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Glucose-6-phosphate dehydrogenase (G6PD) deficiency: insights into the genetic basis and potential therapeutic strategies

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Abstract

Glucose-6-Phosphate dehydrogenase (G6PD) is an oxidoreductase enzyme that plays an active role in the protection of erythrocytes (red blood cells) from oxidative stress-induced hemolysis. The protection is provided by the vital role of G6PD being the first enzyme in the pentose phosphate pathway (PPP) which produces the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) that maintains reduction/oxidation balance within the cell. Deficiencies in this enzyme are one of the most common X-linked genetic disorders, G6PD deficiency, which is attributed to various genetic mutations in the coding gene *G6PD*. The severity of the enzyme deficiency correlates with the type and location of the mutation, and the disorder is inherited as a recessive trait that affects males more than females. Clinical manifestations of G6PD enzyme deficiency include a wide range of symptoms starting from sudden episodes of hemolytic anemia and neonatal jaundice to renal and hepatic failure which can be lethal. In this review, we provided insights into pathophysiology and the genetic basis of the disorder and highlighted with comparison the latest therapeutic strategies applied which included enzyme replacement therapy, small molecules therapy, gene therapy and stem cell transplantation. We concluded that this disorder, although somehow preventable by public awareness, can still be treated in a manner that maintains a near normal lifestyle to the affected individuals.

Keywords: G6PD deficiency, Genetic variants, Hemolytic anemia, Oxidative stress, X-linked.

Introduction

Glucose-6-phosphate deficiency is a widespread hereditary monogenic disorder with up to 400 million people affected around the world with marked demographic variation among populations of Mediterranean, Asian, and African origins. Prevalence ranges from 3-29% in the Middle East and varies

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between 6.0-15.8% in Asia and between 3.6-28.0% in Africa. It arises from mutations or genetic variants in *G6PD* gene coding for the enzyme glucose-6-phosphate dehydrogenase which is the starting enzyme of the cellular metabolic pathway, the pentose phosphate pathway (PPP) [1, 2]. The gene *G6PD* belongs to the X chromosome with more than 200 amino acid substitutions in the enzyme have been reported to arise from mutations or variants along the gene leading to enzyme deficiency [3].

The primary role of G6PD enzyme is the production of reduced nicotinamide adenine dinucleotide phosphate (NADPH) which is required for considerable number of cellular pathways regarding biosynthesis and reduction/oxidation reactions particularly in erythrocytes where they lack other sources of NADPH to protect them during oxidative stress [4]. Exposure to oxidative stress in individuals having G6PD deficiency leads to clinical presentation of jaundice and hemoglobinuria which was firstly noticed in the Mediterranean region by the twentieth century after inhalation or ingestion of raw fava beans, so it became known as the clinical syndrome "favism" where familial patterns and male predominance were noted [5]. In this review, we aimed to provide a summarized overview of the emerging strategies in treatment of this disorder and the future potentials they have in treatment of this disorder.

G6PD function and pathophysiology

G6PD is a cytosolic oxidoreductase enzyme which carries out the oxidative reaction that converts glucose-6- phosphate into 6-phosphoglucono-lactone and reduces NADP+ into NADPH. The defense of cells against oxidative stress is attributed to the reducing power of the electron donor NADPH which is often called G6PD coenzyme [6]. NADPH plays a fundamental role in maintaining redox balance by its action as an antioxidant when cells undergo stress situations, aging or rapid proliferating. NADPH production by G6PD is the first reaction of the oxidative phase of the pentose phosphate pathway (PPP), which is an essential element of the cellular metabolism considering its four main functions of supplying precursors for biosynthesis of nucleotides and amino acids, maintaining carbon homoeostasis, subduing oxidative stress and supplying the reducing agents for anabolism [7]. Deficiencies in G6PD lead to decreased levels of NADPH through disruption of its only source in erythrocytes, the PPP. The outcome of this NADPH decrease is the loss of protection of the sulfhydryl groups in hemoglobin molecules from oxidation by any oxidative stress-inducing agents like reactive oxygen species (ROS) [8]. ROS include free hydroxyl radical (OH^-), superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) which represents the most potent oxidizing agents that when available enough around biosystems, it induces protein dysfunction and lipid's peroxidation along with nucleic acids damage [9].

