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G6PD Deficiency and COVID-19 in Burkina Faso: A Possible Link?

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Abstract

Burkina Faso is a malaria-endemic country, with a high incidence of G6PD deficiency (G6PDd), which recorded its first case of COVID-19 in March 2020. G6PDd leads to a decrease in the efficiency of erythrocytes to combat oxidative stress, while SARS-CoV-2 infection induces massive production of Reactive Oxygen Species (ROS) in patients. In the present review, we discuss a possible link between G6PDd and SARS-CoV-2 infection. The mean prevalence of G6PDd in Burkina Faso is estimated at 16.6% among males and 6.5% among females. A total of 21,128 cases of COVID-19 have been recorded in Burkina Faso with 387 deaths reported (with a mortality rate of 1.15% among diagnosed cases) as of August 30, 2022. To our knowledge, no association study between G6PDd and SARS-CoV-2 infection has been conducted to date in Burkina Faso. However, several case reports around the world have described elevated risks of hemolysis and thrombosis, and other complications among G6PD-deficient patients infected with SARS-CoV-2. The use of Hydroxychloroquine (HCQ) has also been deemed unsafe by some authors for the treatment of COVID-19 among patients with G6PDd. Although HCQ has been shown to be well tolerated in COVID-19 patients in Burkina Faso, the drug could induce hemolytic crises in people with G6PD deficiency. G6PD is important in regulating ROS and maintaining erythrocyte homeostasis. In view of its high prevalence in Burkina Faso, determination of the G6PD status is required in COVID-19 patients for adequate management such as identifying a subset of COVID-19 patients for whom close monitoring and supportive care may be essential and to restrict treatment with HCQ.

Keywords

G6PD Deficiency, COVID-19, CQ/HCQ, Hemolysis, Burkina Faso

1. Introduction

Burkina Faso is an endemic country for malaria with a high frequency of G6PD deficiency (G6PDd) [1] [2] [3] [4] [5], an X-link inherited disorder that affects more than 500 million people worldwide [6]. With an estimated prevalence of 16.6% in men and 4.5% in women, G6PDd affects more than 2 million people in Burkina Faso [4]. It has been suggested that the maintenance of such a genetic abnormality at high frequencies would be due to the selective advantage that they generally confer in the heterozygous state on individuals living in malaria-endemic areas [2] [3] [4] [7] [8]. Indeed, G6PDd has been shown to be associated with a decreased risk of cerebral malaria and an increased risk of severe malaria anemia [8] [9]. G6PDd leads to a decrease in the efficiency of erythrocytes to combat oxidative stress [6]. People affected by this genetic disorder are sometimes vulnerable to Reactive Oxygen Species (ROS) induced by the ingestion of certain foods, drugs, or infections such as COVID-19.

Burkina Faso recorded its first case of Coronavirus Disease-2019 in March 2020 with 387 deaths reported so far [10] [11]. Coronavirus Disease-2019 (COVID-19) is the clinical manifestation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Since its outbreak in 2019, SARS-CoV-2 has continued to evolve and adapt [12]. A seroprevalence of 18% (36/200) of SARS-CoV-2 IgM and/or IgG has been reported in People Living with HIV with no COVID-19 symptoms in Burkina Faso [13]. The rapid development of effective anti-COVID-19 vaccines has enabled control of the pandemic which has shaken national and global health systems and disrupted socio-economic activities [14] [15]. It is well known that SARS-CoV-2 infection leads to massive production of ROS in patients [16]. Such an infection could, therefore, have serious consequences in people with a G6PDd whose antioxidant defense is impaired [2] [4]. Indeed, most viral infections have a strong association with G6PD, and COVID-19 posed new challenges in diagnosing G6PDd, given its association with hemolysis [17]. In addition, renewed interest in Chloroquine (CQ) and Hydroxychloroquine (HCQ), which has been suggested as a treatment for COVID-19 despite a lack of evidence of its effectiveness, has prompted the government of Burkina Faso to set up the Chloroquine Clinical Trial (CHLORAZ) [18].

