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Research Article
Was a Mysterious Lab Involved in the Development and Production of the SARS-CoV-2 Virus?

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Abstract

Background and Objective: In less than a year, approximately 90 million people worldwide have been infected with the SARS-CoV-2 highlighting the urgent need for scientists to understand the spread of the virus. This study aims to investigate the abnormal biochemical reactions that occur when there are high levels of Fe^{2+}, which significantly contribute to the spread of SARS -CoV-2. **Materials and Methods:** This review made use of data from 1986 to 2023 from scholarly journals and databases, including Elsevier, Taylor & Francis Online, the National Institute of Health, BMC, Scientific Research, the Centers for Disease Control and Prevention and Google Scholar. For information on SARS-CoV-2, COVID-19, RBCs, Fe^{2+}, Fe^{3+}, Zn^{2+}, Mg^{2+}, Ca^{2+}, NO_2^-, P^{3-}, Cl_2^- and S^{2-} and biochemical reactions, several databases were accessed. **Results:** The presence of Fe^{2+}-rich proteins leads to hypoxic conditions due to the increased formation of Fe^{2+} and Fe^{3+}. **Conclusion:** Key factors in the spread of SARS-CoV-2 involve the use of faulty metabolic reactions that produce RNS, resulting in NO_2^-, ROS, leading to MetHb and Fe^{3+}-H_2O_2 complex, RSS resulting in Fe-S cluster and RPS resulting in $[Fe\ (PO_4)_6]^{-3}$ complex for the production and release of virions.

Key words: SARS-CoV-2, Fe^{2+}, Fe^{3+}, RNS, ROS, RSS, RPS, abnormal biochemical reactions, defective metabolic reactions

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INTRODUCTION

Will the human body become an incubator for this ferocious virus and all its strains? There is no evidence to support the claim that SARS-CoV-2 was manufactured as a weapon in laboratories. Instead, it is believed that an unbalanced diet, lacking essential food elements[1] and increased environmental pollution[2] contributed to the emergence of SARS-CoV-2. This article aims to explore the consequences of elevated iron (Fe) levels and its correlation with the high rate of SARS-CoV-2 infection. Clauss and Paglia[3] stated that a large variety of captive mammal species have been shown to exhibit Fe storage disease, or an excessive burden of Fe. Overexposure to Fe causes harm to all of the body's cells and tissues, which frequently sets off a series of unfortunate events that include liver damage[4]. According to Esfandiar *et al.*[5] and Abd-El-Aziz[6], red meat and shellfish are the two most important sources of Fe. It can be inferred from these early findings that although vaccination reduces the risk of severe and fatal COVID-19 infections, patients are still susceptible to them[7]. The SARS-CoV-2 thus seems to have emerged as a result of consuming a lot of Fe-rich wild meat; however other variables like shellfish also had a crucial role in the virus's spreading.

Furthermore, environmental pollution surrounding COVID-19 patients can accelerate the spread of the virus, particularly among individuals with pre-existing comorbidities. Urban areas have a higher prevalence of respiratory allergies compared to rural areas[8]. A study conducted by Metere *et al.*[9] found that carbon monoxide (CO) increased the concentration of reduced glutathione in Red Blood Cells (RBCs), leading to significant hemoglobin deglutathionylation. In New York, approximately 203,000 confirmed cases of SARS-CoV-2 were reported between March and May, 2020[10], possibly due to complications arising from air pollutants[2]. Similarly, when the first COVID-19 patient was diagnosed on February 20, 2020, approximately 222 out of 1,506 confirmed cases were reported across all Lombardy Provinces[11], potentially due to groundwater pollution[12]. Zhu *et al.*[13] also noted that sewage water in Southern China contributed to pollution in the Pearl River Delta. Consequently, it is expected that the number of COVID-19 deaths will increase in regions with polluted environmental conditions.

These factors can lead to abnormal biochemical reactions, including the formation of Hydrogen Peroxide (H_2O_2). Therefore, an unbalanced diet over a long period can contribute to the spread of SARS-CoV-2 and increased mortality rates, particularly in the presence of environmental pollution. Excessive intake of Ferrous (Fe^{2+}) can lead to its accumulation, which can have contrasting effects on Fe^{2+} behavior in chronic diseases[14]. The scientific community of human and clinical nutritionists, industry and government regulatory authorities should carefully consider solutions to these problems while debating marketing and policy ideas. One way to lessen the Zinc (Zn^{2+}) inhibiting effects of Fe^{2+} might be to intentionally alter the Fe^{2+}/Zn^{2+} ratios in foods, medicines and human diets[15]. The Zn^{2+} plays a crucial role in maintaining protein structure and stability, with over 300 enzymes relying on this element for their activities[16]. The Zn^{2+} deficiency can lead to dysregulation of proinflammatory cytokines[17]. The Zn^{2+} and Fe^{2+} compete for absorption pathways[18]. Niles *et al.*[19] showed that elevated cell and tissue Fe^{2+} concentrations are considered a consequence of Zn^{2+} deficiency. The researchers also concluded that Zn^{2+} deficiency can lead to changes in proteins responsible for transporting, storing and regulating Fe^{2+}, ultimately leading to an accumulation of Fe^{2+}. Moreover, increased levels of phosphorus (P) and Calcium (Ca^{2+}) can lead to the formation of hazardous Ca^{2+} deposits in blood vessels, lungs, eyes and heart. Many fruits are good sources of Magnesium (Mg^{2+}), Ca^{2+}, P and Sodium (Na^{+}). Also, green leafy vegetables, as highlighted by Lidder and Webb[20] and Blekkenhorst *et al.*[21], are rich in Nitrites (NO_2^-), Mg^{2+}, Zn^{2+}, Fe^{2+}, Ca^{2+} and Sulfur (S^{2-}). Furthermore, Chloride (Cl_2^-) is found in various foods, as reported by Mason[22].

