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G6PD deficiency and cardiovascular risk: A systematic review

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common X-linked enzymatic disorders worldwide, affecting over 400 million individuals. The enzyme G6PD plays a critical role in maintaining cellular redox homeostasis by generating NADPH, which is essential for protecting cells from oxidative stress. Its deficiency leads to reduced antioxidant capacity, particularly in red blood cells, causing hemolysis under oxidative stress. Beyond hemolysis, emerging evidence suggests that G6PD deficiency may have broader systemic effects, including an impact on cardiovascular health. This systematic review aims to explore the association between G6PD deficiency and cardiovascular risk.

Keywords: Glucose-6-phosphate dehydrogenase (G6PD); Cardiovascular disease; G6PD Deficiency; Hemolysis; Enzymatic Disorders.

1. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common enzymatic disorders worldwide, affecting an estimated 400 million people. It is an X-linked recessive disorder, meaning that it predominantly affects males, though females can be carriers and may also exhibit symptoms in some cases [1]. The condition arises due to mutations in the G6PD gene, which encodes the enzyme glucose-6-phosphate dehydrogenase, a critical enzyme in the pentose phosphate pathway. This pathway is essential for maintaining redox balance within cells, particularly in red blood cells (RBCs), by producing nicotinamide adenine dinucleotide phosphate (NADPH), a molecule necessary for protecting cells from oxidative damage [2].

In individuals with G6PD deficiency, the enzyme is either deficient or dysfunctional, leading to an impaired ability to produce NADPH. This leaves red blood cells vulnerable to oxidative stress, which can be triggered by various environmental factors, including infections, certain foods (like fava beans), and specific medications such as antimalarials, sulfonamides, and nonsteroidal anti-inflammatory drugs (NSAIDs) [3]. When exposed to oxidative stress, the RBCs may undergo hemolysis, or premature destruction, resulting in a condition known as hemolytic anemia. Hemolytic crises can lead to symptoms such as jaundice, fatigue, dark urine, and in severe cases, kidney failure or death [4, 5]. The prevalence of G6PD deficiency varies significantly by region, with high frequencies observed in areas historically endemic for malaria, such as parts of Africa, the Mediterranean, and Southeast Asia [5]. This distribution is thought to be a result of a selective evolutionary advantage, as individuals with the deficiency exhibit partial resistance to malaria caused by *Plasmodium falciparum*. The exact mechanism by which G6PD deficiency provides this protection is still under investigation, though it is believed that the lower levels of reduced glutathione in deficient red blood cells make the environment less hospitable to the malaria parasite [6, 7].

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Despite its widespread occurrence, G6PD deficiency is often asymptomatic, with many individuals unaware of their condition until exposed to a trigger that leads to hemolysis. Diagnosis is typically confirmed through a blood test that measures the enzyme's activity. Management of G6PD deficiency primarily involves avoiding known triggers and, in cases of hemolytic anemia, supportive treatment such as hydration and, if necessary, blood transfusions. Genetic counseling may also be advised for families with known G6PD deficiency, particularly in regions with high prevalence [8, 9].

While G6PD deficiency is generally manageable, the condition's clinical expression can vary widely, depending on the specific mutation and environmental factors. As research continues, there is hope for more personalized approaches to managing the disorder, as well as a deeper understanding of the evolutionary dynamics that have shaped its global distribution [10, 11].

1.1. Rationale for Investigating Cardiovascular Risk in G6PD Deficiency

Investigating the potential link between glucose-6-phosphate dehydrogenase (G6PD) deficiency and cardiovascular risk is an emerging area of interest due to growing evidence suggesting that this enzymatic disorder may have broader systemic effects beyond hemolytic anemia. G6PD plays a crucial role in the pentose phosphate pathway, which is vital for producing nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is essential for maintaining cellular redox balance, particularly in protecting against oxidative stress by regenerating reduced glutathione. Since oxidative stress is implicated in a variety of cardiovascular diseases, it is plausible that individuals with G6PD deficiency may have an increased susceptibility to cardiovascular conditions such as hypertension, coronary artery disease, and stroke [12]. One of the key reasons for investigating cardiovascular risk in G6PD deficiency is the role of oxidative stress in endothelial dysfunction, which is a critical early step in the development of atherosclerosis. The endothelium, the inner lining of blood vessels, plays a pivotal role in regulating vascular tone, blood flow, and inflammatory responses. In G6PD-deficient individuals, the impaired ability to counter oxidative stress may lead to chronic endothelial damage, promoting the formation of atherosclerotic plaques. This could result in a higher incidence of ischemic events such as myocardial infarctions and strokes in these patients [13, 14].