Although HCQ has been shown to be well tolerated in COVID-19 patients in Burkina Faso, the drug could induce hemolytic crises in people with G6PD deficiency [19] [20] [21]. Despite the high prevalence of G6PDd in Burkina Faso, to our knowledge, no study determines the role of this genetic pathology in SARS-CoV-2 infection. In this review, we suggest that G6PD deficiency with a frequency of about 14% in Burkina Faso could worsen the clinical course of

SARS-CoV-2 infection and induce hemolytic crises following or not treating with CQ or HCQ.

2. COVID-19 Pandemic in Burkina Faso

Since December 2019, the world has been dealing with a new coronavirus that causes Severe Acute Respiratory Syndrome (SARS) called SARS-CoV-2 and the associated disease known as Coronavirus Disease-2019 or COVID-19 [22].

COVID-19 continues to wreak havoc around the world challenging the most sophisticated healthcare systems with 606,774,762 cases and 6,490,433 deaths reported as of August 30, 2022 [23]. It was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020. Since then, several controversial treatments including CQ, HCQ and azithromycin have been proposed to fight against the COVID-19 which is not yet finished revealing all its secrets [24] [25]. The unprecedented development of vaccines in a short time has renewed hope for defeating COVID-19, although vaccine hesitancy remains a significant barrier to achieving widespread vaccine uptake.

The first official case of coronavirus was notified in Burkina Faso on March 09, 2020, with 21,128 cases recorded and 387 deaths reported (*i.e.* a mortality rate of 1.15% among diagnosed cases) as of August 30, 2022 [11]. In line with the differences on the effectiveness of CQ in the treatment of COVID-19, the government of Burkina Faso has set up the clinical trial on CQ (CHLORAZ) [18]. The preliminary results of the CHLORAZ study in December 2020 indicated a benefit of the treatment with the combination HCQ + azithromycin in COVID-19 patients in Burkina Faso without being able to conclude on the effectiveness of the treatment in question [18]. The researchers also reported that 2/3 of patients infected with SARS-CoV-2 in their study were males, with 75% of their study population being under 42 years old [18].

Another study conducted between March and April 2020 demonstrated that treatment with CQ or HCQ in combination with azithromycin had no effect on the mortality or the hospital recovery rate associated with COVID-19 in Burkina Faso [26]. Mortality from COVID-19 is relatively high among the elderly and those with comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer [17]. People of black descent appear to be more affected by complications from COVID-19 than white populations [17].

Literature data show that infection with SARS-CoV-2 leads to massive production of ROS that can be a source of complications in people with G6PD deficiency [17]. Genetic abnormalities such as G6PDd are therefore to be considered in the risk of complications from COVID-19, especially in Burkina Faso where the frequency of this genetic pathology is high [2] [3] [4].

3. G6PD Deficiency in Burkina Faso

The prevalence G6PDd is high in Burkina Faso due to malaria selection pressure [2] [3]. An estimated prevalence of 16.6% in males and 6.5% in females of

G6PDd have been reported in the country [4]. The enzyme deficiency is due to mutations in the G6PD gene located on the X chromosome [3]. Males, therefore, have only one G6PD allele and can be either hemizygous normal or hemizygous deficient. Conversely, females with 2 G6PD alleles may be either homozygous normal, homozygous deficient or heterozygous for G6PDd. An heterozygous female may thus present a mosaic of cells expressing the wild-type enzyme and cells expressing a deficient variant, with a variable proportion of normal and deficient erythrocytes due to a random X-chromosome inactivation (lyonization) (**Figure 1**).

There are 230 G6PD variants with known mutations [6]. The most common deficient variant or G6PD A- in Sub-Saharan Africa has two mutations G202A (rs1050828, Class III variant) and A376G (rs1050829, Class IV variant) in cis with high linkage disequilibrium. It is the most studied variant in Burkina Faso and reported in 99.8% of G-6-PDd cases in the country [2] [4]. Santamaria 542T (rs5030872, Class II variant) and Betica Selma 968C (rs76723693, Class III variant) variants have also been identified in Burkina Faso [3] (**Figure 2**).

The gene encoding G6PD is located on the telomeric part of the long arm of the X chromosome, in position q28 [27]. It extends over approximately 18 kb and comprises 13 exons and 12 introns and codes for a polypeptide chain of 514 amino acids whose dimer and tetramer are the active enzymatic forms of G6PD [6]. Exon 13 is approximately 800 nucleotides long and contains the translation stop codon.

