Original Article

Iodine and Selenium as Antiviral Agents: Potential Relevance to SARS-CoV-2 and Covid-19

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Abstract

Iodine and selenium are linked through their effects on thyroid function. Both also have anti-viral properties relevant to SARS-CoV-2 infection. In the form of povidone-iodine solution, iodine is a virucidal agent that has been shown *in vitro* to kill the coronaviruses SARS-CoV and MERS-CoV, implicated in previous coronavirus epidemics. Viral loads of SARS-CoV-2 are high in the nasal cavity, nasopharynx, and oropharynx. Under *in-vitro* conditions mimicking nasopharyngeal secretions, povidone-iodine solution significantly inactivated SARS-CoV-2, hence some health-care workers in intensive-care units, dental treatment or maxillofacial surgery are using topical povidone-iodine solution, at 0.5%. However, those using topical povidone-iodine solution prophylactically over a period of months might experience adverse effects on thyroid function from exposure to excess iodine, particularly if they have insufficient intake of selenium. Selenium has a protective function on the thyroid; on exposure to excess iodine, too much hydrogen peroxide is produced which is removed by a selenoprotein, glutathione peroxidase. In addition to its protective function on the thyroid, selenium is acknowledged, independently, to combat a number of viral diseases. Observational studies have associated higher selenium status with better recovery from COVID-19 and poorer selenium status is associated with COVID-19 death. *In-vitro* evidence shows that SARS-CoV-2 reduces the expression of selenoproteins that protect against viral disease. It is therefore advisable to ensure adequate selenium intake, particularly in countries with low or marginal selenium status. Finally, for those using povidone-iodine prophylactically in such countries, a modest oral supplement of selenium, such as 100 μg/d, might be advisable.

Keywords

Iodine, Selenium, Povidone-Iodine, SARS-Cov-2, COVID-19, Topical treatment

Introduction

Both iodine and selenium are essential trace elements required in microgram quantities that are known to have anti-viral effects. They are both essential for the functioning of the thyroid and its hormones. Since the advent of SARS-CoV-2, a further synergy between these elements in the potential control of COVID-19, the disease caused by this new virus, has become apparent.

Potential Efficacy of Mouthwashes to Reduce SARS-Cov-2 Viral Load and Transmission

During early COVID-19 disease, the throat and salivary glands were shown to be major sites of viral replication and transmission suggesting that oral antiseptics might be effective anti-viral agents [1]. If so, they would be particularly relevant to oral health-care providers who are at an elevated risk of exposure to COVID-19 due to their proximity to the nasopharynx of patients and the use of aerosol-generating equipment. Thus, Meister and colleagues evaluated the virucidal activity of eight commercially available oral rinses, including recognised antiviral agents such as hydrogen peroxide and clorhexidine, against three

different strains of SARS-CoV-2 under *in vitro* conditions that mimicked nasopharyngeal secretions. In the case of three products, exposure times of 30 seconds were sufficient to inactivate SARS-CoV-2 significantly, supporting the idea that oral rinsing might reduce the viral load in saliva thus potentially reducing transmission [1]. The three effective mouthwashes were Dequonal (active ingredients: equalinium chloride, benzalkonium chloride), Listerine Cool Mint (active ingredients: ethanol, essential oils) and Iso-Betadine mouthwash 1.0% (active ingredient: povidone-iodine). These reduced viral infectivity by up to three orders of magnitude compared to the background level, i.e. with log reduction factors of ≥ 3.11, ≥ 2.78 and ≥ 2.61 for the three strains of

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SARS-CoV-2 [1].