The connection between G6PD/NADPH and protection from ROS lies mainly in the role of NADPH in a metabolic process called glutathione reduction pathway (fig.1) where glutathione reductase enzyme utilizes NADPH to convert the oxidized glutathione disulfide (GSSG) to its reduced state (GSH), then this molecule will be used as an electron donor by the enzyme glutathione peroxidase to reduce the harmful H_2O_2 and convert it to H_2O [10]. The end result of metabolic interference of G6PD in PPP, produced NADPH and glutathione will consequentially prevent the detrimental effects on erythrocytes that might happen by ROS exposure including increased fragility of the plasma membrane, hemolysis, release of

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hemoglobin into the plasma, systemic nitric oxide scavenging and finally vasoconstriction. As the rate of erythrocytes hemolysis increases, a clinical condition called anemia will develop which is defined according to the World Health Organization (WHO) as "hemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men" [11-12].

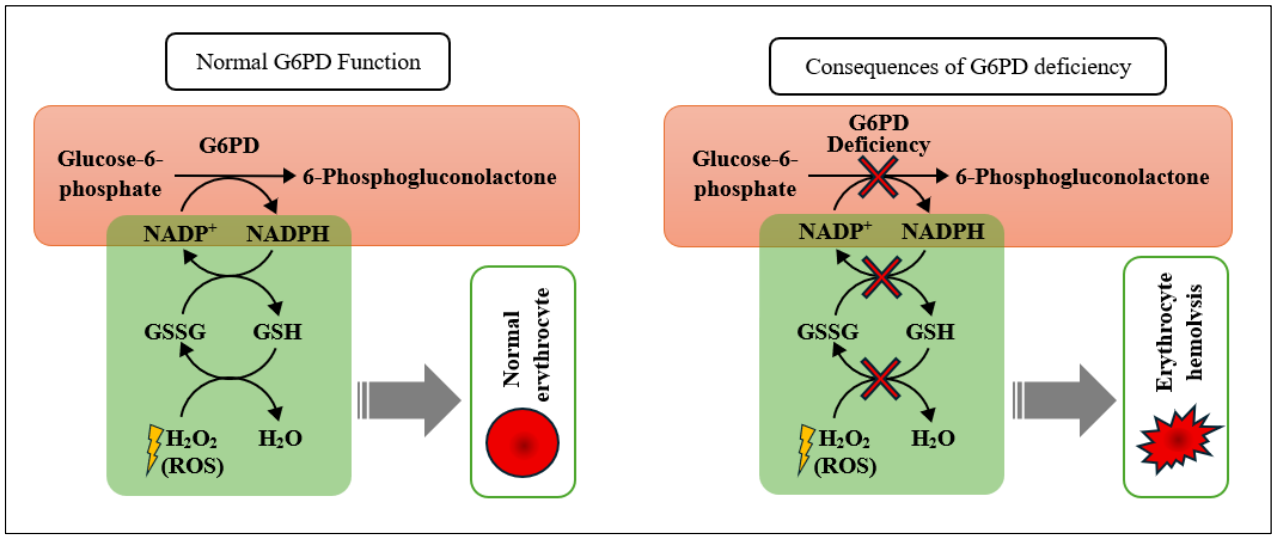

Figure 1. The role of G6PD in protection of erythrocytes from hemolysis by reactive oxygen species (ROS). Equations in orange: part of Pentose Phosphate Pathway; in green: glutathione reduction oxidation pathway.

The clinical spectrum of G6PD Deficiency

Most individuals who carry polymorphic *G6PD* gene remain asymptomatic throughout life. Nevertheless, the broad genetic heterogeneity of this gene and the variability of mutations result in a spectrum of enzyme activity such that individuals with specific genotypes display varying degrees of enzyme deficiency. Consequently, a wide spectrum of clinical presentations appear particularly when individuals are exposed to oxidative stress. The most common clinical conditions are acute or chronic hemolytic anemia, neonatal jaundice and favism [13]. In addition to these well-recognized manifestations, a number of cases were described in the literature confirming the clinically significant interaction of G6PD deficiency and hepatitis A and E with potential severe outcomes of severe intravascular hemolysis, hepatic failure and renal failure [14].

Beyond its classical contribution to hemolysis, several extended studies reappraised G6PD deficiency as a risk factor for a wider spectrum of diseases with underlying inflammatory pathogenesis. These conditions include celiac disease, asthma and cardiovascular disease. In contrast to genetically determined G6PD deficiency, individuals with certain endocrine disorders, such as diabetes and

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hypothyroidism, as well as those with preeclampsia, micronutrients deficiency and obesity may develop an acquired transient G6PD deficiency despite the absence of any genetic mutation in *G6PD* gene [15].

