Selenium and RNA viruses interactions: Potential implications for SARS-Cov-2 infection (Covid-19)

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Abstract:

SARS-Cov-2 is an RNA virus responsible for the Covid-19 pandemic which already claimed more than 215,000 lives worldwide as of April 28, 2020. Selenium has a key and complex role in the immune system. It is very clear that selenium deficiency is associated with higher susceptibility to RNA viral infections and more severe disease outcome. We present here how selenium deficiency promotes mutations, replication and virulence of RNA viruses. Selenium might be beneficial via various mechanisms including virus-host cell attachment interaction, restoration of host antioxidant capacity, anti-inflammatory and anti-clotting effects, to name a few. Selenium has been overlooked but probably has a significant place in Covid-19 management, especially in the elderly, and might represent a game changer in the global response to Covid-19.

Key words: Selenium. Sodium selenite. Covid-19, SARS-Cov-2, RNA viruses

Introduction

SARS-Cov-2 is responsible for the Covid-19 pandemic which already claimed more than 215,000 lives worldwide as of April 28, 2020. It is an RNA virus whose complex metabolism remains comparable to the RNA viruses responsible for epidemics such as Influenza virus, some hemorrhagic fever viruses (such as Ebola virus or Hantavirus) or Coxsackie virus. In addition to the more obvious respiratory symptoms, secondary symptoms that are now known to contribute to Covid-19 associated morbidity and mortality include heart problems like myocarditis (a primary feature of Coxsackievirus infection) and systemic blood clotting (a feature of hemorrhagic fever viruses).
We present here, firstly, a brief review of how selenium deficiency promotes mutations, replication and virulence of RNA viruses and secondly, the mechanisms by which selenium could act in SARS-CoV-2 infection.

Method

The current literature was searched using PubMed and Google Scholar for articles containing the terms Covid-19 or SARS-Cov-2 or RNA viruses and Selenium. Grey literature was searched using the same terms using BioRxiv-MedRxiv, Preprints, ResearchGate and Figshare and Preprint Archive Search.

Selenium deficiency promotes mutations, replication and virulence of RNA viruses, and Selenium has clinical benefit in RNA viral infections

- Coxsackie virus

More than twenty years ago Beck and Levander demonstrated that a usually mild Coxsackie virus could become highly virulent in selenium deficient mice (1-4). Keshan disease in China is a spectacular illustration of this. It is an acute myocarditis of viral origin (Coxsackievirus) occurring in a well-known geographic belt of China deficient in selenium (Northeast / Southwest). At one time responsible for thousands of deaths each year, this viral disease has almost disappeared with the increased intake of selenium.

- Hantavirus

Hantavirus (in the RNA Bunyaviridae family) can cause hemorrhagic fever with renal syndrome (HFRS) that is a group of clinically similar illnesses including Korean hemorrhagic fever, epidemic hemorrhagic fever, and nephropathia epidemica.
(https://www.cdc.gov/hantavirus/hfrs/index.html)
In China, the incidence of HFRS is six times higher in selenium-deficient geographic areas. Viral replication is also higher in the event of selenium deficiency (5). The intake of selenium was also found to significantly inhibit the replication of the Hantavirus at low viral titres (5).

Significantly, Hou et al observed an 80% reduction in mortality in a study including 80 patients with Hantavirus epidemic hemorrhagic fever treated with a short 10-day course of high dose sodium selenite (6). Combined with the results of the 2015 study cited above, this is an important precedent showing that, like Keshan disease/coxsackievirus, a virus that

shows increased incidence or severity in low selenium regions responded clinically to a therapeutic intervention with a selenium compound.

- Influenza virus

During the H1N1 influenza pandemic, Moya et al (7) showed that their group of patients with H1N1 pneumonia was more deficient in selenium than the group which served as a control (non-H1N1 but presenting influenza-like illness). In addition, patients with H1N1 pneumonia who had a blood selenium level considered to be optimum for normal Glutathione Peroxidase (GPx) activity recovered faster and had a better survival rate compared to the patients with H1N1 pneumonia but with lower selenium levels.

Data in mice infected with the H1N1 virus and fed with either a selenium deficient diet or supplemented with selenium are striking: 75% mortality in selenium deficient mice vs. 25% in selenium supplemented mice (8). Similarly Nelson et al showed that in selenium deficient mice, increased viral mutations in the influenza virus A/Bangkok/1/79 (H3N2) genome were observed, resulting in a more virulent phenotype (9). Indeed, mice deficient in selenium and infected with H3N2 had more severe pulmonary histological damages than infected mice without selenium deficiency.

