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Review

People with blood disorders can be more vulnerable during COVID-19 pandemic: A hypothesis paper

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ABSTRACT

The world has been encountered with COVID-19 pandemic since at the beginning of 2020 and the number of infected people by COVID-19 is increasing every day. Despite various studies conducted by researchers and doctors, no treatment has been developed until now, therefore self-protection and isolation are strongly recommended to stop the spread of the virus. The elderly population and people with chronic diseases such as hypertension, cardiovascular diseases, diabetes, and cancer are categorized as risk groups, however, we suggest that people with hemoglobinopathies or porphyria can be described as risk groups as well. Current in silico studies have revealed that the COVID-19 virus can attack heme and hemoglobin metabolisms which are responsible for the oxygen transport to the tissues, iron metabolism, elevated levels of oxidative stress, and tissue damage. Data of the in silico study have been supported with the biochemistry and hemogram results of the COVID-19 patients, for instance hemoglobin levels decreased and serum ferritin and C-reactive protein levels increased. Indicated biochemistry biomarkers are tightly associated with inflammation, iron overload, and oxidative stress. In conclusion, since people with hemoglobinopathies or porphyria have already impaired heme and hemoglobin metabolism, COVID-19 infection can enhance the adverse effects of impaired hemoglobin metabolism and accelerate the progression of severe symptoms in patients with hemoglobinopathies or porphyria compared to the normal individuals. Thus those people can be considered as a risk group and extra precautions should be applied for them to protect them.

1. Introduction

COVID-19 pandemic affects almost all countries in the world and numbers of infected people and deaths are increasing every day worldwide [1]. COVID-19 virus is transmitted from one individual to another by respiratory droplets via infected person's cough, sneeze, or direct contact with infected individuals and objects like other influenza viruses' transmission ways. Since no effective drugs, treatments or vaccines against COVID-19 have been developed until now and virus spreads very quickly, self-isolation and protection are strongly suggested for all people especially the ones who are at the risk groups [1–3]. People over 65 years old and population with chronic diseases including hypertension, cardiovascular diseases, diabetes, cancer, immune system disorders and metabolic disorder are categorized as major risk groups [3].

Another risk groups can be stated patients with porphyria and hemoglobinopathies since COVID-19 impairs human heme metabolism via attacking it and impairs hemoglobin function in the erythrocytes and affects oxygen transport according to a recent in silico study [2]. Heme is porphyrin containing iron and found in the hemoglobin structure. Data obtained by in silico study have been supported with the serum biochemical and hemogram analysis of patients infected by COVID-19. For instance, hemoglobin levels of the infected people significantly decreased, on the other hand serum ferritin, erythrocyte sedimentation rate and C-reactive protein (CRP) levels increased which indicate impaired hemoglobin metabolism. Thus people with hemoglobinopathies and porphyria can be considered as risk groups as a result of enhanced impairment in the heme and hemoglobin metabolisms compared to the their general situation. Therefore, extra precautions should be considered for those people suffering from impaired heme and hemoglobin metabolisms [1,2,4].

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2. Hemoglobinopathies and porphyrias

Hemoglobinopathies such as alpha (α), beta (β) thalassemia and sickle-cell anemia, are most common monogenic disorders in the clinic and affect millions of people worldwide [5,6]. Thalassemia is a genetic disorder caused by defects in either α or β globin chain of hemoglobin which is a heterotetramer consisting of two α and two β globin chains. 280 millions of people are affected by thalassemias all over the world [7]. On the other hand, sickle cell anemia is inherited blood disorder caused by a point mutation in the 11. Chromosome of the β-globulin subunit of the hemoglobin. Approximately, 250 millions of people are affected of sickle cell anemia worldwide and the number of the newborn having sickle cell anemia is increasing every day [8]. Porphyrins are the major precursors of heme involving in the hemoglobin structure. Dysfunction of the porphyrin metabolism results in the accumulation of intermediates of the heme biosynthesis as a result of decreased heme synthesis and this condition is called as porphyria. Porphyrias can be categorized as liver or erythropoietic based depending on the sire where heme precursors accumulate such as liver, erythrocytes or bone marrow [9,10].