There are different types of biochemical reactions, including hydrolysis, oxidation-reduction and neutralization. It is known that the electronic configuration of Fe^{2+} is less stable than Ferric (Fe^{3+}); Fe^{2+} can donate an electron, while Fe^{3+} can accept one. A lack of Mg^{2+} can result in increased production of free radicals and the release of inflammatory cytokines[23]. The Fe^{3+} is stored in ferritin in the body due to the activity of ferroxidase[24]. Hence, an excess of Fe^{3+} ions has been linked to an increased risk of cancer, according to Stevens *et al.*[25]. The Ca^{2+} influx plays a significant role in the response of cultured human mesangial cells to vasoconstrictors[26]. Intracellular regulation of Ca^{2+} can also activate an alternative pathway involved in Transforming Growth Factor-β (TGF-β) signaling[27]. According to She *et al.*[28], Fe^{2+} functions as a direct agonist to stimulate the promoter activity of Nuclear Factor Kappa-B (NF-κB), Tumor Necrosis Factor-alpha (TNF-α) and inhibitor B kinase. A weekly 500 mL phlebotomy is typically advised until the serum ferritin drops to about 50 ng/mL, as it is believed that an increased ferritin level is associated with Fe excess[29]. The Fe^{2+} cannot bind to heme-free albumin, which makes up 52-60% of total plasma protein, as Fe^{3+}. Additionally, SMAD are proteins that mediate the canonical signaling cascade of the TGF-β superfamily

of ligands[30]. Wang *et al.*[31] discovered that the protein nucleocapsid of SARS -CoV-2 causes cell damage through its interaction with SMAD3. Bone morphogenetic proteins (BMP) are also crucial for cell growth, apoptosis and differentiation[32]. Cysteine and methionine are the two common S-containing amino acids incorporated into proteins[33]. Rouault and Tong[34] demonstrated that disruption of Fe-S proteins can lead to cell death. Consequently, SARS-CoV-2 can exploit these defective metabolic reactions to induce abnormal biochemical reactions through the formation of reactive nitrogen species (RNS), resulting in NO_2^-, reactive oxygen species (ROS), resulting in MetHb and Fe^{3+}-H_2O_2 complex, reactive sulfur species (RSS), resulting in Fe-S cluster and reactive phosphorus species (RPS), resulting in $[Fe\ (PO_4)_6]^{-3}$ complex for virion production and release. Therefore, the objective of this study is to investigate the abnormal biochemical reactions that occur when there are high levels of Fe^{2+}, which significantly contribute to the spread of SARS -CoV-2.

MATERIALS AND METHODS

Data from scientific publications and databases, including Elsevier, Taylor and Francis Online, the National Institute of Health, BMC, Scientific Research, the Centers for Disease Control and Prevention and Google Scholar, spanning from 1986 to 2023, were utilized for this review. Various databases were searched for information on SARS-CoV-2, COVID-19, RBCs, Fe^{2+}, Fe^{3+}, Zn^{2+}, Mg^{2+}, Ca^{2+}, NO_2^-, P^{3-}, Cl_2^-, S^{2-} and biochemical reactions. The keywords used helped identify the key elements for this review. A total of 36,500 items were retrieved from the databases. A preliminary assessment of article titles and abstracts was conducted to highlight relevant technical details. The review article was developed using a robust scientific methodology to elucidate these key points. Additionally, the authors analyzed existing scholarly publications and previous studies on the topic.

RESULTS

Vaccination rates vary across the state among different age groups and demographic populations, making certain groups more vulnerable to these severe outcomes (Fig. 1 and Table 1-2). According to Fig. 1, the rates of unvaccinated individuals in the age groups of 12-34, 35-64 and over 65 were 9.5, 24.7 and 148.9 per 100,000 population, respectively. In contrast, the rates of individuals in the age groups of 12-34, 35-64 and over 65 who had received at least one booster dose were 2.3, 3.6 and 77.3 per 100,000 population, respectively. The hospitalization rates for COVID-19 among unvaccinated individuals were 4.1, 6.8 and 1.9 per 100,000 population for the age groups of 12-34, 35-64 and over 65, respectively, compared to those who had received at least one booster dose. It is important to note that while vaccinations are highly effective, they may not prevent all illnesses.

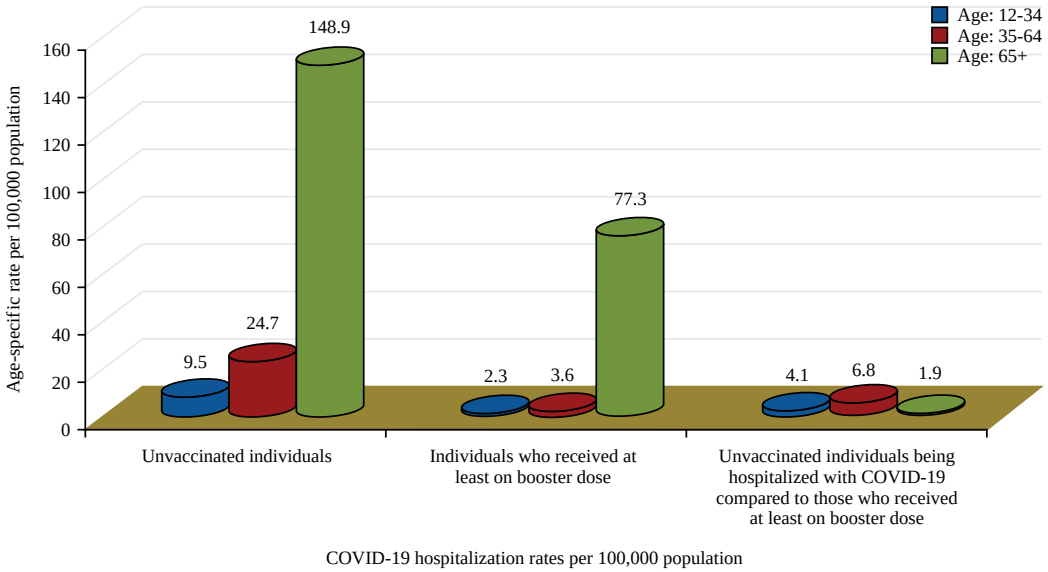

Fig. 1: COVID-19 hospitalization rates per 100,000 population by age and vaccination status from August, 30 to September 26, 2023

