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Short Communication

Periodontal disease and hemolysis in glucose-6-phosphate dehydrogenase deficiency: Is there a nexus?

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ABSTRACT

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an erythrocyte enzyme defect that amplifies the susceptibility of erythrocytes to oxidative stress due to excessive levels of reactive oxygen species. Consequently, erythrocyte destruction and hemolysis occur.
Highlight: The possible mechanism of oxidative stress-mediated destruction of erythrocytes in G6PD deficient individuals induced by periodontal infection is highlighted.
Conclusion: Periodontal diseases feature systemic loading of reactive oxygen species, and they may increase the risk of hemolysis in individuals with G6PD deficiency.

1. Introduction

Reactive oxygen species (ROS) are crucial signaling molecules in various cellular events. Molecular oxygen is the source of ROS. Once formed, ROS impair various cellular events if they are not balanced by anti-oxidants. ROS are the critical components of the host defense to various insults such as bacteria, [1] trauma, and burns [2]. ROS are produced by mitochondria, cytochrome P-450 reactions, peroxisomal fatty acid metabolism, and NADPH oxidase activity [3,4]. ROS mediated oxidative stress is lessened by anti-oxidant systems that do not involve enzymes, which include reduced glutathione (GSH); ubiquinols; uric acid; vitamins A, C, E; flavonoids, and carotenoids, as well as enzymatic systems (superoxide dismutase, catalase, glutathione peroxidase, and myeloperoxidase). Oxidative stress is generated by a disturbance in balance between the oxidant (ROS) and anti-oxidant systems. An increase in the levels of oxidants and/or a decreased level of antioxidants triggers an array of oxidative reactions that result in tissue injury. Upregulated levels of ROS result in oxidative stress, which has been incriminated in the pathology of various systemic disorders, including diabetes mellitus and cardiovascular disorders [5–7]. The deficiency of glucose-6-phosphate dehydrogenase (G6PD) can lead to increased levels of ROS. Periodontal infections act as a continuous reservoir of ROS. Hence, these infections can pose a risk of hemolysis in individuals with G6PD deficiency.

2. G6PD Deficiency

G6PD deficiency is common and affects over 400 million people globally. X-linked inheritance and hereditary mutations in the gene encoding G6PD are the causes of this deficiency. The mutations result in variants of the protein with varying enzymatic activities that are accompanied by a large number of biochemical and clinical phenotypes. Clinically, G6PD deficiency presents with neonatal hyper-bilirubinemia and acute hemolysis, which is commonly provoked by an oxidative stressor. Chronic hemolysis is also a feature of variants of G6PD [8]. G6PD deficiency is prevalent in sub-Saharan Africa and the Arabian Peninsula. In Arab countries, G6PD deficiency is one of the most prevalent genetic diseases with reported prevalence rates of 39.8% in Saudi Arabia, 30% in Syria, and 29% in Oman [9–11].

G6PD is essential for the first event of the pentose phosphate pathway (PPP), where glucose is transformed into a variety of pentose sugars that are necessary for glycolytic and other biochemical processes. In its oxidative phase, the PPP supplies reducing power in the form of NADPH (Fig. 1a), through the action of G6PD and 6-phosphogluconate dehydrogenase. NADPH is an electron donor for most of the enzyme reactions necessary in biochemical events, and its synthesis is critical for cellular defense against oxidative stress [8]. The PPP supplies NADPH for the conversion of oxidized glutathione

Abbreviations: ROS, Reactive oxygen species; GSSG, oxidized glutathione; GSH, reduced glutathione; PPP, Pentose phosphate pathway

