), the use of CSF samples data instead of blood and plasma data about selenium levels in PD patients was actually supported in recent years by different authors, in order to perform more reliable studies [194-196]. An attempt to determine the different selenium species present in CSF of PD patients was carried out by Maass *et al.*[197]. 75 PD patients and 68 age-matched controls were enrolled; 8 different selenium species were detected in the CSF samples. Only selenoprotein P, human serum albumin-bound Se (Se-HSA), selenomethionine (Se-Met) and an unidentified Se-compound (U2) were shown to have significant quantification values. No significant differences between the cases and controls were found. According this study, the role of selenium neurotoxicity in the onset of PD pathology may thus be not so relevant as previously hypothesized.

An additional interesting point is related to the gut-brain axis; 21.5% of gut microbiota sequenced bacteria express selenoproteins [196]. It has been demonstrated that alterations in the human microbiome represent a risk factor for PD [198]. Thus, the gut-brain axis may have a strong implication in the pathogenesis of Parkinson's disease that is worthy to be further investigated.

12. . Schizophrenia, anxiety and depression

Schizophrenia is a severe neuropsychiatric disorder occurring in childhood, adolescence or adulthood. It is characterized by a heterogeneous mixture of positive, negative and cognitive symptoms such as flat affect, catatonia, impaired attention and memory, hallucinations. This condition is influenced by multiple environmental and genetic risk factors. Several studies highlighted that the nervous system damage possibly connected to schizophrenia pathophysiology may be associated to oxidative stress [199]. In fact, ROS can damage neurons by lipid peroxidation, protein carboxylation, DNA strand breaks, and alter cell signalling cascades which regulate several neurotransmitter systems, resulting in altered dopaminergic, glutamatergic, and GABAergic neurotransmission. Considering that glutathione peroxidases, thioredoxin reductases, and iodo-

thyronine deiodinases are critically involved in the protection mechanisms operating against oxidative stress, an impaired biosynthesis and function of these selenoproteins may contribute to the pathogenesis of schizophrenia [200].

Decreased levels of Glutathione (GSH) in schizophrenic patients were first noted in 1934 [201] and several following studies have documented a correlation between low GSH levels and schizophrenia [202,203] also providing genetic evidence for a link between schizophrenia and impaired GSH synthesis [204]. Significantly reduced GPx activity has been reported in groups of patients with schizophrenia receiving treatment with antipsychotic medication [200, 205]. Furthermore, an inverse relationship between blood GPx activity and structural assessments of brain atrophy has been observed in a population of patients with chronic schizophrenia, suggesting a potential link between redox dysregulation and neurodegeneration [200]. Circumstantial evidence also suggested that altered function of the mitochondrial selenoprotein thioredoxin reductase 2 (TrxR2) may contribute to schizophrenia.

Intriguingly, among the United States population, higher incidences of schizophrenia have been reported in States with low levels of selenium in the food chain [200]. In addition, impaired selenium transport was previously hypothesized to be a risk factor for a subtype of schizophrenia characterized by negative symptoms. This is supported by the reduced platelet and erythrocyte GPx activity in schizophrenic patients [200]. Several studies also highlighted that dopaminergic signalling was related to dietary selenium intake, suggesting a potential indirect relationship with schizophrenia. Indeed, dietary selenium deficiency elevates and extends high potassium-induced dopamine release in the striatum, and increases the turnover rate of dopamine in the substantia nigra, prefrontal cortex, and hippocampus [200]. Furthermore, selenium deficiency up-regulates both tyrosine hydroxylase and dopamine transporter mRNAs in nigrostriatal neurons, with concomitant increases in dopamine synthesis and uptake [206].

Conversely, dietary selenium supplementation reduces the activity of the dopamine catabolic enzyme monoamine oxidase (MAO) that also generates peroxides in a process coupled with the enzymatic activity of GPx1 [200,207]. Collectively, these findings suggest that dietary selenium modulates the turnover and metabolism of dopamine, which may profoundly affect the pathogenesis of schizophrenia.

Recently, a study conducted on 21 schizophrenic patients showing low baseline serum selenium levels highlighted the effect of selenium supplementation. Patients were administrated with 60μg of selenium a day, in the form of selenium-enriched yeast, via a commercially available supplement. After 3 months of treatment the serum selenium levels resulted increased and the patients showed enhanced appetite and improved memory [208].

In 2020 Ma *et al.* reported a case-control study (99 cases, 99 controls) investigating the potential association existing between metal elements, including selenium, and the risk of schizophrenia in China [199]. Consistently with the results obtained by Li *et al.* [208], a decreased selenium concentration in serum was significantly associated with the risk of schizophrenia and the disease severity. Notably, as stated above, [208] a selenium supplementation improves appetite and memory of schizophrenic patients. [199]. According the authors, the suppression of oxidative stress by selenoproteins may exert a neuroprotective role. Moreover, the role of selenium in the dopamine pathways was pinpointed. In the same study, the authors also highlighted that serum selenium concentration was positively correlated with the serum levels of several metabolic biomarkers of glucose metabolism (fasting blood glucose), lipid metabolism, (triglycerides, total cholesterol), liver function (aspartate transaminase, alanine transaminase, albumin and total protein), renal function (blood urea nitrogen, creatinine, uric acid), and blood cell count (red blood cells white blood cells, platelets and haemoglobin). These markers were significantly altered in schizophrenic patients with respect to the healthy controls, suggesting a possible correlation with large-scale metabolic disorders in schizophrenic patients [199].