Table 1: COVID-19 death rates per 100,000 population by age and vaccination status from August 8 to September 4, 2023

Age group	Unvaccinated individuals	Unvaccinated individuals	Unvaccinated individuals being hospitalized with COVID-19 compared to those who received at least one booster dose
35-64	0.8	0.1	11.9
65+	14.8	6.3	2.4

Table 2: Effective vaccines are given to humans from the beginning of the pandemic until September, 2022

Country	Dosage amount per 100 people	Total cases	Unvaccinated individuals being hospitalized with COVID-19 compared to those who received at least one booster dose
USA	183	0.1	11.9
65+	14.8	6.3	2.4

According to Table 1, the percentage of unvaccinated individuals in the age groups 35-64 and over 65 was 0.8 and 14.8 per 100,000 population, respectively. In comparison, the percentage of unvaccinated individuals in the age ranges of 35-64 and over 65 was 0.1 and 6.3 per 100,000 population, respectively. Meanwhile, the hospitalization rates for COVID-19 cases among unvaccinated individuals in the age groups 35-64 and over 65 were 11.9 and 2.4 per 100,000 population, respectively, compared to those who had received at least one booster dose.

Table 2 indicated that effective vaccines were consistently administered to individuals from the beginning of the pandemic until September, 2022. The vaccination rates were 183 and 14.8 per 100 people for the USA and individuals over 65, respectively. In contrast, the total number of cases reported was 0.1 and 6.3 for the USA and individuals over 65, respectively. The hospitalization rates for unvaccinated individuals with COVID-19 were significantly higher compared to those who had received at least one booster dose, with rates of 11.9 and 2.4 for the USA and individuals over 65, respectively.

DISCUSSION

The risk of hospitalization or death is significantly lower for those who have completed the primary series and received a booster dose compared to the unvaccinated. Individuals who have received at least one booster dose have a reduced risk of COVID-19-related hospitalization or death. Based on the information provided, it is noted that although all vaccines are effective against SARS-CoV-2 and its variants, there have been cases where vaccinated individuals have experienced re-infection more often than unvaccinated individuals. This could be attributed to factors such as the patient's dietary habits, medical history or exposure to polluted environments. The Fe^{2+}, when free, can lead to the creation of highly dangerous compounds, including the hydroxyl radical (OH^{-}). This ultimately leads to deficiencies in Zn^{2+} and imbalances in other trace elements such as Na^{+} and Ca^{2+}, disrupting the levels of antioxidant enzymes in the serum due to this electrolyte disorder. Electrolyte disorders can harm the immune system and overall health. Euvolemic hyponatremia occurs when the body's Na^{+} levels are low but the overall fluid volume in the body remains normal. This can be caused by medications, hormonal imbalances or underlying medical conditions. Hypervolemic hyponatremia occurs when there is an excess of fluid in the body, leading to a dilution of Na^{+} levels. This can be seen in conditions such as congestive heart failure or liver cirrhosis. These effects include increasing levels of Low-Density Lipoprotein Cholesterol (LDL-cholesterol) and triglycerides, reducing hepatic catalase, activity and affecting the distribution of glutathione reductase and glutathione-S-transferase. Figure 2 illustrates that increased Fe^{2+} levels above the normal range result in the production of extra free radicals from O_2, N, S^{2-} and P molecules. As a result, the reduction of peroxides such as H_2O_2 and/or hydroperoxides (ROOH) will not occur and the conversion of Glutathione (GSH) to Glutathione Disulfide (GSSG) will be hindered in the presence of higher levels of Fe^{2+} ($2\ GSH+ROOH \rightarrow GSSG+ROH+H_2O$).

The decreased ratio of GSH to GSSG in the plasma is indicative of oxidative stress[35]. Therefore, the rise in Fe^{2+} and Fe^{3+} levels is anticipated to elevate H_2O_2 and/or ROOH levels, resulting in lipid peroxidation. This, in turn, will result in noticeable changes in RBC morphology and the presence of cell-free hemoglobin. The RBCs cannot utilize intracellular enzymes for cell signaling and ion transportation due to their distribution within the cell. It appears that Fe-rich proteins are formed under hypoxic conditions due to the accumulation of Fe^{2+}. These ROOH can further generate radical fluxes when they interact with transition-metal ions. Karami *et al.*[36] reported that Fe^{3+} negatively affects the activity of the plasma enzyme butyrylcholinesterase more than Fe^{2+}.