Topical Iodine, Povidone-Iodine, as an Antiseptic Agent against Coronaviruses Including SARS-CoV-2

Of these three mouthwashes, it has been hypothesised that povidone-iodine (PVP-I) at 0.5%, administered as a nasal spray and mouthwash/gargle [2], will kill SARS-CoV-2 *in vivo* in the oronasal cavities and hence may reduce cross infection from patients to healthcare workers and vice versa. Clearly, this may be relevant for hospitalised patients with COVID-19. However, it is potentially just as important in reducing cross-infection from those with asymptomatic COVID infection to healthcare workers who work close to the nose and mouth, i.e. dentists, oral and maxillofacial surgeons, ENT surgeons, ophthalmologists, anaesthetists, and *vice versa*.

PVP-I is a stable chemical complex of polyvinyl pyrrolidone (povidone, PVP) and iodine that contains the I_3^- ion and is able to release elemental iodine on contact with tissues; it is extensively used as an antiseptic in surgical procedures [3,4]. PVP-I has higher virucidal activity than other commonly used antiseptic agents including chlorhexidine and benzalkonium chloride [2]. PVP-I has been shown to be active *in vitro* against coronaviruses that caused earlier epidemics, namely SARS-CoV that was implicated in the SARS epidemic of 2002-2003 and MERS-CoV that caused the MERS epidemic of 2012-2013 [2,5-7].

Numerous *in-vitro* studies have concluded that PVP-I solution, even at concentrations as low as 0.5%, has rapid and effective virucidal activity against SARS-CoV-2; for instance the SARS-CoV-2 USA-WA1/2020 strain was completely inactivated within 15 seconds of contact [1,8,9]. Frank and colleagues have reviewed the literature on the use of PVP-I and have concluded that it can safely be used in the nose at concentrations up to 1.25% and in the mouth at concentrations up to 2.5% for up to 5 months [10]. A number of groups now advocate the use of 0.5% PVP-I solution in healthcare workers and their patients in addition to the recommended personal protective equipment to minimise the risk of spread of COVID-19, [2,11-13]. At the time of writing, two randomised trials had been registered that were aimed at reducing the viral load in confirmed COVID-19 patients; these plan to use solutions of antiviral agents including PVP-I as nasal sprays and oropharyngeal washes [1].

Are There Risks in Using PVP-I As an Oral Rinse and Nasal Spray?

Use of 0.5% PVP-I solution as a nasal spray, mouth-wash and gargle by staff in intensive care units as suggested by Kirk-Bayley and colleagues [2,12] and by Pullen and Croser in dental procedures [13] may run the risk of over-exposure to iodine if used frequently; this could well be the case for healthcare workers who may be tending patients over a period of months or for dental practitioners. The doses of iodine recommended by Kirk-Bayley and colleagues are a maximum iodine intake of 3.52 mg/d for healthcare workers. For healthcare workers or dental practitioners whose exposure is

likely to endure for a longer period, that dose, 3,520 µg/d, is more than three times the US Tolerable Upper Limit of intake of 1,100 µg/d [14] and almost six times the European Food Safety Association (EFSA) Upper Limit of 600 µg/d [15]. Of course, not all the dose will be ingested but a proportion will be, suggesting the need for monitoring of thyroid function in healthcare workers or dental personnel exposed to this level of iodine exposure over a period of many weeks or months. Another factor to be considered is that the kidneys are the major route by which excess iodine is excreted [16] suggesting that such iodine treatment may be contraindicated in anyone with poor kidney function.

Despite the concerns expressed above, there are a number of examples of human exposure to iodine solution by mouth over an extended period that gave no evidence of toxicity [17-19]. For instance, once-daily use of a PVP-I-containing mouth rinse during a 6-month course of therapy, despite resulting in significant iodine absorption (estimated as 6 mg/rinse, though measurements of urinary iodine excretion suggested the lower value of 2-4 mg), showed no evidence of development of thyroid dysfunction [17]. This was despite an apparently quite high concentration in the mouth-rinse, i.e. 5% polyvinylpyrrolidone (PVP-I)-1.5% H_2O_2 mixture (Perimed) or a 5% PVP-I-water mixture [17].

What are the Effects of Consumption of Excess Iodine?