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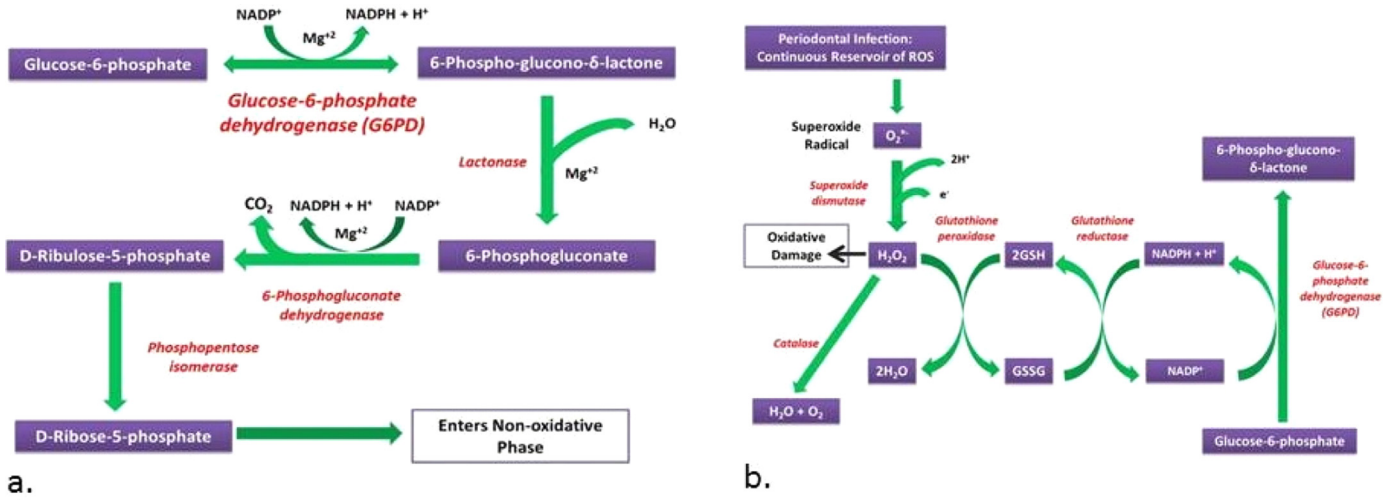

Fig. 1. a. Oxidative Phase of Pentose phosphate pathway; b. Role of NADPH and glutathione in preventing oxidative damage in cells.