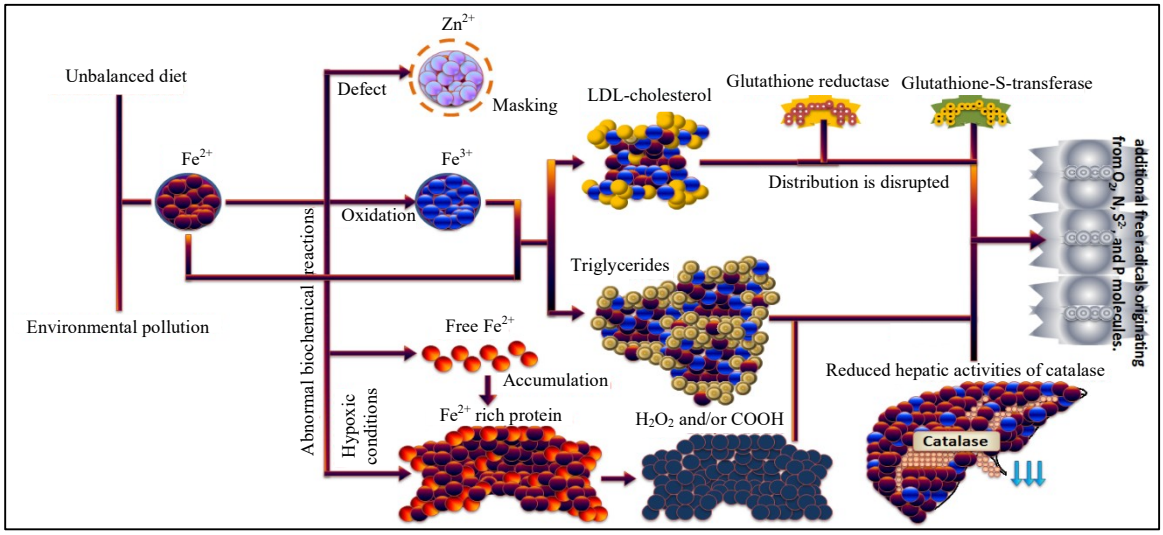

Fig. 2: Additional free radicals are generated from O_2, N, S_2^- and P molecules in the presence of elevated levels of Fe^{2+} above the average

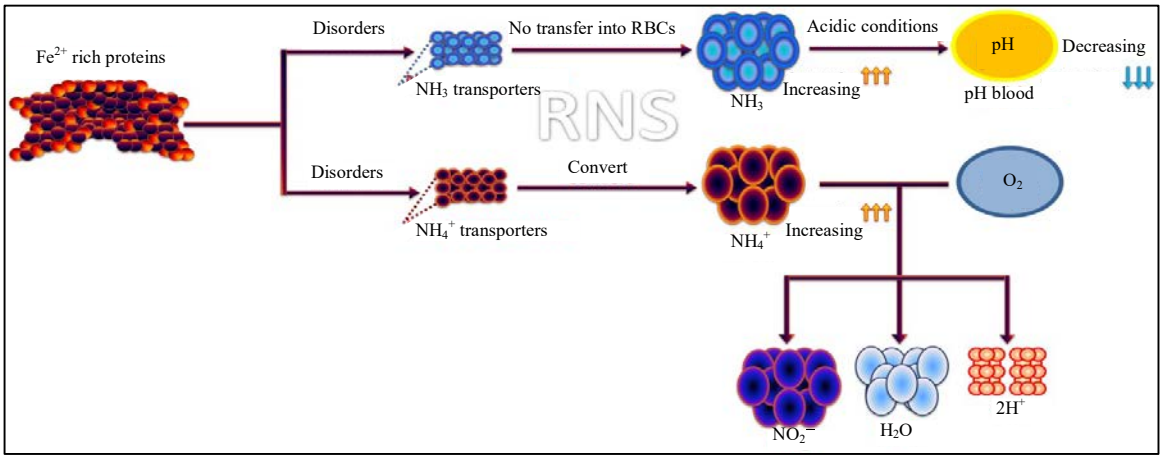

Fig. 3: Expected formation of NO_2^- as a result of SARS-CoV-2 infection

These abnormal biochemical reactions are likely to produce additional free radicals originating from O_2, N, S^{2-} and P molecules. In the case of a SARS-CoV2 infection, it can cause an elevation in Fe^{2+} levels exceeding 35 µM in the patient's plasma. These abnormal biochemical reactions can occur when there is an excess of fluid in the body or when the overall fluid volume in the body remains normal. Consequently, ionization energy is expected to occur when hydrogen (H) loses an electron [$H \rightarrow H^+ + e^-$] and when H gains an electron [$H + e^- \rightarrow H^-$] under these circumstances.

Redox reactions involve chemical reactions where there is a net change in atomic charge. Free radicals can be highly reactive and induce unpaired electrons, allowing them to oxidize various minerals. It is believed that a decrease in the body's acid status leads to the generation of ROS, RNS, RSS and RPS by SARS-CoV-2, which rely on additional free radicals with unpaired electrons. This leads to the formation of ROS, resulting in MetHb and Fe^{3+}-H_2O_2 complex, RNS, resulting in NO_2^-, RSS, resulting in Fe-S cluster and RPS, resulting in $[Fe(PO_4)_6]^{-3}$ complex. The ROS, including O_2^-, OH^- and H_2O_2, are produced within cells when there is an excess of Fe^{2+} and unpaired electrons are present. The RNS can be generated through the transporters of Ammonium (NH_4^+) and Ammonia (NH_3), which are affected by SARS-CoV-2 (Fig. 3). The presence of Fe^{2+}-rich proteins may interfere with these transporters. Free radicals are produced as a result of Fe poisoning[37]. The NH_3 levels are negatively impacted by this biological response, which inhibits their transfer into RBCs. As a result,

there is an increased release of NH_3, which leads to a decrease in blood pH. This biological condition enables gastric acid in the proximal duodenum to enhance the activity of a Fe^{3+} reductase enzyme, converting insoluble Fe^{3+} into absorbable Fe^{2+} ions. The NH_4^+ then reacts with O_2 to produce NO_2^- [$NH_4^+ + O_2 \rightarrow NO_2^- + H_2O + 2H^+$]. Additionally, imbalanced NH_4^+ can impair aerobic glycolysis by interfering with the mitochondrial consumption of pyruvate. Consequently, this can lead to defects in metabolic reactions due to changes in pH and Na^+/H^+ exchangeability. The dominance of the Fe^{3+} state over the Fe^{2+} state at physiological pH has been reported[38]. This biological situation is likely to worsen as the level of Cl_2^- decreases below recommended levels. Thus, an increase in mitochondrial permeability transition with the accumulation of adenosine triphosphate (ATP) will likely occur, which will facilitate electron leakage from complexes I and III. The H-transport with mitochondrial consumption of pyruvate will also be disrupted across the inner mitochondrial membrane. This, in turn, is expected to negatively impact kidney function due to the acidic conditions of the blood. As a result, several sites in glycolysis may become disordered and H^+ ions will be confounded by the accumulated ATP. This biochemical reaction will lead to disorganized ion gradients. A mechanism has been identified that generates Zn^{2+} gradients using a Na^+ gradient[39].