Iodide, needed for the biosynthesis of the thyroid hormones, thyroxine (T4, pro-hormone) and tri-iodothyronine (T3, active hormone) is taken up by the thyroid through the sodium-iodide symporter (NIS) [20]. One or two days of a high dose of iodide inhibits the synthesis of thyroid hormones, a process known as the Wolff-Chaikoff effect, which is an attempt to prevent the thyroid from synthesising excessive quantities of thyroid hormone [21]. This acute inhibition is mediated by the inactivation of the NIS at the plasma membrane and is dependent on the production and activity of reactive oxygen species (ROS) [22]. The inhibitory effect of excess iodide on NIS-mediated iodide transport can be triggered by hydrogen peroxide (H_2O_2) treatment and reversed by ROS scavengers [22]. Indeed, excess iodide has been shown to increase H_2O_2 levels in slices of human thyroid glands [23]. Acute consumption of iodide of as little as one order of magnitude higher than the recommended dose for humans (i.e. 1,500 µg/d *vs.* recommended intake of 150 µg/d [14] can cause the inactivation of the NIS at the plasma membrane [22]. The acute Wolff-Chaikoff effect lasts for some days, but thyroid-hormone synthesis can resume when the intrathyroidal inorganic iodine concentration falls as a result of downregulation of the NIS [21]. However, in some individuals, the escape from the inhibitory effect of large doses of iodide is not achieved and clinical or subclinical hypothyroidism ensues [21].

A lesser level of excess iodine intake than described above, or a rise in intake following iodine fortification of an iodine-deficient population, is known to increase the risk of thyroid autoimmunity, as attested by studies in many countries [24-35]. This is partly because highly iodinated thyroglobulin
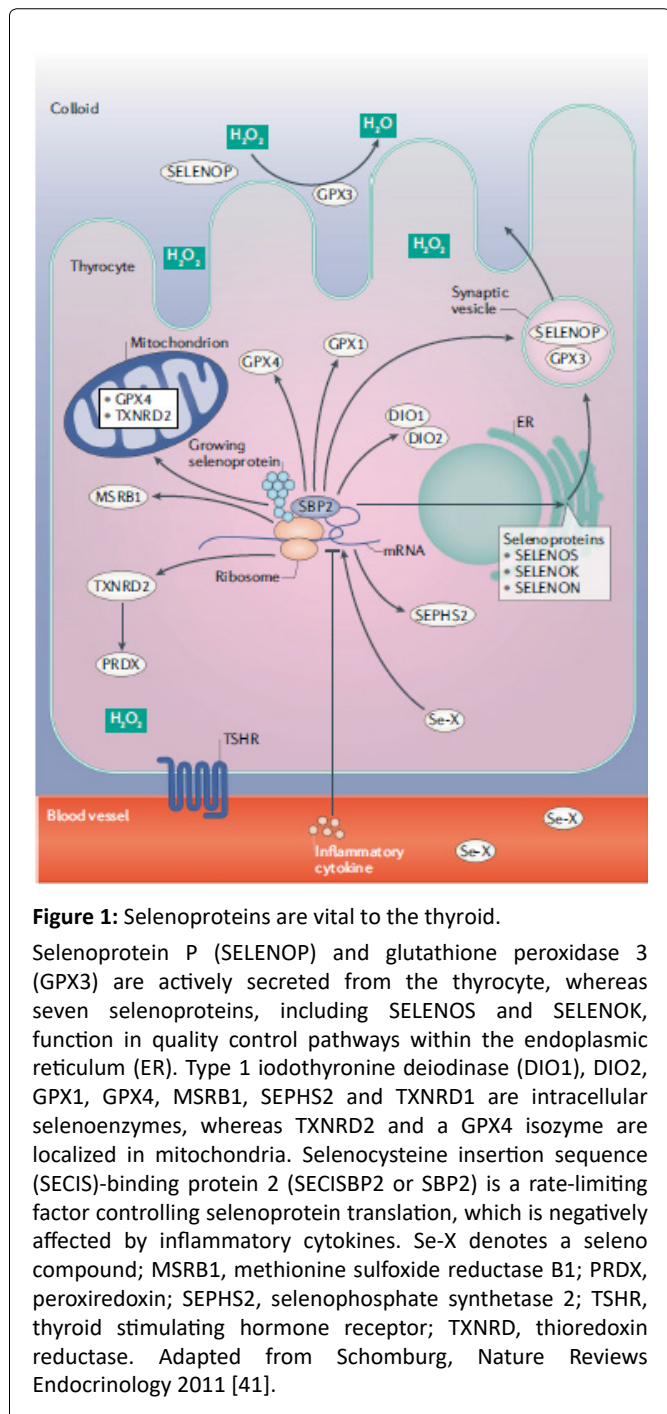
Figure 1: Selenoproteins are vital to the thyroid.