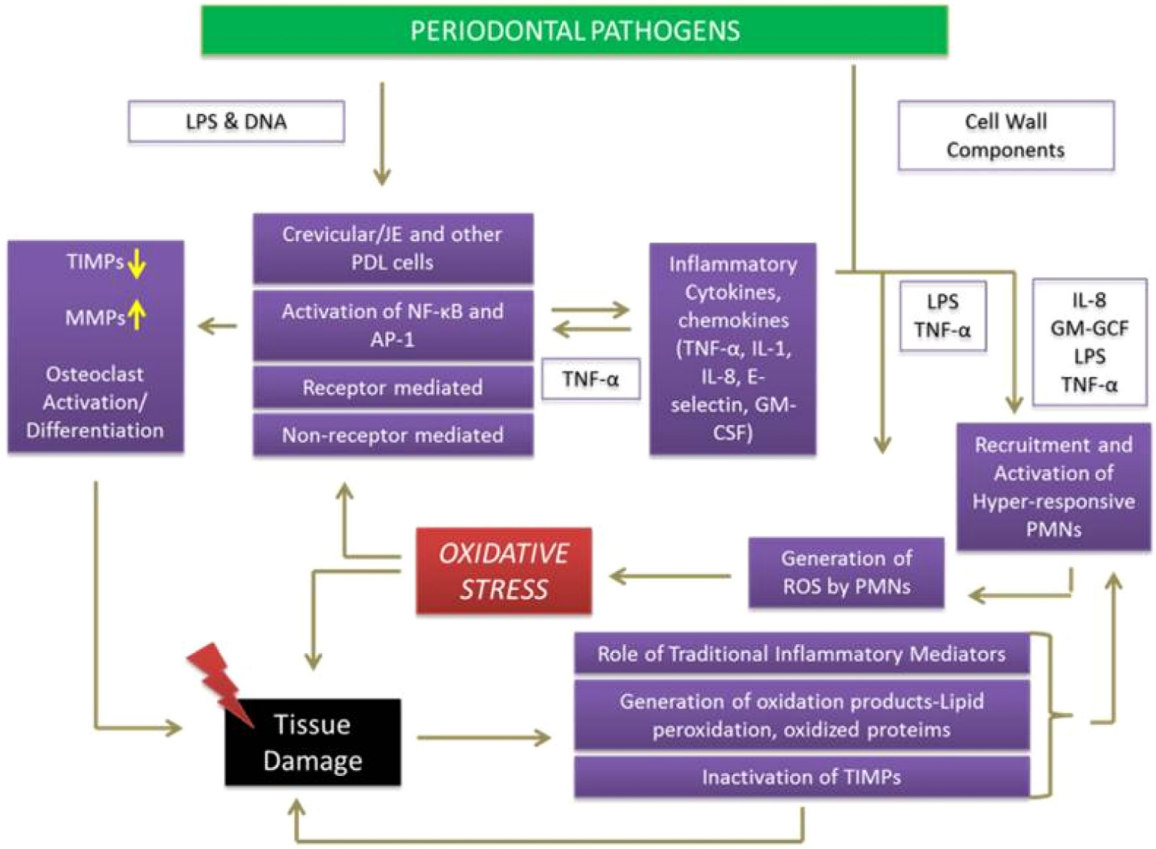

Fig. 2. Periodontitis: Reservoir of oxidative stress.

(GSSG) to reduced glutathione (GSH). This reaction is mediated by glutathione reductase, an FAD-containing flavoprotein. GSH eliminates hydrogen peroxide (H_2O_2) from cells in a reaction catalyzed by glutathione peroxidase (Fig. 1b). This reaction is crucial (especially for erythrocytes), since the accumulation of H_2O_2 may reduce the life span of erythrocytes by oxidative stress related damage to the cell membrane, which leads to hemolysis [12]. NADPH is the key to cellular antioxidant systems. It acts as a balancing agent to counteract oxidative stress conditions that can be provoked by a variety of oxidants, and to maintain GSH levels. Erythrocytes do not possess mitochondria, so the PPP is the sole supply of NADPH. Therefore, resistance of erythrocytes to oxidative damage relies on G6PD activity. When G6PD is deficient, erythrocytes become more vulnerable to oxidative damage [8].

Exposure to any type of oxidant/oxidative stressor (mainly infection, oxidative drugs, or fava beans) can set up a state of hemolysis in patients with G6PD deficiency [13]. Of these stressors, infection is considered the most common etiology of hemolysis, although the precise mechanism is unclear. It may be that oxidants released by leukocytes during the host response create oxidative stress that affects the erythrocytes [14]. In this context the continuous production of ROS during periodontal infections can pose a threat.

3. Periodontal infection and ROS

Periodontal disease is a complex multifactorial disease that features an up-regulated or maladapted immune-inflammatory host response to bacterial plaque. The response predisposes to periodontal breakdown. The infection features the formation of surface-adherent biofilms that are associated with damage to the periodontium [15]. Susceptibility to periodontal destruction is due to a phenotype typified by a"hyper-inflammatory" reaction to the bacteria enmeshed within the biofilm [16].

A plethora of evidence has established that oxidative stress is part of the pathological destruction of periodontium in various periodontal diseases. Increased ROS production and decreased levels of anti-oxidants from the gingival crevicular fluid are observed in periodontal diseases (Fig. 2) [17–19]. ROS are responsible for the activation of inflammatory reaction in the localized environment and for the destruction of periodontal tissue. Recruitment of polymorphonuclear leukocytes (PMNs) with the production of ROS and proteolytic enzymes is an important aspect of the host immune-inflammatory reaction to bacteria in individuals susceptible to periodontitis. In these individuals, hyper-active/reactive PMNs from the peripheral blood migrates via chemo-attraction to the periodontal tissues and exuberantly produce ROS spontaneously and following provocation of Fc γ-receptors or Toll-like receptors on the PMN surface by their corresponding ligands [20,21]. The increased ROS present in the local periodontal environment produced by PMNs during the process of inflammation is thought to cause further collateral tissue breakdown by direct and indirect induction. Direct induction occurs through the oxidation of components of vital tissue. Indirect induction occurs through redox sensitive gene transcription factors like nuclear factor-kappa β and activating protein-1 which downregulate an array of pro-inflammatory peptides and accelerate cellular senescence [22].