Genetic Basis of G6PD deficiency and variant classification

The enzyme G6PD is encoded by the X-linked *G6PD* gene measuring 18.5 Kb and located at Xq28 telomeric region which is referred to as a "hot spot" due to its relationship with several genetic disorders. The gene contains 13 exons and 12 introns producing a 59 KDa protein of 514 amino acids. Mutations throughout the gene can produce the hereditary disease 'G6PD deficiency' with varying severity at the population level [16]. Most of these mutated genotypes cause a single amino acid substitution with the vast majority being clinically relevant and producing a wide range of phenotypes. These phenotypes are frequently characterized according to their biochemical properties, including their enzymatic activity, electrophoretic mobility, thermal stability and the Michaelis constant (K_m) [17].

Upon identification of G6PD enzyme and recognition of its deficiency and genetic heterogeneity, studies focused on its phenotype's characterization according to two protein level criteria: the activity of the enzyme and its electrophoretic mobility leading to the initial classification of the disorder into two major phenotypes designated (A) and (B). The less deficient phenotype showing a faster electrophoretic mobility and activity of 7 to 20 percent of normal enzyme activity was recognized as G6PD A^- as it was first discovered in individuals of African ancestry. As for the more deficient second phenotype, it showed a typical electrophoretic mobility and activity of 0 to 7 percent of normal and became identified as G6PD Mediterranean (or G6PD – B) since it was observed in Italy, Greece and the Middle East [18].

Following that, in 1971, Yoshida *et al.* proposed a now called WHO classification of G6PD variants depending on erythrocytes activity and the clinical manifestations associated. The classification consisted of five categories as follows: Class I includes severe enzyme deficiency with chronic non-spherocytic hemolytic anemia, Class II includes severe deficiency with enzyme activity <10% of normal, Class III includes moderate to mild enzyme activity ranging between 10–60% of normal, Class IV includes very mild or no deficiency with 60–100% activity and Class V includes increased enzyme activity with >200% of normal [19]. Later on, in 1986, the human *G6PD* gene sequence was published, and it was made possible to identify the individual genetic mutations underlying previously described *G6PD* variants. In fact, additional variants were discovered and classified accordingly despite the reliance on limited number of cases observed [20].

Interfering factors on the severity and prevalence of the deficiency

Since G6PD gene lies within the X chromosome, males (XY chromosomes) with a mutant allele will express a phenotype of total enzyme deficiency due to their hemizygous state (having only one copy of the gene). Females (XX chromosomes) with two mutant alleles will also express total enzyme deficiency considering they're homozygous (having two identical gene copies), while heterozygous females (having one mutant and one normal alleles) will express partially deficient phenotype. The partial deficiency is attributed to the inactivation of one of the somatic cells X chromosomes which occurs randomly in early

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embryonic life leading to a subsequent erythrocytes' mosaicism of enzyme activity [21]. While X-linked inheritance explains susceptibility mechanisms of individuals, it does not fully account for population level prevalence. In fact, a social factor has been contributing to the elevation of G6PD deficiency prevalence which is consanguineous marriages where it is done between individuals (who may be carriers) and their first or second cousins (who may also be carriers). This type of family endogamy is widespread in Arab countries, and it is considered one of the causal factors in prevalence of genetic disorders where it increases the probability of homozygosity for mutant alleles [22].

However, clinical severity of the disorder is determined by factors distinct from those influencing its prevalence. At the molecular level, severity and phenotypic variability is governed by functional and structural properties including the three-dimensional (3D) structure of the enzyme and its structural assembly, the formation and stability of its active state (either a dimer or a tetramer), affinity to bind to substrates and its catalytic efficiency. Consequently, the clinical phenotype is strongly affected by the mutation location within the 3D structure of the enzyme, for example, G6PD variants near or at structural binding site of NADP+ or the dimer interface have been suggested to cause enzyme instability and result in severe deficiency in most cases [23].

Diagnosis and newborn screening tests

G6PD enzyme activity can be detected by either quantitative or qualitative biochemical laboratory tests; however, in clinical practice, the condition is frequently identified following the occurrence of an acute hemolytic episode triggered by an inducing factor which becomes evident on the patient on a clinical exam. In such cases, the diagnosis is indicated by normocytic normochromic red blood cells with mean corpuscular volume (MCV) between 80-95 femtoliters and mean corpuscular hemoglobin (MCH) of ≥ 27 picograms, in addition to a marked reduction in hemoglobin level which can decrease below (<7gram/deciliter) in severe cases [24-25].

Given the clinical significance of early detection, neonates (or any suspected patient) may routinely undergo screening tests to assess the activity of the enzyme. Commonly used point-of-care methods include rapid fluorescent spot test and the dye decolorization method which provide quick results and ease of application. In addition to these biochemical tests which are considered valuable for initial diagnosis, a more definitive characterization of the disorder can be achieved through molecular diagnostic approaches. Accordingly, genetic diagnostic methods, particularly gene sequencing, are currently used and revealed through previous studies the presence of more than 200 distinct mutations of *G6PD* gene [26-27].