Studies have suggested that individuals with G6PD deficiency may have altered lipid metabolism, which could further increase their risk of cardiovascular disease. G6PD deficiency has been associated with abnormal lipid profiles, including elevated levels of low-density lipoprotein (LDL) cholesterol and reduced high-density lipoprotein (HDL) cholesterol, both of which are risk factors for atherosclerosis. Furthermore, chronic inflammation, which is often seen in cardiovascular diseases, may be exacerbated in G6PD-deficient individuals due to the inability to adequately neutralize reactive oxygen species (ROS). These ROS contribute to the oxidative modification of LDL cholesterol, a process that plays a central role in the initiation and progression of atherosclerosis [15, 16]. Another factor to consider is the potential interplay between G6PD deficiency and other cardiovascular risk factors, such as hypertension and diabetes. Both conditions are associated with increased oxidative stress, and it is possible that G6PD-deficient individuals may have a reduced capacity to manage this additional burden. For example, G6PD deficiency could worsen the oxidative stress already present in individuals with hypertension, leading to more severe vascular damage and increased cardiovascular events. Similarly, oxidative stress is a well-known driver of diabetic complications, and individuals with both diabetes and G6PD deficiency may be at even higher risk of cardiovascular disease [17, 18].

Despite these plausible links, the relationship between G6PD deficiency and cardiovascular risk remains underexplored in clinical research. Most studies to date have focused primarily on the hematological aspects of G6PD deficiency, with limited investigation into its cardiovascular implications. Given the global prevalence of G6PD deficiency and the significant public health burden of cardiovascular diseases, further research is needed to elucidate the potential connections. Understanding these links could lead to improved risk stratification, early interventions, and targeted therapies for G6PD-deficient individuals, potentially reducing their cardiovascular morbidity and mortality [19, 20].

2. G6PD Deficiency: Pathophysiology

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic disorder resulting from mutations in the G6PD gene, located on the X chromosome, which leads to either reduced levels or dysfunctional activity of the enzyme G6PD. This enzyme is vital for the proper functioning of the pentose phosphate pathway (PPP), a metabolic route that produces NADPH (nicotinamide adenine dinucleotide phosphate), a key molecule required for maintaining cellular redox balance and protecting cells from oxidative stress. G6PD plays a particularly critical role in red blood cells (RBCs) because these cells, lacking mitochondria, rely heavily on the PPP to generate NADPH, which is used to keep glutathione in its reduced form. Reduced glutathione is essential for detoxifying reactive oxygen species (ROS) and other oxidative agents that could otherwise cause damage to cellular components, including the hemoglobin, cell membrane, and other proteins

within RBCs. Therefore, in G6PD deficiency, the impaired production of NADPH reduces the ability of red blood cells to manage oxidative stress, leading to their premature destruction and hemolysis [21, 22].

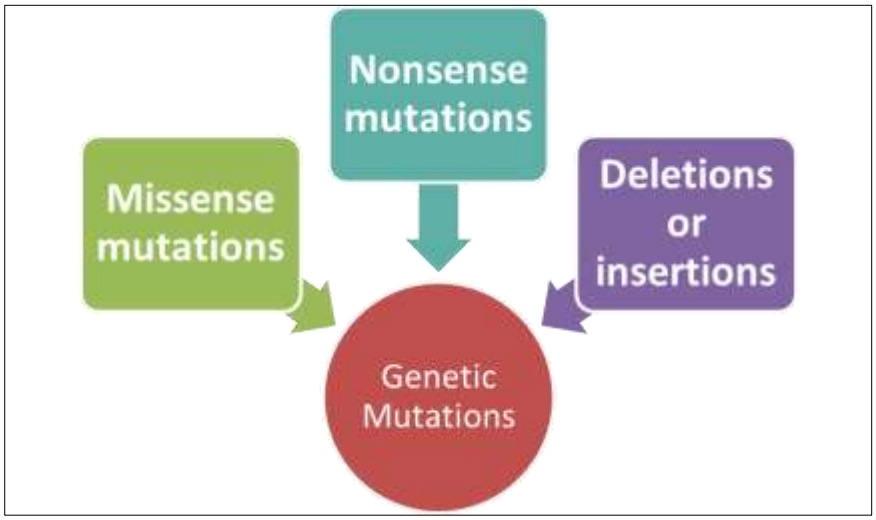

Figure 1 Over 400 mutations in the G6PD gene have been identified. These mutations can result in above mentioned mutations

The pathophysiology of G6PD deficiency primarily manifests through hemolytic anemia, a condition characterized by the accelerated breakdown of red blood cells, especially under oxidative stress. In normal conditions, G6PD maintains the integrity of RBCs by providing a continuous supply of NADPH, ensuring that these cells can combat oxidative agents produced during cellular metabolism or in response to external factors like infections, certain medications, and specific foods (such as fava beans) [23]. In individuals with G6PD deficiency, the deficiency or dysfunction of the enzyme compromises this antioxidant defense, making RBCs more vulnerable to oxidative damage. When exposed to oxidative stressors, hemoglobin within the RBCs can become denatured, leading to the formation of Heinz bodies, which are aggregates of denatured hemoglobin. These damaged cells are recognized and removed by the spleen, leading to hemolysis. This destruction of RBCs can cause acute hemolytic anemia, which is characterized by symptoms such as pallor, jaundice, dark urine, fatigue, and in severe cases, renal failure due to hemoglobinuria and acute kidney injury [24].