Increased oxidative stress in the periodontium is localized in the periodontal tissues and leads to an overall systemic inflammatory reaction [23]. Animal studies have revealed high levels of lipid peroxidation, H_2O_2, and oxidative DNA damage in experimental periodontitis [24]. Also, the levels of antioxidant compounds are decreased in the serum of periodontitis patients [18,19,25,26]. Reports have described raised serum levels of markers of oxidative stress, including diacron-reactive oxygen metabolites [27], protein carbonyl [28], and the hyperoxide ROOH [29] in periodontitis patients. Decreased plasma small molecule antioxidant capacity [30,31] and increased plasma levels of cytokines as well as C-reactive protein [32,33] have been demonstrated in periodontitis. The collective findings indicate that periodontal infections could result in a significant systemic loading of ROS pertinent to various systemic diseases.

This systemic loading of ROS and inflammatory markers that occurs during periodontal infections may induce hemolysis in an environment of G6PD deficiency (Fig. 3). This speculation warrants further attention. There is a lack of literature regarding the link between periodontal disease and hemolysis in individuals with G6PD deficiency. One report mentioned periodontal considerations in G6PD deficiency [34]. The authors described that in healthy systemic conditions, acute gingival inflammation can increase G6PD expression in response to lipopolysaccharide stimulation in primary gingival epithelial cells. They suggested that this may be a host response to attenuate oxidative stress by generating NADPH rather than via the PPP. These changes are not seen in chronic periodontitis, which may be an adaptation of the localized tissue response to create a more homeostatic glycolic local environment [35].

4. Clinical relevance of the link between G6PD deficiency and periodontal infections

The key to management of G6PD deficiency is prevention of exposures triggering hemolysis (Fig. 3). Oxidative stress inducing