G6PD Deficiency therapeutic strategies

The main goal of treatment in G6PD deficiencies is to eliminate hemolysis of erythrocytes before or during exposure to oxidative stress, the most explored approach applied was antioxidant therapy using ascorbate (vitamin C), β-carotenoids, α-tocopherol (vitamin E) and α-lipoic acid (ALA) although it was largely ineffective and induced the search for other pharmacological strategies like GSH metabolism and activation of alternative pathways for NADPH production [28]. Other routes emerged throughout the years, and some are still in trial phase; those include:

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Enzyme replacement therapy

Enzyme replacement therapy has emerged in the twentieth century as a critical approach for treatment of disorders of enzymatic absence or deficiencies with genetic basis primarily in treating lysosomal storge diseases like Gaucher disease [29]. The application of this type of treatment for G6PD deficiency faces challenges of ensuring enzyme delivery and stability within the highly dynamic environment of erythrocytes, where G6PD acts as the sole producer of NADPH, and the subsequent maintenance of oxidative balance [30]. To overcome these challenges, novel strategies of enzyme modification and delivery must take place in order to ensure sustained enzyme activity within the targeted erythrocytes [31]. Furthermore, the potential immunogenic reactions must be taken into consideration since anti-drug antibodies may develop against the exogenously administered enzymes leading to neutralization of the therapeutic efficacy and adverse reactions [32].

Small molecules activator therapy

Small-molecule activators or pharmacological chaperones are small molecules that bind to malfunctional enzymes to correct their function basically by three mechanisms: firstly, by binding to enzymes at their active site to increase interactions between the substrate and the catalytic residues, secondly by binding at disordered region to allosterically correct it, and thirdly by binding in a way that prevents misfolding [33]. These molecules provide more advantages over genetic editing therapies since they provide technical ease in treatment of cells with less optimization requirements as well as being readily synthesized and maintaining in vivo activity with reversible dose sensitive effects. However, their function engineering can be difficult, and they may have off-target cellular effects which are displayed as disadvantages [34]. One small molecule chaperone, AG1, was used by Hwang *et al.* (2018) to correct G6PD deficiency in Canton variant (having ~10% of normal activity) resulting in 78% enhancement in enzyme activity, increased NADPH and GSH levels and reduced ROS. Ultimately, cells' viability and protection from oxidative stress were improved since AG1 molecule acts by stabilizing and activating mutant G6PD variants by promoting dimer formation and facilitating $NADP^+$ binding [35]. Preclinical trials on model organisms with G6PD deficiency such as mice and zebrafish showed that activator molecules are required to overcome many challenges before they can be considered and identified as new drugs, these challenges include the full elucidation of their effective dosage and therapeutic potential [36].

Gene therapy

Gene therapy was initially introduced for the treatment of monogenic diseases and cancer involving two essential strategies: firstly, stem cells receive the therapeutic gene, divide and transmit the newly introduced gene to their daughter cells and secondly, slow dividing cells receive the therapeutic gene through a vector, and the new gene is expressed throughout the lifespan of these cells [37]. In contrast to the traditional treatment strategies where symptoms are the main focus, gene therapy targets the root cause

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which is the malfunctional gene and provides precision in treatment and the possibility of cure of genetic diseases [38]. G6PD deficiency gene therapy trials began in the early 2000s by using a retroviral vector loaded with the complementary DNA of human *G6PD* gene. The vector was used in the transduction of hematopoietic stem cells which were then transferred into recipient syngeneic mice and ultimately resulted in stable expression of the enzyme; however, clinical human trails have not been attempted yet [39].

Stem Cell Transplantation

Hematopoietic stem cells are the progenitors of red blood cells and any genetic defect in them will drag its effect onto the produced cells; therefore, they have been targeted in treatment of G6PD deficiency. Stem cell therapy routes include either genetic engineering of the individual's own hematopoietic stem cells for the repairing of *G6PD* gene (when the underlying mutation is known) or the replacement of the defective cells with new normal hematopoietic stem cells from matching healthy donors [40]. The first route was applied to cure the monogenic red cell related disease, sickle cell anemia. The researchers used a gene therapy technique called "Clustered Regularly Interspaced Short Palindromic Repeats technique" (CRISPER) to edit the hemoglobin gene in hematopoietic stem cells of patients from bone marrow and peripheral blood. Erythrocytes derived from these gene-edited cells showed increased level of normal hemoglobin indicating the efficiency in gene correction [41].