The presence of free Fe^{2+} can generate ROS (Fig. 4a), which can result in the formation of Met-Hb[40]. This may be attributed to the conversion of Fe^{2+} to Fe^{3+} as a result of NO_2^- accumulation. It appears that the original strain of SARS-CoV-2 can exacerbate this situation, possibly due to its requirement for more Fe^{2+}, Fe^{3+} and O_2^- during viral genome transcription and replication. Consequently, it is anticipated that RBCs will lose their protective mechanisms against MetHb, resulting in production exceeding 1%. The Fe^{3+} forms insoluble Ferric Hydroxides ($FeHO_2$) and generates harmful ROS through the Fenton reaction[41]. The Fenton reaction is most favorable at a pH range of 3 to 4, as reported by Pignatello *et al.*[42]. Deoxygenated hemoglobin refers to the unbound state of hemoglobin with O_2. Interestingly, the masking of Zn^{2+} can lead to the inactivation of oxidative stress enzymes. Therefore, the increased oxidation of Fe^{2+} to Fe^{3+} appears to enhance the spread of SARS-CoV-2 within the body. The oxidation of Fe^{2+} to Fe^{3+} requires normal oxygenation, similar to the deoxygenation of hemoglobin, which results in the formation of a small amount of MetHb [$Fe^{2+} + O_2 \rightarrow O_2^- + Fe^{3+} + MetHb$].

Consequently, as Fe^{2+} levels rise above normal, the quantities of MetHb and O_2^- will also increase. An individual afflicted with SARS-CoV-2 will exhibit higher Fe^{2+} levels relative to normal; this metabolic response signifies modifications in O_2^- reactions. In these conditions, blocking the inhibitor kB-α (IκBα) can activate NF-κB. The presence of Fe^{2+} can result in a reaction with O_2^- (in the presence of $2H^+$) to form a ferric state with H_2O_2 [$Fe^{2+} + O_2^- + 2H^+ \rightarrow H_2O_2 + Fe^{3+}$]. Figure 4b shows the expected Fe^{3+}-H_2O_2 complex as a result of SARS-CoV-2 infection.

This suggests that SARS-CoV-2 can enter RBCs in the absence of Cl_2^- ions, leading to the formation of the Fe^{3+}-H_2O_2 complex. Under these conditions, the complex (Fe^{3+}-H_2O_2) can lead to the formation of coagulation. Subsequently, H_2O_2 will decompose into OH^- through interactions with nutrients that have multiple redox states. The OH^- radicals are known to be highly toxic oxidants. The Fe^{3+} can transform into Fe^{2+} in the presence of various forms of O_2^- through the Haber-Weiss reaction, as reported by Filipovic and Koppenol[43]: $Fe^{3+} + O_2^- \rightarrow Fe^{2+} + O_2$. Other chemical processes can also be generated under these conditions, including $Fe^{3+} + H_2O_2 \rightleftharpoons FeHO_2^{2+} + H^+$, $FeHO_2^{2+} + FeOH^{2+} \rightarrow 2Fe^{2+} + H_2O + O_2$ and then $FeOH^{2+} + H_2O_2 \rightleftharpoons Fe(OH)(HO_2)^+ + H^+$. In the presence of catalysts, additional chemical processes can occur, such as $Fe(OH)(HO_2)^+ \rightarrow Fe^{2+} + HO_2 + OH$ and then $Fe^{2+} + OH \rightarrow Fe^{3+} + OH^-$. Furthermore, other chemical processes can take place, such as $Fe^{3+} + HO_2 \rightarrow Fe^{2+} + O_2^{2-} + H^+$. Moreover, other chemical processes can be generated, such as $Fe^{2+} + O_2^- \rightarrow Fe^{3+} + O_2^{2-}$, $Fe^{3+} + H_2O_2 \rightleftharpoons FeHO_2^{2+} + H^+$ and then $H_2O_2 \rightleftharpoons HO_2^- + H^+$.

Moreover, it is expected that there will be no stability of Fe complexes such as Fe^{2+} carbonate due to the low pH. As a result, cellular Ca^{2+} levels are likely to increase in the blood due to the decomposition of this complex. It is important to note that conformational changes induced by Ca^{2+}-binding to recovery were found to be responsible for autoantibody reactivity, as mentioned by Adamus and Amundson[44]. In the context of SARS-CoV-2, Lippi *et al.*[45] revealed an imbalance in Ca^{2+} levels in the electrolyte disturbance of patients. This can lead to disorganized renal tubular Ca^{2+} reabsorption in response to changes in extracellular Ca^{2+} concentration, which in turn can disrupt the Na^+/Ca^{2+} exchange and negatively affect intracellular Ca^{2+} stores. This provides a favorable environment for SARS-CoV-2 to control ACE2 receptors. Consequently, fetuin-A will be affected, leading to the destabilization of calciprotein particles and hydroxyapatite. This dysregulation of TGF-β1 expression in renal tubular epithelial cells, along with the resulting electrophilic aromatic substitution reaction disorders will impact the plasma membrane localization of the furin protease receptor and hinder its enhancement by TGF-β. As a result, the phosphorylation of the furin protease is likely to release a modified activator, leading to the recruitment and subsequent phosphorylation of specific receptors in RBCs. Therefore, we believe that SARS-CoV-2 can regulate the influx of Ca^{2+} through an alternative pathway by causing actin cytoskeleton alterations and enhancing cytoskeletal alterations.