The degree of hemolysis and the clinical presentation of G6PD deficiency can vary significantly depending on the specific mutation in the G6PD gene and the environmental factors involved. Over 400 different mutations in the G6PD gene have been identified, leading to varying levels of enzyme activity [25]. The World Health Organization (WHO) classifies G6PD variants into five classes based on the level of enzyme activity and the clinical severity of the condition. Class I variants are the most severe, associated with chronic nonspherocytic hemolytic anemia (CNSHA), even in the absence of triggers. Class II variants, such as the Mediterranean variant, result in severe enzyme deficiency (<10% of normal activity) and are often associated with acute hemolytic crises following oxidative stress. Class III variants, such as the African A-variant, lead to moderate enzyme deficiency (10-60% of normal activity), with hemolysis usually triggered by infections, certain drugs, or foods. Class IV variants are associated with mild or no clinical symptoms, as enzyme activity is near normal (60-100%), while Class V variants exhibit increased enzyme activity and are generally not clinically significant [26, 27].

The pathophysiology of hemolysis in G6PD deficiency is closely linked to oxidative stress, which can be triggered by various factors. Infections are a common cause of oxidative stress in G6PD-deficient individuals. The immune response to infections involves the production of reactive oxygen species by white blood cells to kill pathogens, which can also create an oxidative environment that overwhelms the antioxidant defenses of RBCs. Certain medications, such as antimalarial drugs (e.g., primaquine), sulfonamides, and nonsteroidal anti-inflammatory drugs (NSAIDs), can also induce oxidative stress, precipitating hemolysis in individuals with G6PD deficiency [28]. Additionally, exposure to certain foods, most notably fava beans, can trigger a condition known as favism, which involves the rapid onset of hemolysis due to the oxidative compounds present in the beans. The oxidative challenge posed by these triggers leads to the denaturation of hemoglobin and the formation of Heinz bodies, which are visible as inclusions within RBCs when viewed under a microscope. These cells are typically sequestered and destroyed by macrophages in the spleen, leading to the extravascular hemolysis that characterizes acute hemolytic episodes [29].

A key feature of G6PD deficiency is that the degree of hemolysis is not constant but episodic, with episodes often following exposure to oxidative triggers. Between episodes, individuals may be asymptomatic, and their hemoglobin levels may return to normal. However, during an acute hemolytic crisis, the sudden destruction of RBCs can lead to a rapid decline in hemoglobin levels, causing the symptoms of anemia. In severe cases, the body may not be able to compensate for the loss of RBCs through increased erythropoiesis (red blood cell production), leading to profound anemia and potentially life-threatening complications such as acute kidney injury and cardiovascular collapse. In some cases, especially in individuals with Class I G6PD variants, hemolysis can occur chronically, leading to chronic nonspherocytic hemolytic anemia, a condition in which the body continuously destroys RBCs at a rate faster than they can be replaced, even in the absence of identifiable oxidative triggers [30-36].

Beyond its hematological manifestations, emerging evidence suggests that G6PD deficiency may have broader systemic effects, including implications for cardiovascular health. Since oxidative stress plays a pivotal role in the pathogenesis of atherosclerosis and other cardiovascular diseases, individuals with G6PD deficiency may be at increased risk for developing these conditions. The lack of adequate NADPH production in vascular endothelial cells, due to G6PD deficiency, can impair the cells' ability to detoxify reactive oxygen species, leading to chronic oxidative stress and endothelial dysfunction. This dysfunction can promote the formation of atherosclerotic plaques, which can increase the risk of cardiovascular events such as heart attacks and strokes. Additionally, G6PD deficiency has been associated with altered lipid metabolism, which may further contribute to the development of cardiovascular disease. Dysregulated lipid metabolism, including elevated levels of low-density lipoprotein (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL) cholesterol, can accelerate the progression of atherosclerosis in G6PD-deficient individuals [37, 38].