Selenoprotein P (SELENOP) and glutathione peroxidase 3 (GPX3) are actively secreted from the thyrocyte, whereas seven selenoproteins, including SELENOS and SELENOK, function in quality control pathways within the endoplasmic reticulum (ER). Type 1 iodothyronine deiodinase (DIO1), DIO2, GPX1, GPX4, MSRB1, SEPHS2 and TXNRD1 are intracellular selenoenzymes, whereas TXNRD2 and a GPX4 isozyme are localized in mitochondria. Selenocysteine insertion sequence (SECIS)-binding protein 2 (SECISBP2 or SBP2) is a rate-limiting factor controlling selenoprotein translation, which is negatively affected by inflammatory cytokines. Se-X denotes a seleno compound; MSRB1, methionine sulfoxide reductase B1; PRDX, peroxiredoxin; SEPHS2, selenophosphate synthetase 2; TSHR, thyroid stimulating hormone receptor; TXNRD, thioredoxin reductase. Adapted from Schomburg, Nature Reviews Endocrinology 2011 [41].

is strongly immunogenic and may trigger an immune reaction against the thyroid gland [36,37]. An additional factor may be that excess iodine intake increases the expression of the intercellular adhesion molecule-1 on the thyrocyte causing accelerated mononuclear cell infiltration and inflammation [37]. Other likely effects of high iodine intake in susceptible individuals are an increased production of thyroid-infiltrating T-helper 17 cells, inhibition of T-regulatory-cell development and an abnormal expression of TNF-related apoptosis-inducing ligand in thyrocytes, resulting in apoptosis and tissue destruction [38].

Recommended Intake of Iodine for Adults

To reduce the risk of autoimmune thyroiditis, as far as possible, iodine intake should fall within the recommended levels, i.e. for adults, 150 µg/d [14]. The Tolerable Upper Intake Level (UL) of iodine for adults according to the European Food Safety Authority (EFSA) is 600 µg/d [15], though the US Institute of Medicine has set the Tolerable Upper Limit at the higher value of 1,100 µg/d [14]. Higher intake than that is not recommended and may cause thyroid dysfunction [14].