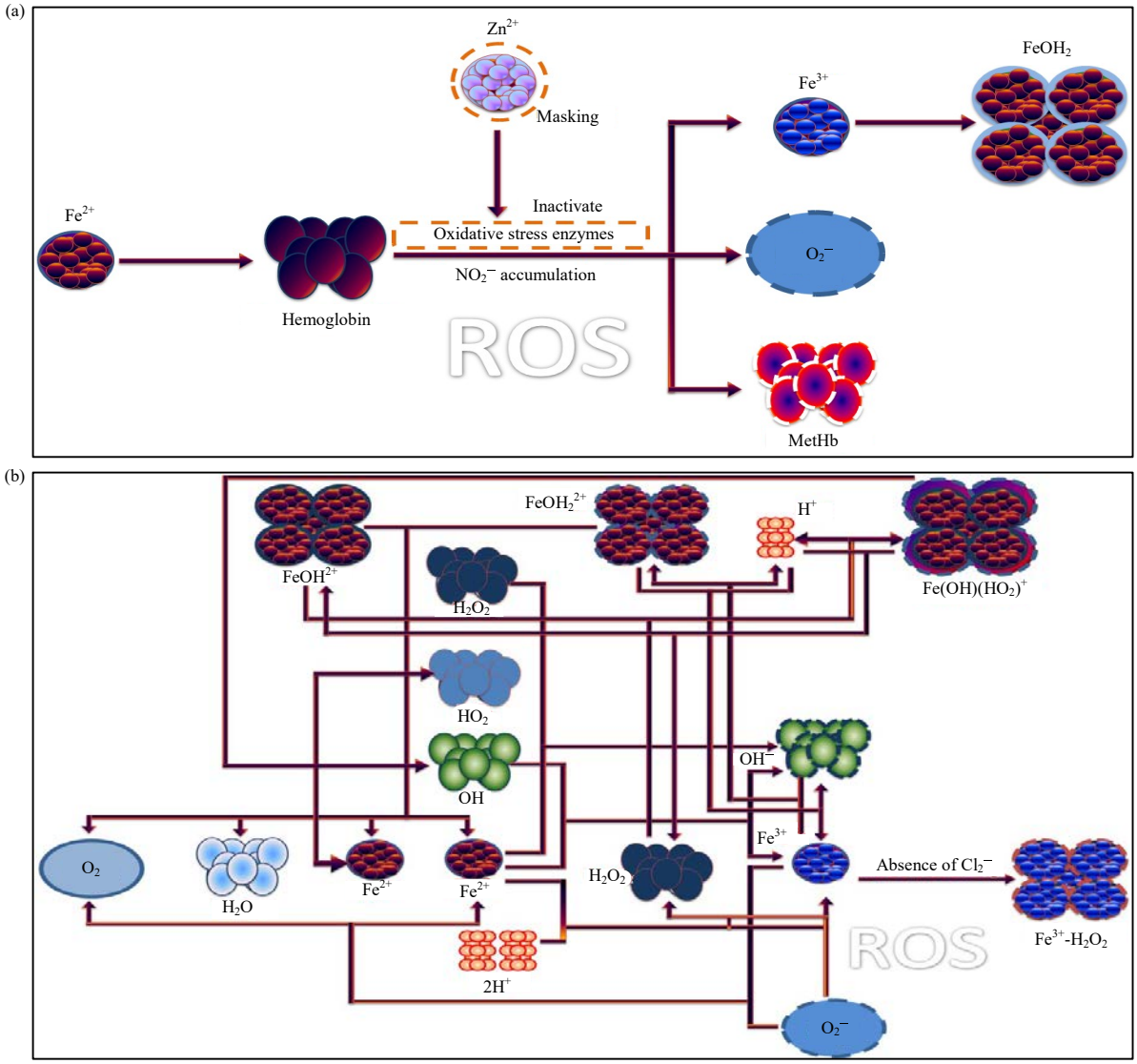

Fig. 4(a-b): (a) Expected MetHb formation in response to SARS-CoV-2 infection and (b) Expected Fe^{3+}-H_2O_2 complex as a result of the SARS-CoV-2 infection

Therefore, electronic disorders can lead to the oxidation of lipids and sugars. This can result in disorders in lipid metabolism in the liver due to oxidative stress and inflammation. Dysregulation in hepcidin may occur, possibly due to a defect in transferrin receptor 2. This can reduce the liver BMP-SMAD signaling pathway, leading to increased ferritin synthesis. Additionally, there may be disability in apoferritin and dysregulation in the release of Fe^{2+} in different tissues, resulting in higher ferritin levels than normal. These disorders inhibit the export of Fe^{2+} from macrophage, leading to Fe-blockage. As a result, ferritin is encouraged to sequester Fe^{2+} in storage sites. Walker *et al.*[46] and Bjørklund *et al.*[47] conducted studies on adults and found that most of the research showed no impact on plasma ferritin levels when Zn^{2+} was consumed orally. Nevertheless, because distinct processes for the O_2^- molecule occur, it is anticipated that ferritin cannot be converted to Fe ions by the SARS-CoV-2 infection. Under such circumstances, the body cannot transfer the majority of its Fe^{2+} to the bone marrow, which results in an RBC deficiency. This can lead to toxification in various cell types, including macrophages, enterocytes and hepatocytes. The disability of SMAD proteins in controlling Fe^{2+} metabolism can also result in the disorganization of hepatic stellate cells' development and growth. Furthermore, disturbances in beta-oxidation and mitochondrial malfunction can occur due to disorders in hepcidin regulation. Consequently, defective metabolic reactions can result in kidney malfunction due to a deficiency of Cl_2^-.