- Human Immunodeficiency Virus Type 1, HIV-1

Unlike the above examples, in which the incidence, virulence or outcome of a viral infection was shown to correlate with selenium status in specific geographic region, multiple reports over decades have shown that disease progression or mortality risk in HIV/AIDS is correlated with selenium status in specific cohorts (10, 11). In addition, a therapeutic benefit of selenium supplementation has been demonstrated in a number of clinical trials (12-15). Even in the case of HIV-1, one study was able to associate AIDS-related mortality in the US African-American population as of the year 1990 with selenium status based on forage crop selenium data (ranked as low, medium and high) in the various US States (16)

- Coronavirus SARS-Cov-2

A recent epidemiological study by Zhang et al shows striking data comparing recovery rates from Covid-19 in 17 Chinese cities with population selenium status (hair selenium) for which they found a very significant positive correlation. The lower the selenium status in a population, the lower the recovery rate from Covid-19. Similarly, the higher the selenium status, the higher the recovery rate (17). Although this study does not prove direct correlation, data are in the same line as other previously mentioned studies on RNA viruses and selenium. However, one notable aspect in their results was that in the city of Enshi, which has one the highest Se intakes in the world, the recovery rate from Covid-19 was almost triple the average for the rest of the cities in Hubei Province, including Wuhan. This strongly suggests that the selenium effect is not only of importance in selenium deficient Populations, but that having a higher than normal selenium status may offer a protective benefit against the detrimental effects of the viral infection. This observation (like the Hou study cited above for epidemic haemorrhagic fever) goes against the conventional wisdom that there is no benefit in selenium supplementation above the minimal required dietary intake.

Mechanisms by which sodium selenite could act in RNA virus infections including SARS-Cov-2:

- *Inhibition of virus entry into the host cell*

Sodium selenite (a quadrivalent form of selenium) inhibits reduction reactions (thiol / disulfide catalytic exchanges) of the Protein Disulfide Isomerase (PDI) which is involved in particular in viral glycoproteins attachment to the host cell membrane, first step to viral entry (18).

- *Restoration of the host cell Thioredoxin Reductase biosynthesis*

Taylor et al. presented computational and in vitro evidence that HIV-1 and the Zaire strain of Ebola virus (EBOV) target cellular selenoprotein mRNAs by RNA:RNA antisense interactions for the purpose of hijacking the selenocysteine insertion sequence ("SECIS element") of the cellular messenger RNA (mRNA) in order to express a viral selenoprotein (19). In both cases, the mRNAs of isoforms of thioredoxin reductase (TrxR) appear to be targeted. They also presented evidence in support of this mechanism via green fluorescent protein reporter gene assays, in which read-through of the 3'-UGA stop codons of the respective HIV-1 nef and EBOV nucleoprotein genes was evident (20). This mechanism would also be expected to lead to down regulation of the targeted TrxR protein, which could contribute to pathogenic effects of the virus, because it could lead to increased oxidative stress (19).

Taylor and Ruzicka later presented evidence of a similar antisense targeting of several selenoprotein mRNAs, including selenoprotein P and TrxR1, by Zika virus mRNA, and proposed that the antisense knockdown of TrxR isoforms could be a general mechanism by which RNA viruses can increase the pool of ribonucleotides for viral RNA synthesis, by inhibiting the synthesis of DNA (21). Because of the essential role of TrxR as part of the thioredoxin system, which is a hydrogen donor for the reduction of ribose to 2'-deoxyribose, they proposed that this could be an effective strategy for RNA viruses. Because of the fact that TrxR is a selenoprotein in mammals, this might help to explain why various RNA viruses, including SARS-CoV-2, have shown a relationship to selenium status, as reviewed above.

The antioxidant capacities of the host cell would certainly be affected by TrxR knockdown (22), which could be partially rectified by increasing selenium intake to boost the availability of selenocysteine for selenoprotein synthesis. Sodium selenite is a rapidly bio-available form that may cross the blood-brain barrier more readily than other forms of selenium. Pharmacological doses could help to restore the biosynthesis of TrxR, thus re-establishing cellular DNA synthesis and antioxidant capacities.

- *Decrease in viral-induced cell apoptosis*

Viral infection is associated with oxidative stress with induction of enzymes producing reactive oxygen species (ROS) (22). There is an increase in ROS in a cell model infected with the influenza AH1N1 RNA virus (23). Sodium selenite decreases the production of ROS and the induced cell apoptosis in these infected cells.