Protective Effect of Selenium in Excessive Iodine Intake

Selenium (Se) is of vital importance to thyroid health and protection [39]. Of all tissues, the thyroid gland contains the highest Se concentration in the human body, largely independent of the Se content of other organs [20]. The thyroid contains a large number of selenoproteins (Figure 1) [40,41]; extracellular glutathione peroxidase (GPX3), additional GPX family members (GPX1, GPX4), and several other selenoproteins are expressed in thyrocytes, in particular the thioredoxin reductases, TXNRD1 and TXNRD2, the iodothyronine deiodinases, DIO1 and DIO2 (which convert T4 to T3), SELENOF, SELENOP, SELENOM and SELENOS, the last of which reduces the inflammatory response in the thyroid [40,42,43]. The incorporation of iodide into thyroid hormones is catalysed by the haemoprotein, thyroid peroxidase (TPO), which uses H_2O_2 as co-substrate [20]. TPO catalyses both the iodination of tyrosyl residues of thyroglobulin and the H_2O_2-dependent coupling of iodinated tyrosyl residues to generate the iodothyronines, T4 and T3 [20]. When iodine intake is greater than requirements, the NIS is inhibited by production of ROS such as H_2O_2 at the plasma membrane, as explained above [22]. H_2O_2 builds up in the colloid lumen, as it is not being utilised for thyroid-hormone synthesis and can cause thyroid damage [22]. The high expression of the selenoprotein, GPX3, in thyrocytes and its secretion into the closed and protected colloid lumen (Figure 1) can remove H_2O_2 there [20]. However, additional precautions are required to protect both the cell membrane and the intracellular compartments from any H_2O_2 diffusing into the thyrocytes [20]. Selenoprotein involved in these functions are the GPX1 and GPX4 isozymes and the selenium dependent TXNRD enzymes [20].

There is evidence from cell culture, animal and human studies that Se protects the thyroid from excessive iodine exposure. Leoni and colleagues examined the effects of high iodide doses in rat thyroids and in PCCl3 thyroid cells from 0-72 hours following iodide administration [44]. The increased production of ROS led to an increase in TXNRD mRNA levels and enzyme activity which reduced the oxidative stress. Inhibition of TXNRD at either gene expression or activity levels prevented NIS recovery [44]. Besides its effects on NIS, the antioxidant role of TXNRD after excess iodide administration seems to be crucial for re-establishment of thyroid homeostasis and the recovery of thyroid hormone biosynthesis [44].

In a situation of more-than-adequate iodine intake such as currently exists in China following the introduction of Universal Salt Iodisation [24], higher serum Se [median (IQR) 103.6 (79.7, 135.9) *vs.* 57.4 (39.4, 82.1) µg/L] was shown to be associated with significantly lower odds [OR (95 % CI)] of hypothyroidism 0·75 (0·63, 0·90), subclinical hypothyroidism 0·68

(0·58, 0·93),enlarged thyroid (0·75 (0·59, 0·97) and, most notably, of autoimmune thyroiditis [0·47 (0·35, 0·65)] [45]. The most common form of autoimmune thyroiditis (Hashimoto's thyroiditis) is defined by the presence of antibodies to thyroid peroxidase (TPO), the thyroid enzyme that oxidises iodide to iodine for thyroid hormone synthesis [39]. Numerous studies, though not all, have shown a reduction in TPO-antibody titre on Se supplementation [40,41].

Independent Relevance of Se to Viral Diseases

Apart from the fact that adequate Se intake or status appears to protect against excessive iodine intake (most particularly by removing excessive H_2O_2 that can build up in the thyroid in iodine excess [20], Se is an important anti-viral factor in its own right as explained below.

Significant clinical benefits of Se supplementation have been demonstrated in a number of viral infections, as reviewed previously [46,47]. These include most notably, cocksackie B3 and Keshan Disease, named after the area in northeast China where it was endemic [48]; when the population was supplemented with Se, the incidence of Keshan-disease fell dramatically [49,50]. Other examples are HIV-1, where a negative correlation between Se status and mortality has been established [50,51], in liver cancer linked to hepatitis B [52], and in patients with "epidemic haemorrhagic fever", that was successfully treated with oral sodium selenite, giving an overall 80% reduction in mortality [46,53]. From the above data it appears that Se intake or status is relevant to a number of evolutionarily distinct viruses, *via* potential immunomodulatory effects that are fully consistent with the many essential roles of Se in the immune system [49] and its ability (especially in deficiency) to influence viral mutation and evolution [48].