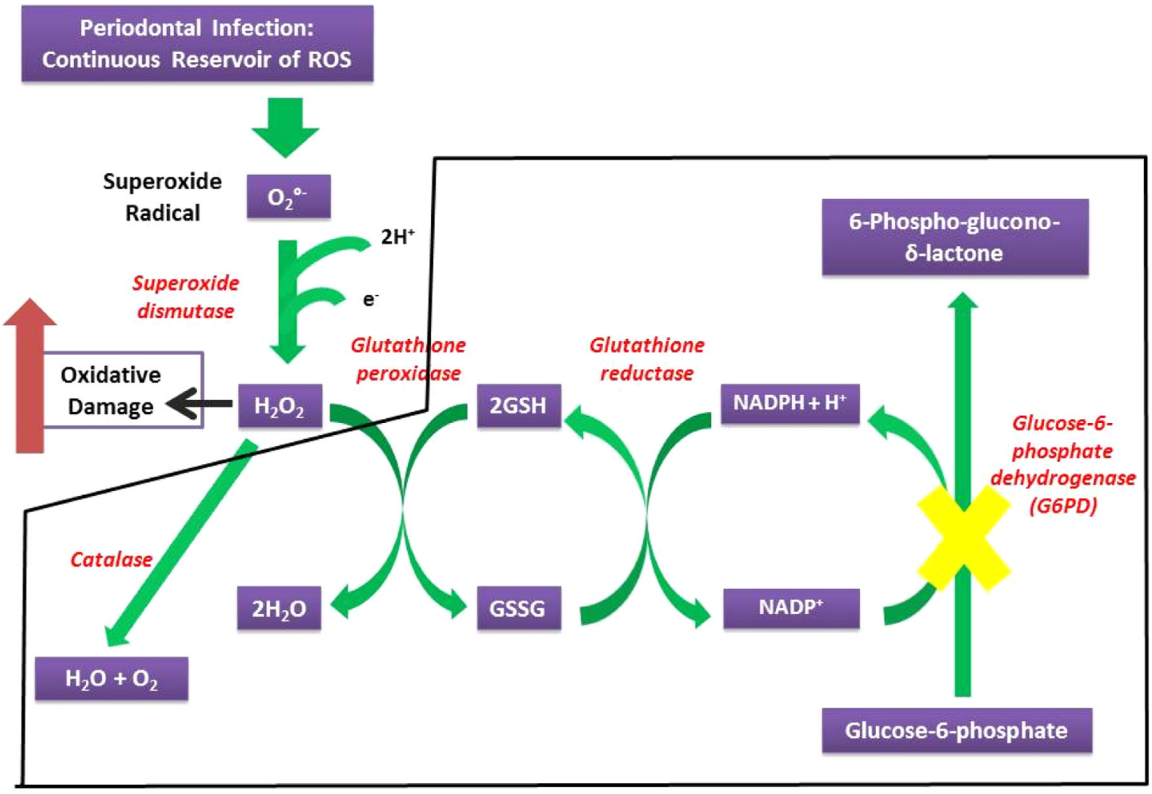

Fig. 3. Role of Periodontal infection in Acute Hemolysis in G6PD deficiency (Boxed mechanism is absent in G6PD deficient patients).

agents need to be avoided for patients with G6PD deficiency [14]. Other treatment modalities are phototherapy for neonatal jaundice, folic acid supplements, and blood transfusions [36]. Infection is a potent trigger for hemolysis, so any infection in the body, including periodontal infection, must be promptly treated. Periodontal diseases are chronic infections that can be easily prevented by simple oral hygiene measures.

Individuals with G6PD deficiency need to maintain adequate levels of oral hygiene and comply with routine recall dental visits to prevent periodontal infections. Once diagnosed, the prompt and aggressive treatment of periodontal infections is important to prevent hemolysis. Oxidative stress levels can be decreased within one month following non-surgical periodontal therapy [27,31,37]. Periodontal therapy might change the local ROS generation, the anti-oxidant status [18], and the systemic oxidative state. This could further prevent or reduce hemolysis in G6PD deficiency. Moreover, if any patient in the dental clinic with periodontal infection presents with jaundice symptoms, then G6PD evaluation may be advised in addition to routine suspicion of hepatitis.

5. Future directions

To explore the association between G6PD deficiency and hemolysis in periodontitis, further well designed longitudinal controlled clinical trials should be conducted in countries with a high prevalence of G6PD deficiency. It is recommended that physicians refer patients with G6PD deficiency to oral health care providers for comprehensive oral health evaluation.

6. Conclusions

Dentistry has progressed a long way from 1900, when Miller and Hunter proposed oral diseases were the cause of a number of systemic diseases [38,39]. A century later, the understanding of this connection continues to grow with advances in scientific technology. Although G6PD deficiency in most of the affected individuals is asymptomatic, exposure to oxidative stress inducers, such as certain drugs or any infection, could result in hemolysis. Periodontal infections are an active source of raised levels of ROS and inflammatory markers, which can result in a significant systemic burden to hemolysis in individuals with G6PD deficiency. Hence, it can be put forth that periodontal infections could be a potential underlying cause of hemolysis in G6PD deficiency.

CRediT authorship contribution statement

Neelesh Singh: Conceptualization, Investigation, Methodology, Resources, Writing - original draft. **Ashita Uppoor:** Project administration, Resources, Validation, Visualization, Writing - review & editing, Supervision. **Valliammai Rajendran:** Resources, Investigation, Visualization, Writing - review & editing. **Dilip G. Naik:** Investigation, Visualization, Writing - review & editing.

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Declaration of conflict of interest

The authors have no conflict of interest to disclose.

Ethical statement

There were no ethical issues/concerns in the preparation of this report.

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