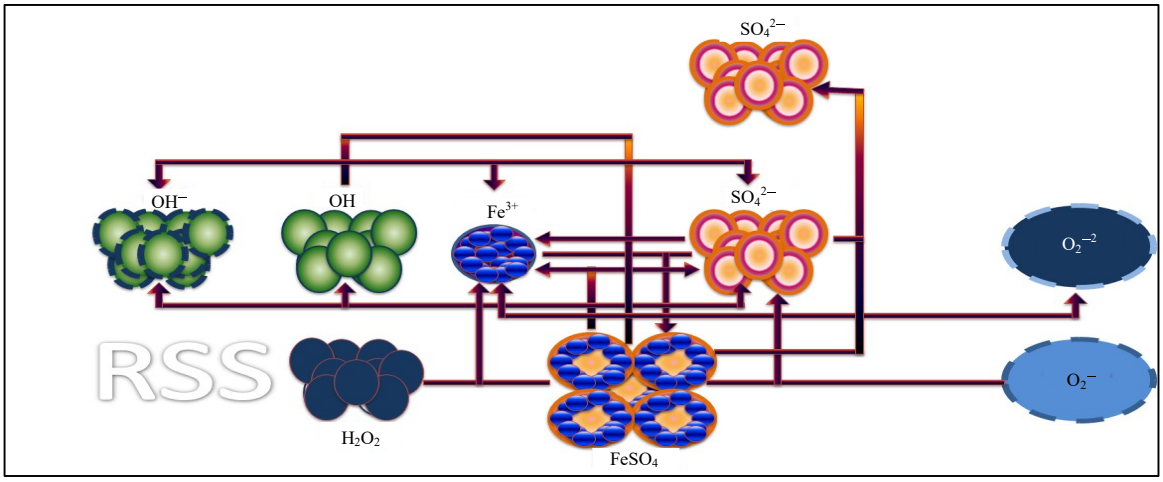

Fig. 5: Expected Fe-S cluster development as a result of infection with SARS-CoV-2

In the presence of these conditions, SARS-CoV-2 infection can enhance and activate hypoxia-inducible factor 2α. These metabolic reactions will result in a reduction of O_2, an increase in OH^- generation and collagen deposition in their lung tissues. As a result, the transporter proteins responsible for the uptake of Zn^{2+} into cells and its transport into and out of intracellular organelles will be impaired. The SARS-CoV-2 can create disulfide bonds, which can increase the activity of lactate dehydrogenase and alkaline phosphatase. This serves as a redox switch and alters the extracellular environment during viral genome transcription and replication. Consequently, RSS may be produced under these circumstances. This biological state will disrupt the biosynthesis of Hydrogen Sulfide (H_2S), leading to the formation of cystathionine-γ-lyase and cystathionine β-synthase, which in turn increases H_2O_2 levels. It is expected that H_2S will lose its ability to counteract the increased free radicals. Cystathionine β-synthase and cystathionine γ-lyase, as well as methionine, play a major role in H_2S biosynthetic pathways[48]. Therefore, it is likely that cystathionine and S-adenosylhomocysteine levels will increase and homocysteine will accumulate due to abnormal methionine metabolism. Rouault and Tong[34] mentioned that S^{2-} can react with Fe^{2+} and bind to the protein through cysteine residues, as the expected Fe-S cluster resulting from SARS-CoV-2 infection.

It is worth noting that Ferrous Sulfate ($FeSO_4$) can be formed as follows: $Fe^{3+}+SO_4^{2-}\rightleftharpoons FeSO_4$ and then $FeSO_4+H_2O_2\rightarrow Fe^{3+}+SO_4^{2-}+OH+OH^-$ (Fig. 5). In addition to these chemical processes, other reactions can occur under such conditions, such as $FeSO_4+OH\rightarrow Fe^{3+}+SO_4^{2-}+OH^-$ and $FeSO_4+O^{2-}\rightarrow Fe^{3+}+SO_4^{2-}+O_2^{2-}$. Therefore, it is anticipated that levels of tyrosine 3-monooxygenase will be disrupted in such circumstances. The reactions triggered by the original strain of SARS-CoV-2 may utilize additional O_2^- to exploit the Fe-S cluster, potentially due to heightened mitochondrial permeability transition, which could contribute to the development of certain clotting factors.

Consequently, the Fe-S cluster biogenesis pathway could serve as a potential target for SARS-CoV-2 to utilize S-containing amino acids during viral genome transcription and replication. As a result, SARS-CoV-2 can lead to complications in kidney metabolism, impairing the ability of your kidneys to effectively eliminate P. The Ca^{2+}, P and Mg^{2+} are transported between the blood, bone, renal and gastrointestinal cells bidirectionally.

Elevated serum P levels have been linked to cardiovascular disease in both chronic kidney disease patients and the general population[49]. Elevated levels of P can be detrimental to your body, as it triggers changes that deplete Ca^{2+} from your bones, resulting in weakened bones. Additionally, in these circumstances, the dysfunction of transporters in the proximal tubule may hinder the ability of renal excretion to regulate systemic Phosphate (PO_4^{3-}) levels. Figure 6 shows the expected $[Fe(PO_4)_6]^{3-}$ complex as a result of SARS-CoV-2 infection.

It is believed that the generation of RPS depends on the reactivity of Dihydrogen Phosphate ($H_2PO_4^-$)-radicals with OH^- to produce mono Hydrogen Phosphate (HPO_4^{2-}) according to the following reaction: $H_2PO_4^-+OH^-\rightleftharpoons HPO_4^{2-}+H_2O$. Then, HPO_4^{2-} reacts with oxalate ($C_2O_4^{2-}$) to produce PO_4^{3-} as follows: $HPO_4^{2-}+C_2O_4^{2-}\rightleftharpoons HC_2O_4^-+PO_4^{3-}$. Additionally, Mg^{2+} can interact with PO_4^{3-} ions in an unbalanced manner, resulting in the release of protons during catalysis. This process completes the phosphodiester bond, which forms the backbone of viral RNA.