Relevance of Se or Selenoproteins to SARS-CoV-2 Infection and COVID-19 Disease

There is already some evidence for a link between SARS-CoV-2 infection and selenoproteins; infection of cultured Vero E6 cells with SARS-CoV-2 significantly reduced the expression of a number of selenoproteins (GPX4, TXNRD3, and the endoplasmic reticulum selenoproteins, SELENOS, SELENOK, SELENOF, SELENOM) while increasing the expression of the inflammatory cytokine, IL-6 [54]. Concomitant down-regulation of *SELENOF*, *SELENOM*, *SELENOK* and *SELENOS* by SARS-CoV-2 is likely to result in increased concentration of misfolded proteins in the ER and catastrophic ER stress. A direct mechanistic link between the reduced expression of *SELENOS* and the production of inflammatory cytokines has already been well documented [43]; such a mechanism may be relevant to the marked elevation of IL-6 concentration induced by SARS-CoV-2 [55].

Our group analysed COVID-19 cumulative data on the specific date of 18 February 2020 in Chinese cities and found a significant association between cure rate and population Se status in cities outside Hubei province (of which Wuhan is the capital); $R^2 = 0.72$, F-test p < 0.0001 [56]. On inspection of the Hubei data, it was notable that the cure rate in Enshi city, renowned for its high Se intake, at 36.4 %, was much

higher than that of other Hubei cities where the overall cure rate was 13.1%; indeed, the Enshi Cure rate was significantly different from that in the rest of Hubei (p < 0.0001). Similar inspection of data from provinces excluding Hubei showed that Heilongjiang Province in north-east China, a notoriously low-Se region, had a much higher death rate (2.4%) than that of other provinces (0.5%); p < 0.0001. We were also able to show in our analysis of cure rate *vs.* Se status in Chinese cities, that the cure rate reached a maximum (60%) at a status corresponding to an intake of 188 µg/d [56].

Reinforcing our observed association between Se status and outcome of COVID-19 disease is a German study that found a pronounced deficit in total serum Se and SELENOP concentrations in COVID-19 patients when compared to reference data from a large European cross-sectional study [57]. Se status was significantly higher in samples from surviving COVID patients than from non-survivors (Se, 53.3 ± 16.2 *vs.* 40.8 ± 8.1 µg/L; SELENOP, (3.3 ± 1.3 *vs.* 2.1 ± 0.9 mg/L) [57]. Of course, being an observational study, causality cannot be inferred. Indeed, the low Se status associated with severity could reflect reduced expression of *SELENOP* by inflammatory cytokines under acute-phase conditions [57]. However, the exceptionally low level of serum Se reached will inevitably have adverse effects on the concentration of protective selenoproteins which, according to Moghaddam and colleagues [57], argues for the potential relevance of some supplemental Se support in severe COVID disease.

Current Selenium Status in Different Countries

Se status varies markedly across the world. Recommended levels of intake vary between authorities and are largely based on the intake believed to maximise the activity of plasma GPX (GPX3) (though it is now recognised that that intake is insufficient to optimise plasma SELENOP, the selenoprotein that transports Se from the liver to other tissues). The US Recommended Dietary Allowance (RDA) is 55 µg/d for adults [58] while UK recommendations (Reference Nutrient Intake, RNI) are 75 µg/d for adult men and 60 µg/d for adult women [59]. Much of Europe does not meet these recommended intake levels; for instance, the most recent UK National Diet and Nutrition Survey (2014 -2016) found that 47% of women and 25% of men did not even reach the Lower Reference Nutrient Intake (LRNI, enough for only 2.5% of the population) of 40 µg/d [59,60]. (Figure 2) shows the Se intake in different countries and also the level of intake believed to be required to optimise plasma GPX3 activity [58,59] and that required to optimise SELENOP concentration [61]. Inspection of the figure will allow individuals to have some idea of their likely Se intake or status. However, clearly this will vary markedly from one person to another depending on whether rich sources of Se are eaten (seafood, meat and poultry in Europe and additionally cereals and grains in N America) [50]. Brazil nuts are a rich but very variable source of Se [50].