On the other hand, a 2020 review and meta-analysis of 10 studies with a total of 1784 participants compared blood selenium levels in patients with schizophrenia and healthy controls. The results showed no significant association between schizophrenia and blood selenium levels [209].

In the last years some study also showed that selenium intake and plasma levels could be inversely associated with depression [210-213] and anxiety [214]. This association was also demonstrated for patients with euthyroid nodular goiter independently from the thyroid function [214]. In this context, an "omnivore" nutritional pattern including high selenium levels administrated in a cross-sectional study resulted in a significant protection against depression, psychological distress and anxiety [215].

13. Type 2 Diabetes

Type 2 diabetes (T2D) is characterized by defective insulin secretion and/or insulin resistance. Up to date the relationship between selenium and type 2 diabetes remains only partially understood and mainly controversial. Some early case-control and prospective studies have associated higher selenium levels in the body with a reduced diabetes prevalence and lower hyperglycemia risk. On the other hand, in different cohorts high serum selenium concentrations have been correlated with an increased prevalence of diabetes, higher fasting plasma glucose or no effects at all. Results of the first researches have been reviewed by Rayman in 2012 and, therefore, are not covered by this review [2]. Later systematic review and meta-analysis [216-218] agreed in finding a consistent positive association between the exposure to selenium and the increased risk/prevalence of T2D.

Dubey *et al.* included selenium in their complex analysis about the relationship between trace minerals and diabetes. The authors highlighted inconsistent results between different studies and claimed the necessity of further investigation [219]. The most recent epidemiological and interventional trials focused their attention on the association between high selenium intake and increased risk of T2D [220].

In a cohort of 655 subjects serum selenium status was suggested to be correlated with obesity and type 2 diabetes, reasonably through its effects on signalling pathways [221]. Xiao Long *et al.* analyzed data of 2903 participants from the US National Health and Nutrition Examination Survey (NHANES), highlighting that T2D patients have higher selenium levels compared to the healthy subjects. Notably, the risk association was higher especially in younger women [222]. Similarly, in a large population of Italian adults from Moli-sani study cohort (21335 subjects), a high dietary selenium intake was recently associated with increased risk of hospitalization for diabetes [223]. In our opinion, some of the apparently contradictory findings above discussed might be explained considering a U-shape association between selenoproteins levels and type-2 diabetes risk, depending on the baseline level of selenium intake ad levels.

The biochemical mechanisms that underlie the correlation between selenium and insulin resistance/diabetes are not clearly understood. Selenoproteins may exert their role acting on the insulin signalling as well as on oxidative stress modulation [216,217]. The binding of insulin to its receptor initiates a cascade which induces a mild controlled oxidative burst, where H_2O_2 is a secondary messenger. GPx1, by removing hydrogen peroxide, might thus interfere with this pathway. This was preliminary confirmed by experiments on transgenic mice: those over-expressing GPx1 showed insulin resistance, while knockout models exhibited improved insulin sensitivity. Confirmation in humans derived from the insulin resistance already observed in pregnant women in association with increased erythrocyte GPx1 activity [224] and also from the enhanced insulin sensitivity in patients with global genetic selenoproteins deficiency [225].

On the other hand, an excessive oxidative stress may impair the correct function of pancreatic β-cells and, in this case, antioxidant selenoproteins such as GPxs may have a protective role. The overall insulin regulation, thus require a fine tuning. Other seleno-

proteins are also involved in glucose metabolism, such as TrxRxs that influence positively the insulin signalling pathway.

SelP instead inhibits insulin signalling by inactivating the Adenosine monophosphate-activated protein kinase (AMPK), a positive regulator of insulin synthesis in pancreatic β-cells [1]. Clinical studies in Japanese [226] and Korean populations [227] proved that higher SelP concentrations were associated with insulin resistance and type-2 diabetes, glycated A1C haemoglobin and fasting plasma glucose [226].

14. . A gender medicine approach for selenium-related health?

None of the 25 human genes encoding selenoproteins is located on the Y- or X-chromosome, however women and men differ in several aspects of selenium metabolism. Both selenoproteins and Se-binding proteins activity are regulated in a sex specific way. SelP and ApoER2 are abundantly expressed in male testes while they are marginally present or absent in female ovary and uterus. This pronounced difference may be significant for the differential selenium retention and use in males and females. Up to date, the general available data highlighted that males are more responsive to acute changes in the Se-supply, responding with faster kinetics and stronger amplitude. Men seem also to be more sensitive to the toxic effect deriving from an excessive selenium intake [228]. For these reasons, sexual dimorphism should always be considered when analyzing the results of both observational and intervention studies, together with baseline selenium status and the reference population.