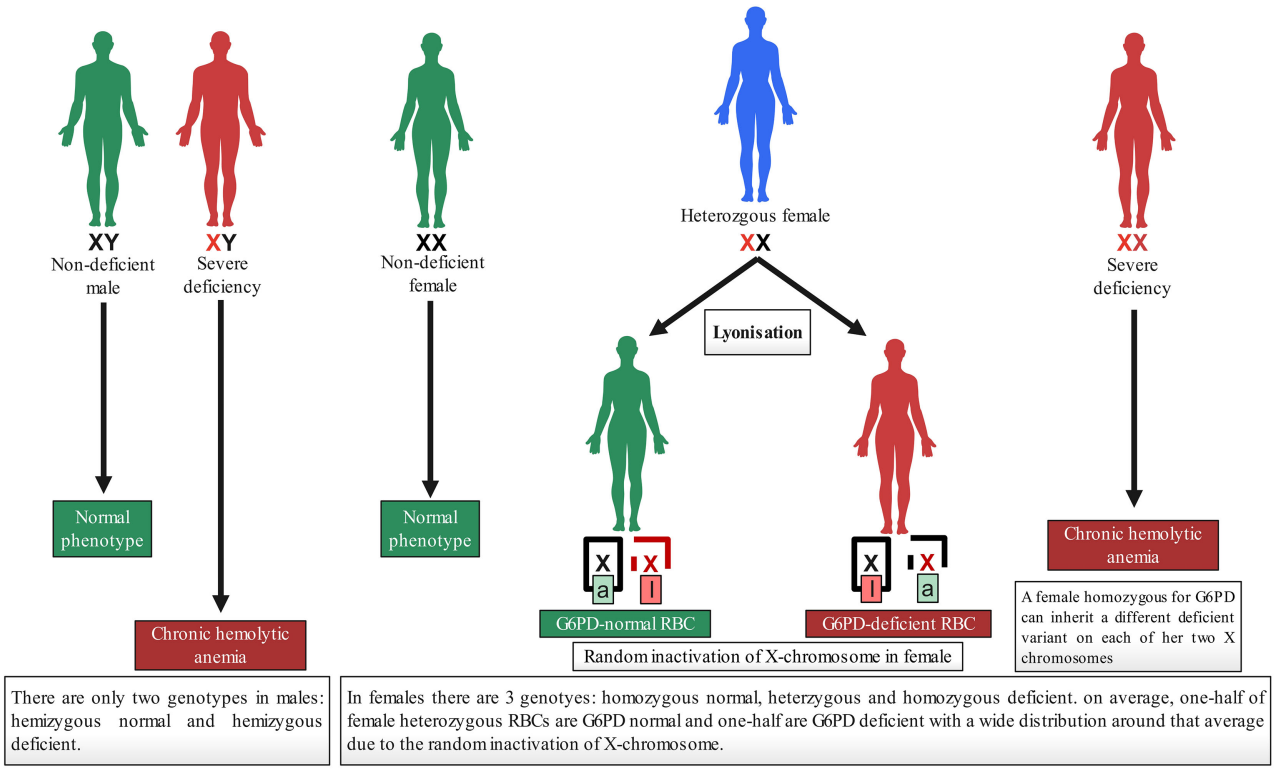

Figure 1. Manifestation of G6PD deficiency in males and females (Source: adapted from Ouattara *et al.*).

The coding region is divided into 12 segments ranging in size from 12 bp to 236 bp [27] [28]. The first exon contains no known coding sequence and intron 2 (II) between exons II and III is extraordinarily long, approximately 9857 bp in size.

4. G6PD Deficiency and Oxidative Stress

Glucose-6-phosphate dehydrogenase is a ubiquitous enzyme present in the cytoplasm of all cells [29]. It catalyzes the first step of the pentose phosphate pathway which generates reduced Nicotinamide Adenosine Dinucleotide Phosphate (NADPH). NADPH plays an essential role in the reduction of oxidizing agents [29], by allowing the red blood cell in particular, to maintain the reduced glutathione pool at a normal level (**Figure 3**).

When the red blood cell has an effective G6PD enzyme, it therefore resists oxidative stress, while the deficiency of G6PD enzyme makes the red blood cell vulnerable to oxidative damage (oxidizing molecules, infections) with consequences such as hemolytic anemia sometimes requiring blood transfusions [29] [30].