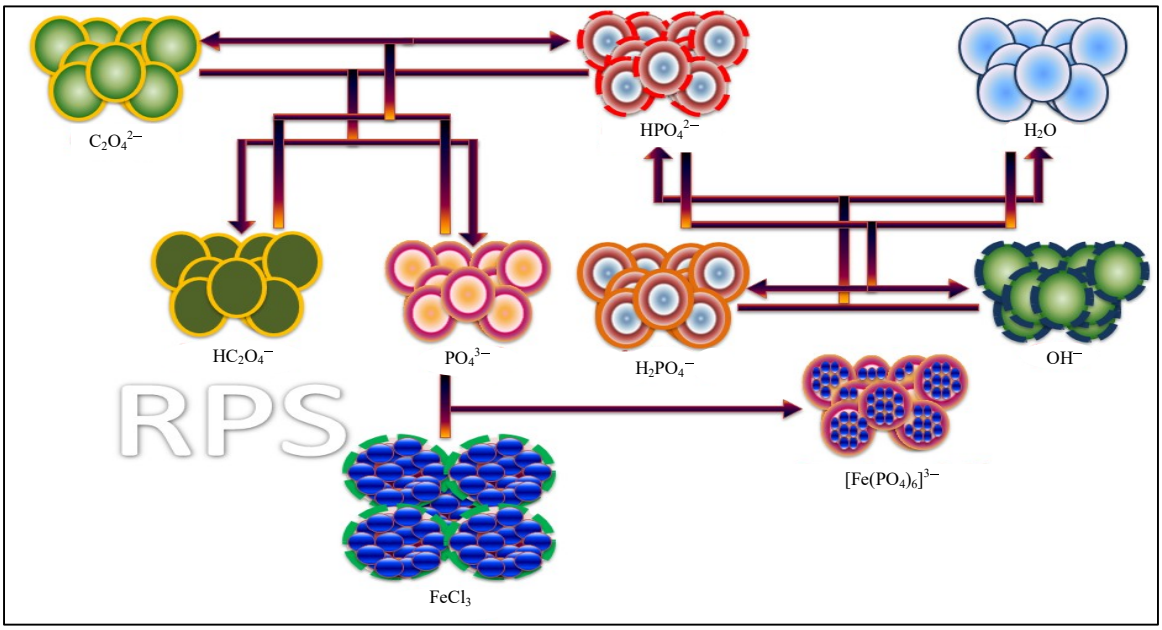

Fig. 6: Expected $[Fe(PO_4)_6]^{3-}$ complex formation during SARS-CoV-2 infection

The formation of the phosphate-ferrite (III) complex is anticipated to occur via $Fe^{3+}+PO_4^{3-}\rightarrow Fe(PO_4)$. Moreover, the production of RPS, which is triggered by the reaction of $FeCl_3$ with PO_4^{3-} to form the phosphate complexes $[Fe(PO_4)_3]^{6-}$, is necessary for the formation of blood clots. This process is triggered by the SARS-CoV-2 infection, which then induces the $[Fe(PO_4)_6]^{3-}$ complex. Subsequently, under unbalanced PO_4^{3-} conditions, abnormal activity of phosphatidylcholine can occur due to Cl_2^- deficiency. This biological situation can reduce the production of omega-3 and omega-6 fatty acids. As a result, the oxidation potential of the Fe^{3+}/Fe^{2+} system decreases. The presence of a sulfolipid biosynthesis protein can potentially lead to acute hypophosphatemia by increasing the levels of PO_4^{3-} transporter, thereby affecting biochemical reactions. Consequently, signal molecules that regulate cell growth and differentiation may be disrupted due to H_2S disturbance. This disruption can lead to defective gene expression, specifically due to a shortage of saturated fatty acid desaturases. Therefore, SARS-CoV-2 has the potential to interfere with the post-transcriptional modification of cellular proteins through S-sulfhydration, resulting in the degradation of lipids, proteins and nucleic acids. This disruption is caused by a disturbance in H_2S and can also impact liver lipid metabolism. Consequently, SARS-CoV-2 may alter the host cell to produce lipids for its envelope. Thus, the adverse effects of SARS-CoV-2 infection may depend on oxidative pathways.

Subsequently, the fusion of the viral membrane with the host cell occurs, followed by viral replication and endocytosis and exocytosis of the virus. Additionally, cell adhesion molecules like CD62 may lose their activity, possibly due to elevated Fe^{2+} levels. This biological situation can impact RBC agglutination and fetuin-binding properties due to irregularities in folded proteins. The SARS-CoV-2 is likely to produce recombinant glycoproteins due to defective metabolic reactions and disturbances in N-glycan metabolism. Consequently, SARS-CoV-2 may require higher levels of Fe^{2+} and Fe^{3+} ions during post-translational modifications. Based on the information above, several factors including MetHb, Fe^{3+}-H_2O_2 complex, Fe-S cluster and $[Fe(PO_4)_6]^{-3}$ play a significant role in the coagulation of blood formation, which in turn facilitates the formation of transcription and replication of the viral genome. It is expected that mRNA destabilization will occur in Fe-depleted cells under these conditions. The furin protease is likely to be the primary receptor for SARS-CoV-2 due to abnormal biochemical reactions induced by increased Fe^{2+} levels. These reactions can lead to a deficiency in the expression of the H antigen and confusion of the immunogenic Rh antigens, indicating disorders of memory B cells and effector B cells. As a result, individuals experiencing this biological reaction may be more vulnerable to SARS-CoV-2 infection, possibly due to systemic immunodepression with an elevated CD4:CD8 ratio.

CONCLUSION

Based on the evidence, it can be inferred that the original strain of SARS-CoV-2 relies on elevated levels of Fe^{2+} and Fe^{3+}. The detrimental consequences of SARS-CoV-2 infection are associated with oxidative pathways. Increased levels of RNS, ROS, RSS and RPS have been identified as a significant characteristic of SARS-CoV-2. The development of SARS-CoV-2 is largely attributed to excessive RNS, ROS, RSS and RPS production as well as metabolic imbalance. The original strain of SARS-CoV-2 facilitates the accumulation of harmful lipid peroxides. Although it is not feasible to create SARS-CoV-2 artificially in a laboratory, elevated Fe^{2+} levels are crucial for its spreading.

SIGNIFICANCE STATEMENT

This highlights the importance of managing oxidative stress and regulating Fe levels to combat the infection effectively. Understanding these mechanisms can lead to the development of targeted treatments to mitigate the impact of SARS-CoV-2 on individuals. Additionally, research on the relationship between Fe levels and oxidative stress could provide insights into potential strategies for managing COVID-19. By focusing on these key factors, healthcare providers can tailor interventions to improve outcomes for patients affected by the virus.

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