Proposed Addition of Oral Se Supplementation to those Using PVP-I Prophylactically

For the reasons explained above, i.e., i) protection of the thyroid from exposure to excess iodine and, ii) the potential efficacy of Se in counteracting viral diseases, including
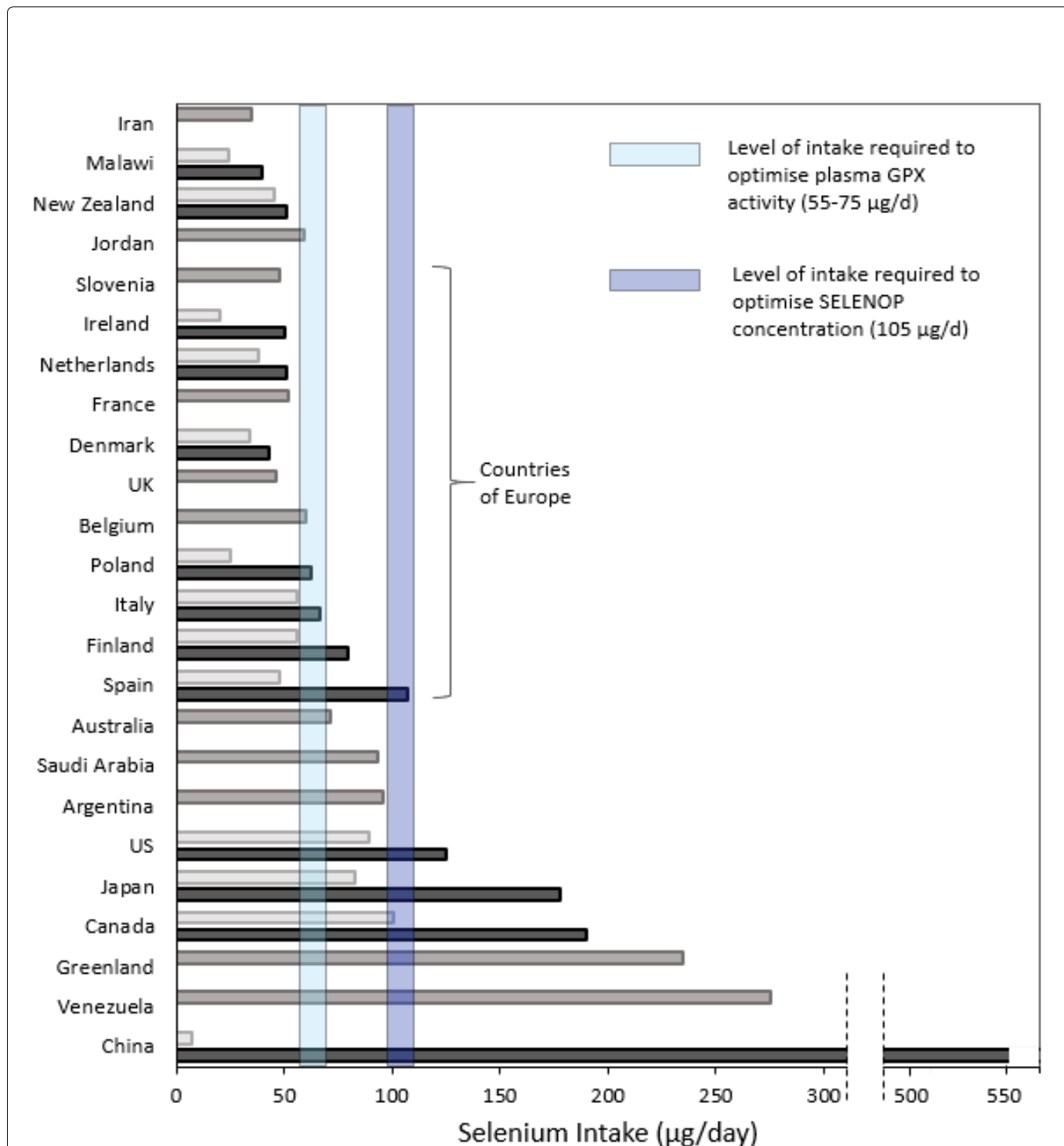
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Figure 2: Selenium intake in different countries based on data published since 2000.