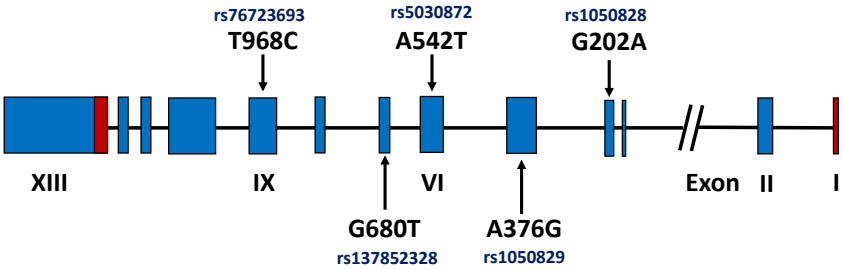

Figure 2. G6PD gene with mutations studied in Burkina Faso (Source: adapted from Cappellini and Fiorelli [27]).

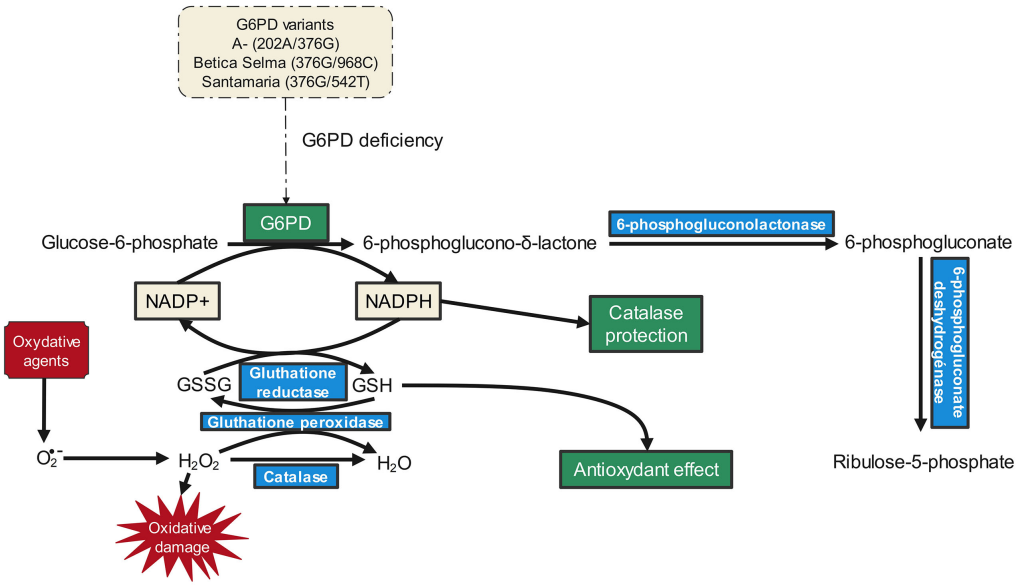

Figure 3. Role of G6PD in combating oxidative stress (Source: adapted from Luzzatto *et al.* [31]).

In G6PD-normal red blood cells G6PD generate enough NADPH to regenerate GSH when it is oxidized by reactive oxygen species (*e.g.* O_2- *and* H_2O_2). O_2- *is one of the most reactive forms of oxygen that can be generated from the metabolism of pro-oxidant compounds and can directly lead to the production of hydrogen peroxide* (H_2O_2), *the accumulation of which causes oxidative damage to the cell.*

The appearance of symptoms in a patient with G6PDd depends on two main factors, namely the level of G6PDd in the host and the intensity of oxidative stress within the erythrocytes [30]. The main clinical manifestation of G6PDd is hemolysis, which can result in three clinical pictures, namely:

Acute hemolytic anemia, induced by the ingestion of some drugs or foods, or during an infection;

✓ Chronic hemolytic anemia;

✓ Neonatal jaundice, with neurological sequelae in the most severe and untreated cases.

Most often, apart from the forms of chronic hemolytic anemia which are rare, the deficient patient does not present any particular symptom [29].

A large clinical heterogeneity is observed depending on the molecular nature of the deficiency and the residual activity of the enzyme in the red blood cell [30].