For example, with reference to the cancer risk, the first studies already showed that the preventive effects were different in men and women, being more pronounced in males especially for lung, colorectal and stomach cancer [229-232]. More recently, a different correlation was found for bladder cancer, whose risk seems to be inversely associated to selenium concentration in the body in women, but not in men [228,233,234]. With reference to colorectal cancer, different studies showed opposite conclusions on the best protection to men or women from selenium supplementation [235,236]. Additionally, subfertility and mortality in sepsis have been claimed to be mainly observed in males than in females. Actually, the male reproductive system is more strictly dependent on selenium than the female one; women were underrepresented in the trials for supplementation in sepsis patients.

Selenium-dependent health effects in thyroiditis - and especially Hashimoto's thyroiditis (HT) - are described in females only as well as the associations between selenium status with thyroid volume, goiter, thyroid nodules [237-240]. For cardiovascular disease, results up to date are conflicting. While some studies proved the benefits of selenium supplementation on hearth and coronary health, especially in males, also major side effects (i.e., increased diabetes risk) appear to be male-specific. Other researchers found more positive effects among women or no sex-association. On the basis of these considerations, selenium metabolism and selenium health effects may differ between females and males, and generalizations should not be made across the sexes [4,73,241,228].

Herein we have reviewed recent results that - although males and females differ considerably with respect to selenium metabolism, selenoprotein expression, and medical selenium effects on health and disease - in most cases did not consider gender as a discriminator. The regulation of selenoproteins expression seems now to be not only tissue-specific and age-related but also sex-specific [4]. The levels of selenoproteins mRNA and selenoproteins in different tissues vary between the sexes with specific expression patterns according the selenium status, mainly regulated by controlling the translational aspects [242,243]. Thus, an innovative approach that would take into account the concept of a "gender medicine" [244,245] should also be considered in the setting of future studies aimed at elucidating the relationship between selenium nutritional status, health or disease state and different male or female gender.

15. Conclusions

Selenium is an important microelement involved in a number of biological essential functions. It is mainly up-taken from the diet (including supplements)and it is incorporated in selenoproteins in the form of selenocysteine. The unique features of the selenol moiety of selenocysteine enable selenoproteins to accomplish a wide variety of different biological functions with respect to their sulforated analogues. Selenoproteins are indeed involved in several processes, spanning from biosynthesis of hormones to modulation of oxidative stress. Selenoproteins-mediated biochemical mechanisms also play a central role in the prevention, in the onset, and in the clinical outcome of a wide number of important diseases which, amongst others, include cancer, diabetes, viral infections (including SARS-CoV-2 and HIV), mental and neurological disorders.

Several studies have been carried out in order to elucidate the role of selenium in the prevention and modulation of such pathologies. Herein, we have reviewed these studies, mainly focusing on the last ten years of research. According to the reported data, a positive relationship between selenium status in the body and a favourable prognosis of the above mentioned pathologies has been generally observed. Furthermore, an adequate intake of selenium (from the diet and/or supplements) is crucially involved in the prevention of an array of diseases, particularly those related with thyroid function, fertility and reproduction, skeletal health, inflammatory based diseases and some mental disorders. An optimal baseline serum selenium status has also been suggested to be a favourable prognostic factor for patients with increased risk of developing severe forms of Covid-19. Preliminary supplementation trials have also showed that selenium could be a therapeutic strategy against The SARS-CoV-2 pandemic infection that we are still facing. In this regard the selenium therapeutic potential has also been showcased by the fact that ebselen, a selenium-containing small molecule, exhibited remarkable Mpro inhibitor properties. On the other hand, a potential link between the supra-nutritional exposure to selenium in patients with already optimal status at baseline, and an increased risk of developing some pathologies, has also been suggest. For example a similar behaviour have been observed for some cancers, diabetes, Alzheimer's disease, Parkinson's disease, and cardiovascular diseases.

According to these findings an U-shape for the relationship between selenium status and the onset of disease status could be considered. Additional studies are needed in order to elucidate this point, also providing quantitative parameters.

Different results have been often reported for men and women with regard to the effects of selenium on health. For this reason, future studies should consider sex differences both in the experimental design and in the analyses of the data.

On the basis of all these considerations, a deep comprehension of the biological function of all selenoproteins, as well as the development of selenium containing small molecules as supplements or drug candidates, represent additional challenges ahead in the field of selenium chemistry and biology.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: title, Table S1: title, Video S1: title.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript."Please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

Funding: This research received no external funding.

Acknowledgments: We thank MIUR-Italy (Progetto Dipartimenti di Eccellenza 2018-2022 allocated to Department of Chemistry "Ugo Schiff").

Conflicts of Interest: The authors declare no conflict of interest

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