Where countries had more than one result, the highest value (dark grey) and the lowest value (pale grey) are shown. Where there was only one result, it is shown in mid-grey. Dietary intake data are only estimates and are recognized to be of variable quality and accuracy. (The figure for Venezuela is pre-2000 but is included as the value is notably high.) The turquoise band shows the level of intake believed to be required to optimise plasma GPX3 activity [58,59] and the blue band shows that required to optimise SELENOP concentration [61]. GPX, plasma glutathione peroxidase; SELENOP, selenoprotein P (adapted from [40] with permission).

COVID-19, it is suggested that medical personnel, dental practitioners and patients frequently using nasal/throat sprays of PVP-I should be supplemented with Se at a dose that would achieve a total intake associated with a good cure rate, such as 100-200 µg/d. The relevant supplementary dose must take the background intake into account as this will vary accord-ing to location (Figure 2). The proposed maximum dose (200 µg Se/d) is not toxic, indeed it is consumed naturally in some parts of the world [40] (Figure 2). The Safe Upper Limit of Se intake has been defined as 400 µg/d [58].In a randomised, controlled trial in Denmark, which has only a marginally suffi-cient Se status, a dose of 200 µg Se/d was given for five years

to healthy elderly volunteers with no adverse effects compared to placebo [62].

A meta-analysis of 19 randomized controlled trials concluded that high-dose Se (upwards of 500 µg/day), as sodium selenite, reduced the risk of all-cause mortality of critically-ill patients by 14% (RR 0.86; 95 % CI 0.78, 0.95; p = 0.002) [63]. Further findings revealed that Se shortened the length of hospital stay by an average of 2.3 days. Supplementation with high doses of Se did not lead to an increased occurrence of side effects (RR 1.04; 95 % CI 0.83, 1.30; p = 0.73) [63].

There may be some question as to whether some patients or health-care workers should be assessed for their Se status before being given Se supplementation. This would be problematic insofar as it would delay supplementation by at least a week. Furthermore, with regard to COVID-19 patients, there is likely to be a systemic inflammatory response (as shown by increased C-reactive protein, IL-6 and other inflammatory cytokines [55], in which case, plasma/serum Se will fall owing to a reduction in SELENOP expression. In this situation, measurement of plasma Se or SELENOP will not reflect true (baseline) status. Erythrocyte Se, which is unaffected by the inflammatory response, can be measured to determine status [64] however, it is not a standard measurement in hospital trace-element labs. There is certainly no risk to supplementation up to 200 µg Se/d for a limited period and indeed no evidence that such a level of supplementation is dangerous over a period of five years at the relatively low background Se status that is typical in Europe [62].

It would seem that prophylactic treatment with PVP-I spray (0.5%) to the nose and throat followed by gargling is a strategy worth considering for anyone likely to be exposed to SARS-CoV-2 and particularly for those treating COVID-19 patients, given the safety of such treatment [65]. However, whether the PVP-I spray is effective against SARS-CoV-2 *in vivo* will have to wait for the outcome of the trials that have been registered and are hopefully underway [1].Combining with a daily supplement of 100-200 µg of Se (according to location), preferably in the form of sodium selenite which does not build up in the tissues [62] may be beneficial and is unlikely to cause harm in the short-to-medium term. To the author's knowledge, no randomised trial that will test Se against SARS-CoV-2 or COVID-19 has been initiated, though the author and colleagues have designed a trial protocol.

Acknowledgement

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