The WHO classification of G6PDd into the top five classes is based on the level of erythrocyte activity of the enzyme and the extent of the clinical manifestations. In fact, Class I presents a severe enzyme deficiency (residual enzyme activity <10%) associated with chronic non-spherocytic hemolytic anemia [29]. Class II is also characterized by a severe deficiency with less than 10% residual enzyme activity associated with acute hemolytic anemia while Class III presents a moderate deficiency (10% to 60% residual activity). Class IV enzyme activity is normal while Class V exhibits very high enzyme activity [29].

5. Possible Association between COVID-19 and G6PD Deficiency

Although the exact mechanisms are still unknown, a possible association between COVID-19 and G6PD deficiency has been suggested [32] [33] [34]. Risk of hemolysis and thrombosis may be elevated among G6PD-deficient patient infected with COVID-19 [35]. COVID-19 infection triggers massive ROS production that requires sufficient G6PD activity for large NADPH production to control oxidative stress (**Figure 4**).

G6PD catalyzes the first step of the pentose phosphate pathway which provides NADPH and ribose 5*-phosphate precursor for the synthesis of nucleotides, nucleic acids, and coenzymes. Nucleic acids generated by the pentose phosphate pathway are used for viral infection. In red blood cells deficient of G6PD* (*G6PD A-, Santamaria or Betica Selma*) *where the enzyme activity is reduced, the production of NADPH is limited, and may not be sufficient to cope with the excess*

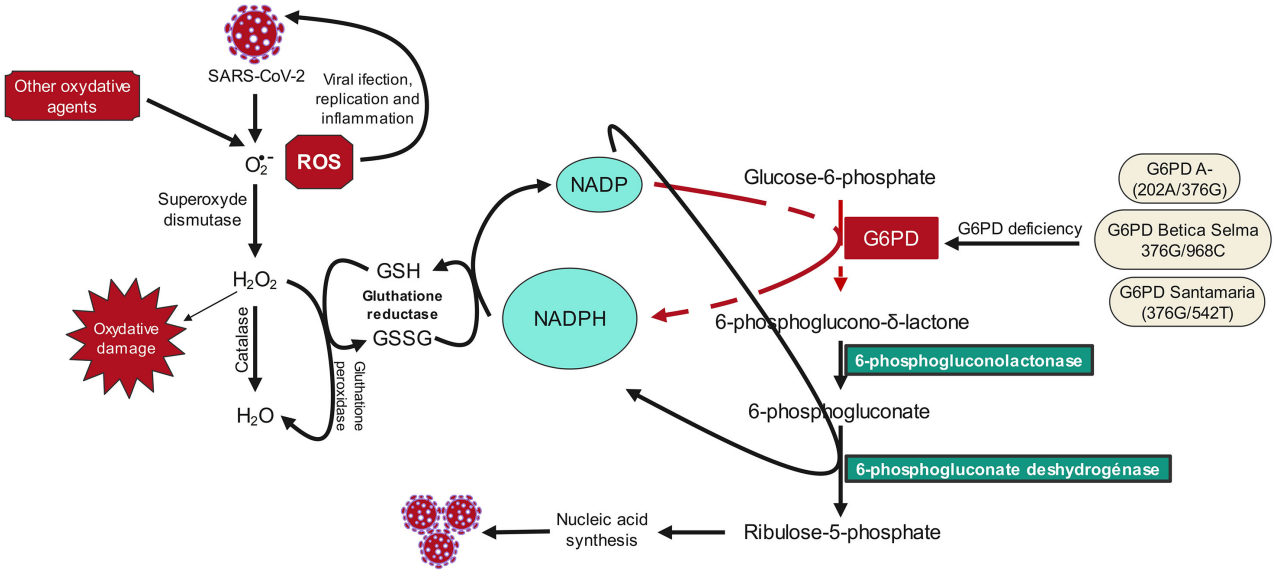

Figure 4. Possible link between COVID-19 and G6PD deficiency (Source: adapted from Luzzatto *et al.* [31] and Jain *et al.* [17]).

of reactive oxygen species generated in the presence of pro-oxidant compounds. Nucleic acids generated by the pentose phosphate pathway are used for viral infection. COVID-19 infection triggers massive production of ROS which in turn requires increased G6PD activity and NADPH production to control oxidative stress. Excessive oxidative stress can promote viral infection, replication, and inflammation.