Function of heme, hemoglobin and RBC have been impaired in both hemoglobinopathies and porphyria's that leads to impairment in the RBCs homeostasis leading to the oxygen transport to the tissues and elevated levels of oxidative stress. Iron overload, impairment in the heme metabolism and elevated levels of the oxidative stress have been occurred as a result of these diseases. In silico data have revealed that COVID-19 virus can attack β-globulin chain of hemoglobin and impairs oxygen transport in the patients that can make people with impaired hemoglobin metabolism more vulnerable against COVID-19 compared to the normal individuals [2]. Additionally, we have previously suggested that people with glucose 6-phosphate dehydrogenase (G6PD) enzyme deficiency can be considered as risk groups because of the impairment in red blood cell (RBC) metabolism leading to the elevated levels of oxidative stress levels [1]. Since people having either hemoglobinopathies or porphyrias have already impaired oxygen transport metabolism because of dysfunction in the hemoglobin, heme and RBC metabolisms, COVID-19 infection may result in the severe symptoms, accelerated progression of disease and death for the people having hemoglobinopathies or porphyrias like people with G6PD deficiency even they do not have other chronic diseases [4–9].

3. Hypothesis: patients with impaired heme metabolism may become more vulnerable since during COVID-19 infection because of elevated levels of oxidative stress

3.1. Heme metabolism and oxidative stress

Heme is iron (Fe) containing porphyrin found in the RBCs and synthesized in the both cytosol and mitochondria. Senescent RBC are degraded by macrophages leading to the releasing heme and iron from hemoglobin structure. Heme groups participate in the protein structures called as hemoproteins involving in the various cellular processes including oxygen transport, redox metabolism, drug metabolism, oxygen storage, mRNA processing and steroid metabolism. Thus impairment in the heme metabolism causes elevated levels of oxidative stress as a result of dysfunction hemeproteins and free heme toxicity [11,12]. Elevated levels of free heme in the extracellular space is resulted from impairment in the heme and hemeprotein metabolisms and tightly associated with increased levels of oxidative stress [13]. Hemoproteins enable to balance free heme via protecting organisms from cytotoxic effects of free heme. Increased levels of free heme result in the overproduction of reactive oxygen species (ROS) which attack lipid, protein and DNA [14]. Increased levels of oxidative stress can damage tissue leading to the organ damage and associated with several diseases including diabetes, cardiovascular diseases, cancer and metabolic syndrome [15–18].

3.2. Hemoglobin and oxidative stress

Besides free heme, hemoglobin (Hb) can be another oxidative stress source in the organisms. Hb is a hemeprotein found in the red blood cells (RBCs) and responsible for the oxygen transport. Oxygen bounds to the hemoglobin molecules in the lungs as a region with high pressure of oxygen and hemoglobin releases oxygen at the tissues as regions with low oxygen pressures. ROS molecules including hydrogen peroxide (H_2O_2) and superoxide (O^{-2}) are produced during this process called as hemoglobin autoxidation [19,20]. This oxidant molecules are neutralized by powerful anti-oxidant metabolism of RBCs, however there is limited anti-oxidant capacity in the RBCs. Extracellular Hg originating by hemolysis of RBCs is the another potential source of oxidative stress and molecules including haptoglobin and hemopexin bind to both extracellular Hg and free heme to neutralize ROS. Impairment of the heme and Hg metabolisms causes adverse health effects as a result of elevated levels of oxidative stress leading to the tissue damage [21].