Furthermore, Nuclear Factor *kappa*B (NF-*k*B) has anti-apoptotic or, on the contrary, apoptotic properties depending on the circumstances (24). RNA viruses can trigger activation of NF-*k*B and divert its function to their benefit (25, 26). Liao et al have shown that this NF-*k*B activation in cells infected with the nucleocapsid protein of SARS-CoV-1 could be responsible, at least in part, for severe inflammatory pulmonary lesions in Severe Acute Respiratory Syndrome (27). Finally, the inhibition of NF-*k*B induced by SARS-CoV-1 in an animal model (mouse) is associated with greater survival (28). Selenium is well established as an NF-*k*B inhibitor (29, 30).

- Restoring the host's selenium stock

At least 25 selenoproteins have been identified in humans, many of which are involved in antioxidant processes. RNA viruses, including the SARS coronaviruses, probably divert cellular selenium for their own selenoproteins (19, 22, 31, 32). Intense viral replication would therefore induce a selenium deficiency in the host cell (19, 33, 34). In this case, an exogenous supply of selenium would restore the "stock" that is essential for the biosynthesis of cellular selenoproteins, particularly those required for antioxidant defense.

- Selenium acts on blood platelets aggregation.

Covid-19 disease has been associated with thrombosis events such as large vessel clots, deep vein thrombosis and pulmonary embolism, and microvascular thrombosis (35).
Coagulopathy is also associated with severe cases.

Thromboxane A2 (TxA2) formation is a key element in blood platelet activation and aggregation, resulting in blood coagulation/thrombosis formation (36, 37).
Sodium selenite has an antiaggregation effect by decreasing TxA2 formation (38).
Covid19 is also associated with thrombocytopaenia (39, 40) and an increasing incidence of strokes, even in younger patients, is a worrisome trend in COVID-19 pathology. .
In healthy adults, higher serum selenium levels are independently and significantly associated with higher platelet count (41). Thus, there is considerable potential for selenite to help reduce the systemic blood clotting that now appears to be a common feature of COVID-19.

Final considerations

Selenium has a key and complex role in the immune system (42). It is very clear that selenium deficiency is associated with higher susceptibility to RNA viral infections and more severe outcome.

It is estimated that up to a billion people are at risk of selenium deficiency worldwide, and this is only likely to increase with global warming (43).

The elderly are particularly at risk of selenium deficiency (44) which may be a reason why they are particularly vulnerable to Covid-19 (average case fatality ratio of 4-5 % above 60 years of age from international data, and probably more than 8 % above 80 years) (45).
Therefore making sure that the elderly are supplemented in selenium before they get infected is a sound and safe strategy.

Particularly based on the precedents for other RNA viruses reviewed in the first section above, there appears to now be ample evidence to justify investigation of selenium as a way to reduce the morbidity and mortality of Covid19 disease. Sodium selenite is a compound already present in pharmacopoeia (in some countries as selenious acid, for addition to total parenteral nutrition solutions, as well as treatment of deficiency) and whose short-term toxicity is minimal, if not absent, and well documented.
It would be desirable to use it as soon as possible before the tissue damages are too advanced, that is to say when first symptoms occur and before the onset of severe acute respiratory distress syndrome. The greatest benefit would probably be in outpatient settings and/or as soon as possible on patient admission to hospital.

However, its use in intensive care as adjuvant therapy could also have advantages. In that case Selenium has to be given well above nutritional recommended daily allowance (RDA) and 200 to 400 micrograms of selenium element per day that is approximately 600 to 1200 micrograms of sodium selenite would seem appropriate for a short period of 14 days (6,12-15, 46). In hospital, the intravenous form is undoubtedly more suitable given a large number of digestive disorders in the context of Covid-19.

Conclusions:

Current knowledge on RNA viruses and selenium interactions, epidemiological data, in vitro and animal models, as well as clinical studies in humans show that selenium might play an important role in Covid-19. Selenium deficiency promotes mutations, replications and virulence of RNA viruses. Selenium acts at various levels from restoring antioxidant capacity of the host cell, reducing apoptosis and platelet aggregation. Sodium selenite is cheap and readily available. Faced with the deadly Covid-19 pandemic and especially the unprecedented pressure it exerts on the healthcare system, the potential use and effectiveness (or not) of sodium selenite must be urgently documented. Similarly, as some countries enter in the post confinement era, preventive selenium supplementation, especially in the elderly, should be part of the global comprehensive strategy.

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Conflicts of Interest: None

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