Based on the reviewed literature, the following table (table 1) was derived to summarize and compare advantages and disadvantages of each of these previously mentioned therapeutic strategies to address the potentials of clinical application and possible negative outcomes.

Table (1): Comparative summary of the emerging G6PD treatment strategies.

Therapeutic strategy	Advantages	Disadvantages
Enzyme replacement therapy	- Rapid correction of enzyme defect - Administered through infusion - Can be applied during acute crises	- Difficulty in delivering G6PD enzyme in red blood cells where it is needed - Possibility of triggering immune response - Temporary effects of treatment
Small molecules activator therapy	- Non-invasive therapy (oral administration route) - Adjustable dose - Successful for partially deficient patients	- Effectiveness is mutation-specific - Possibility of toxicity - Temporary effect of treatment
Gene therapy	- Elimination of root cause permanently - One time treatment - Prevents future hemolysis	- High cost - Risks of off-target mutations - Complicated requirements for preparation

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Stem Cell Transplantation	- Permanent cure when successful - Elimination of enzyme deficiency completely	- High risks of infection. - High risks of rejection - Suitable only for severe deficiency - High cost

Management and Prevention

Acute hemolysis or hemolytic anemia can result from the exposure to a trigger in patients with G6PD deficiency, mostly in pediatrics with or without previous diagnosis, which requires emergency admission to the hospital and treatment with blood transfusion and may also require staying in the hospital for several days [42]. Cost-effective and simple strategies including early detection and phototherapy intervention help in identifying, treating and monitoring infants at risk of hyperbilirubinemia and eventually preventing kernicterus [43]. Children and adults can be managed according to the severity of symptoms by supportive therapy, avoiding oxidative stress inducing agents like food (particularly fava beans) and certain medications and chemicals. Blood transfusion should be applied exceptionally to manage severe hemolytic anemia because less severe hemolytic anemia is self-limiting within 8 to 14 days. [44]

Prevention of this disorder, as any other genetic disease, can be achieved basically by preventing consanguineous marriages which aid in spreading of the disorder among next generations. This can be achieved by increasing awareness of individuals to help reduce this type of marriage and acknowledge the significance of premarital testing [45].

Limitation and Future Directions

Despite the tremendous advances made in understanding the pathophysiology of G6PD deficiency, current therapeutic approaches remain limited and face many challenges particularly because of the wide genetic variability of G6PD mutations. Additional limitations may include the lack of large-scale and randomized clinical trials along with safety concerns which all participate as obstacles in the development of standardized protocols for treatment and elimination of the root cause of the disease.

Future directions focus on achieving accurate genetic diagnosis through next-generation sequencing (NGS) either by whole exome sequencing or through targeted gene panel to enable the selection of appropriate therapeutic modalities. [46]. In parallel, *in silico* analysis, including simulations of molecular dynamics and detailed biochemical and molecular characterization of specific G6PD mutations, are providing valuable insights that may enhance the identification of suitable small-molecule candidates [47]. Moreover, molecular docking and enzyme kinetics analyses can be used in structure-based drug design and activity-structure relationship studies to create more selective and potent activators. Future research should also focus on well-designed clinical trials with the ability to follow up and evaluate the long-term safety and efficacy of emerging therapeutic strategies.

Conclusion

In this review, we concluded that G6PD deficiency is the most common genetic disorder affecting humans and the deficiency in G6PD enzyme in red blood cells can be life-threatening or lead to several clinical manifestations upon exposure to oxidative stress. The clinical outcomes can display varying degrees of hemolytic anemia and organ failure in adults and the risk of neonatal jaundice and hyperbilirubinemia in

infants and newborns. Although early detection and characterization of the genotype/phenotype lead to better management and control, public awareness should be spread through national screening programs in siblings and relatives at risk in addition to the application of routine neonatal screening tests. These programs ensure education regarding avoidance of triggers and the inheritance patterns of the disorder particularly among carriers with intentions of getting married. We also concluded that knowledge in the overall protein function and types of mutations and their specific effect at the molecular level is very important in the application of non-routine therapeutics strategies. Moreover, despite the benefits promised by these techniques, they present uneasy challenges such as high cost, complexity and the possible adverse effects on the patient. However, gene editing techniques provide a promising future for a permanent cure for this disorder in case clinical trials were to be extended to fast-forward any advancement that can be achieved.

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Author's Declaration

- We hereby confirm that all figures and tables in the manuscript are original and have been created by us.
- No conflict of interest is associated with this work.

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