3.3. Blood transfusions, oxidative stress and vulnerability against infections

People with blood disorders including thalassemia, hemoglobinopathies and porphyria's are in need of red blood cell transfusions from either peripheral blood or stem cell derived RBCs as therapeutic approaches [22]. Alloimmunization and iron overload are major clinical complications which limit blood transfusion therapies in those patients. Alloimmunization can be described as a response to donated RBCs leading to the acute hemolysis in the patients [22,23]. On the other hand, iron overload is the main contributor of the elevated levels of oxidative stress in the patients with blood disorders and the ones are in need of blood transfusions. Also, one of the main side effects of the blood disorders is iron overload as a result of impaired heme metabolism [2,20,21].

Blood transfusions can make people more vulnerable against COVID-19 infection as a result of side effects of blood transfusions such as iron overload and alloimmunization, regular hospital visits and transfusion associated infections [24]. On the other hand, people with hematological malignancies are more vulnerable against COVID-19 infection compared to the non-infected patients with hematological malignancies, because immunocompromised status of those patients can enhance the vulnerability of them against various types of infections including COVID-19 [25,26]. Besides, plasma transfusion from fully recovered individuals after infected by COVID-19 to the patients with severe COVID-19 symptoms have become highlighted during this pandemic as a therapeutic tool [26,27]. Since people with co-morbidities such as hematological malignancy or blood disorder are more vulnerable against COVID-19 as risk groups, plasma transfusion can be considered as therapeutic approach especially for those patients [22–27].

3.4. Evaluation of the hypothesis

Hemoglobin is the hemeprotein found in the RBCs responsible for the oxygen transport in the mammalians and hemoglobin synthesis accounts for 85% of heme synthesis daily [28]. Oxygen transport produces ROS by itself in the RBCs that is neutralized by anti-oxidant metabolism of erythrocytes. Anti-oxidant enzymes including glutathione s-transferase (GST), glutathione peroxidase (GPx), glutathione reductase (GR), super oxide dismutase (SOD), glucose 6-phosphate dehydrogenase (G6PD) and 6-phoshogluconate dehydrogenase (6-PGD) are mainly responsible for the homeostasis of the redox metabolism in the organisms. Impairment in the anti-oxidant enzyme metabolism is tightly associated with the elevated levels of the oxidative stress and thus tissue damage [15–18,29–31]. Thus we have previously reported that people with the G6PD deficiency may be more vulnerable against COVID-19 infection as a result of enhanced impairment in the oxidative stress metabolism in the RBCs leading to the hemolysis, tissue damage, and insufficient

oxygenation of the tissues compared to the normal progression of the G6PD deficiency [1].

Following the same logic people with hemoglobinopathies and porphyrias may be more vulnerable against COVID-19 infection, since both diseases result in the impaired oxygen transportation and oxidative stress metabolism as a result of dysfunction in the both heme and hemoglobin metabolisms [32]. For instance, in the thalassemia pathogenesis, unstable hemoglobin molecules are formed and degraded that leads to the elevated levels of free heme and iron which both contribute to formation of the oxidative stress [11,13,33]. On the other hand, sickle cell disease (SCD) is another hemoglobinopathy described by increased autoxidation of hemoglobin, impaired oxygen transportation, iron accumulation and impaired function of RBCs contributing elevated levels of oxidative stress. Additionally, heme degradation significantly increases in the hemoglobinopathies including thalassemias and sickle cell disease [34]. On the other hand, porphyrias arise from the accumulation of the porphyrins and their precursors such as 5-Aminolevulinic acid (ALA), which are known by their contribution to the formation of ROS [35]. Overall, hemoglobinopathies and porphyrias cause impaired oxygen transport, elevated levels of oxidative stress, inflammation and damaged RBC metabolism because of dysfunction in the both heme and hemoglobin metabolism [32–35].