In their retrospective study carried out among hospitalized patients with COVID-19 related pneumonia, Youssef *et al.* (2021) suggested a possible biological role of G6PDd in SARS-CoV-2 viral proliferation [36]. Indeed, massive ROS production due to SARS-CoV-2 infection could trigger hemolytic anemia among G6PD-deficient individuals, thus worsening the COVID-19 disease outcome [17]. For example, ex vivo studies have previously reported an increased vulnerability of G6PD-deficient cells to Human Coronavirus (HCoV 229E) infection compared to cells with a normal level of G6PD [37]. A recent study also reported a high frequency of G6PDd among hospitalized COVID-19 patients [38].

Several case reports have revealed that SARS-CoV-2 infection can trigger a severe acute hemolytic crisis in a patient with G6PDd [39] [40] [41]. Separately, a study suggests that G6PDd may predispose individuals to rhabdomyolysis due to COVID-19, likely due to altered host responses to viral oxidative stress [42]. However, Kumar *et al.* [43] found that complications were not significantly different among hospitalized COVID-19 patients with or without G6PDd. All of this, points to the allelic heterogeneity of G6PDd in males and females with varying clinical effects [3] [9] which requires fine investigations for a more complete overview of the role of G6PDd in the pathophysiology of COVID-19 disease complications. Additionally, older adults with G6PDd are at higher risk of having red blood cells with reduced amounts of G6PD, low glutathione, and increased red blood cell turnover time [44]. This may predispose elderly patients

with G6PDd to be more susceptible to hemolytic crises following exposure to certain triggering events such as SARS-CoV-2.

6. Influence of G6PD Deficiency on COVID-19 Disease Therapies

G6PDd may particularly predispose to hemolysis upon SARS-CoV-2 infection when employing pro-oxidant therapy [19] [45]. Aminoquinolines are believed to exert their antimalarial effect by increasing oxidative stress via the production of heme-based reactive oxygen species [46]. CQ, HCQ and other aminoquinolines used in the treatment of malaria have pharmacogenomic associations with the glucose-6-phosphate dehydrogenase (G6PD) gene [33]. Indeed, in patients with G6PDd, NADPH supply may be insufficient to neutralize ROS induced by CQ, HCQ and other drugs with similar mechanisms of action. HCQ is only licensed for the treatment of malaria, lupus erythematosus and rheumatoid arthritis. However, it has been suggested as a treatment for COVID-19 disease infection, despite the insufficient evidence. Some studies have shown that treating COVID-19 disease with HCQ can worsen hemolytic crisis in a G6PD-deficient patient [39] [47].

Maillart *et al.* (2020) reported severe hemolysis in a COVID-19 patient with G6PDd treated with HCQ. In their study showing that the severity of COVID-19 disease was not associated with G6PDd, the authors clearly noted a restricted use of HCQ in people with G6PDd to avoid side effects [43]. It should also be noted that the benefits of chloroquinotherapy strongly depend on the age of the patient; clinical manifestation and stage of COVID-19 disease.

The use of CQ and HCQ under strict medical supervision is, therefore, necessary to optimize their effectiveness and avoid adverse effects that can lead to serious complications. Some studies suggest that HCQ can be safely administered in the setting of G6PDd [48] [49] [50] [51]. Indeed, a brief report demonstrated that HCQ does not induce hemolytic anemia or organ damage in a "humanized" G6PD A- mouse model [52]. However, caution should be taken with the prior determination of the COVID-19 patients' G6PD status before any treatment with CQ and HCQ, especially since a case of hemolysis following vaccination against COVID-19 disease has also been reported in the literature [53].

7. Conclusion

G6PD is extremely important in regulating ROS and maintaining erythrocyte homeostasis. Studies are needed to elucidate the contributing role of G6PDd in the virulence of SARS-CoV-2 in Burkina Faso. The G6PD enzyme activity deficiency results in an alteration of the red blood cell antioxidant defense systems that can lead to hemolytic crises triggered by SARS-CoV-2 infection or HCQ treatment. Since HCQ as well as SARS-CoV-2 infection are sources of harmful ROS for G6PD-deficient patients, particularly of advanced age. The G6PD status determination for patients with COVID-19 disease should be required for adequate management.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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