A current in silico study has revealed that COVID-19 attacks heme and hemoglobin causing impairment in the oxygen transport and RBCs metabolisms same as pathology of hemoglobinopathies and porphyrias [2]. Data of the in silico study have been validated via serum biochemistry and hemogram data, for instance hemoglobin levels significantly decreased in the COVID-19 patients [2]. Since hemoglobin is responsible for the oxygen transport to the tissues, decreased levels of hemoglobin results in the impaired oxygen transport and increased levels of oxidative stress in the tissues [36]. On the other hand serum ferritin, erythrocyte sedimentation and CRP levels significantly increased in the COVID-19 patients [2]. Ferritin is a cytosolic protein and responsible for the intracellular iron homeostasis. Elevated levels of serum ferritin can be associated with the iron overload which can be resulted from impaired hemoglobin and heme metabolism. Elevated levels of iron is also contributed to the oxidative stress [37–39]. CRP is produced by liver and indicator of the both chronic and acute inflammation in the body [40].

Blood transfusions required for people with blood disorders are another critical point during COVID-19 because of side effects of transfusion, hospital visits and transfusion-associated infection risk. Iron overload and alloimmuzitaion are major drawbacks of blood transfusion therapies and both side effects may contribute to the elevated levels of oxidative stress in patients [22–27]. Since COVID-19 infection attack heme and hemoglobin metabolism leading to the impaired oxidative stress metabolism, repeated blood transfusions make those patients more vulnerable against COVID-19 infection and may increase mortality risk. Besides, hospital visits are dangerous for both people with blood disorders and cancer patients including hematological malignancies, because immunocompromised status of those patients [22–30].

On the other hand, vulnerability to COVID-19 infection correlated with blood group type has been studied previously. Correlation of the ABO blood antigens with the various diseases and infection such as cancer, MERS, SARS-COV and HBV have been reported in the literature previously [41,42]. ABO blood groups system consists of the 3 antigens including A, B and H. Current studies have reported that 0 groups less vulnerable against COVID-19 infection where A groups are more vulnerable. Studies have shown that 0 blood type has lower ACE2 and increased levels of IL-6. COVID-19 virus utilizes ACE2 to entrance into the host cells and reduced numbers of ACE2 may cause less vulnerability of 0 blood type against COVID-19 infection. Additionally, anti A antibody on the red blood cells may inhibit S protein of SARS-COV, thus people with 0 blood type may have advantage on the AB0 blood types [41–43]. Interestingly, Hsieh et al. reported that blood type 0 is less vulnerable against oxidative stress compared to the other blood types [44]. However certainty and possible molecular mechanisms behind these hypothesis should be further investigated.

In brief, COVID-19 is a novel pandemic and world is learning new information related to this virus [45,46]. COVID-19 infection causes elevated oxidative stress levels and inflammatory response which can be resulted from attacking to the heme metabolism and hemoglobin by COVID-19. Thus, people already having impaired hemoglobin and heme metabolisms such as hemoglobinopathies and porphyrias can be more vulnerable against COVID-19 infection, since this virus can attack heme metabolisms and enhanced adverse effects of infection in those patients compared to the normal individuals.

4. Conclusion

In conclusion, CODIV-19 pandemic threatens millions of lives all over the world and there is no treatment against this virus. Thus self-isolation and protection are highly recommended to stop the spread the virus, especially the ones who are categorized as risk groups. Medical doctors and researchers should be determined by the possible risk groups to protect vulnerable population and to stop the spread of the virus. People with blood disorders including hemoglobinopathies, porphyrias and thalassemias can be considered as risk group against COVID-19 infection because of impairment in the oxygen transport and elevated oxidative stress levels caused by the disease itself and enhanced as a result of attack of COVID-19 to the heme metabolism and hemoglobin function. Therefore extra precautions should be taken and self-protection should be applied seriously for those patients. Additionally, during COVID-19 pandemic, data of people with blood disorders infected by COVID-19 should be collected and vulnerability of those patients against infection should be further investigated. Thus, possible mechanism and drug interactions contributing this vulnerability could be revealed.

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Author contributions

D.A. and N.N.U. have made substantial contributions to the conception and design of the manuscript. They both have written the draft and made final revisions.

Declaration of Competing Interest

The authors report no declarations of interest.

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