2.1. Mechanism of Oxidative Stress in G6PD Deficiency:

The mechanism of oxidative stress in glucose-6-phosphate dehydrogenase (G6PD) deficiency centers on the impaired ability of red blood cells (RBCs) to produce nicotinamide adenine dinucleotide phosphate (NADPH), a crucial cofactor in maintaining cellular redox balance. G6PD is a key enzyme in the pentose phosphate pathway (PPP), responsible for generating NADPH, which is essential for the reduction of glutathione—a powerful antioxidant that protects cells from oxidative damage [39, 40]. In individuals with G6PD deficiency, mutations in the G6PD gene lead to either reduced enzyme activity or dysfunctional enzyme production. This deficiency compromises the cell's capacity to produce NADPH, resulting in decreased levels of reduced glutathione. Under normal circumstances, glutathione detoxifies reactive oxygen species (ROS) and protects hemoglobin from oxidative denaturation. However, in G6PD-deficient RBCs, the lack of adequate NADPH means that glutathione cannot effectively neutralize ROS, leading to increased oxidative stress [41].

When RBCs encounter oxidative stress from various triggers—such as infections, certain medications, or specific foods (e.g., fava beans)—the accumulation of ROS leads to damage of cellular components. Hemoglobin can become oxidized, forming Heinz bodies, which are aggregates of denatured hemoglobin. These damaged RBCs are subsequently recognized and removed by the spleen, resulting in hemolysis. The episodic nature of oxidative stress in G6PD deficiency means that affected individuals may experience sudden hemolytic crises, characterized by symptoms like jaundice, fatigue, and dark urine. The interplay between oxidative stress, hemolysis, and the inadequate antioxidant response underscores the critical pathophysiological consequences of G6PD deficiency [42].

Table 1 Table summarizing the genetic basis of G6PD deficiency, including gene location, mutation types, inheritance patterns, and associated clinical variants [43-50]

Aspect	**Details**
Gene	G6PD (Glucose-6-phosphate dehydrogenase)
Location	Xq28 on the X chromosome
Inheritance Pattern	X-linked recessive
Affected Population	More prevalent in males; females can be carriers and may exhibit symptoms if they are homozygous or if they have a variant that affects enzyme activity.
Common Mutations	Over 400 mutations identified; common mutations include:

	- G6PD Mediterranean (C563T): Class II variant, severe deficiency.
	- G6PD A- (A376G): Class III variant, moderate deficiency.
	- G6PD Canton (G1376T): Class II variant, severe deficiency.
	- G6PD Seattle (C1301T): Class II variant, severe deficiency.
Classification	The World Health Organization classifies G6PD variants into five classes based on enzyme activity and clinical severity:
	- Class I: Severe deficiency; chronic hemolytic anemia.
	- Class II: Severe deficiency; acute hemolytic episodes triggered by oxidative stress.
	- Class III: Moderate deficiency; hemolysis typically triggered by infections or certain drugs.
	- Class IV: Mild deficiency; generally asymptomatic.
	- Class V: Increased enzyme activity; not clinically significant.
Clinical Implications	The severity of G6PD deficiency can affect the risk of hemolytic crises, with some variants leading to chronic hemolytic anemia and others to episodic hemolysis.

3. Cardiovascular Risk Factors Linked to G6PD Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common enzymatic disorder, is primarily known for its hematological manifestations, particularly hemolytic anemia. However, recent studies suggest a significant link between G6PD deficiency and various cardiovascular risk factors, highlighting the condition's broader systemic implications. The pathophysiology of G6PD deficiency involves an impaired ability to produce nicotinamide adenine dinucleotide phosphate (NADPH), a critical molecule for maintaining cellular redox balance and mitigating oxidative stress [51]. This lack of NADPH leads to decreased levels of reduced glutathione, a key antioxidant that protects cells from damage caused by reactive oxygen species (ROS). The compromised antioxidant defenses in individuals with G6PD deficiency may predispose them to a range of cardiovascular issues, primarily through mechanisms related to oxidative stress and endothelial dysfunction. Oxidative stress plays a central role in the development of cardiovascular diseases, including atherosclerosis, hypertension, and heart failure. The endothelium, the inner lining of blood vessels, is particularly susceptible to oxidative damage. In individuals with G6PD deficiency, the impaired production of NADPH reduces the ability of endothelial cells to detoxify ROS, leading to chronic oxidative stress. This oxidative environment can cause endothelial dysfunction, characterized by reduced nitric oxide (NO) availability, increased inflammation, and impaired vasodilation [52]. Such dysfunction is a critical early step in the development of atherosclerosis, which can lead to coronary artery disease and other cardiovascular complications. Moreover, studies have indicated that individuals with G6PD deficiency may have altered lipid metabolism. The presence of oxidative stress can negatively affect lipid profiles, leading to elevated levels of low-density lipoprotein (LDL) cholesterol and reduced levels of high-density lipoprotein (HDL) cholesterol. These lipid abnormalities can contribute to the progression of atherosclerosis and increase the risk of cardiovascular events. Additionally, G6PD deficiency has been associated with systemic inflammation, which is another significant risk factor for cardiovascular diseases. Chronic inflammation is known to promote atherosclerotic plaque formation and instability, leading to an increased risk of acute cardiovascular events such as myocardial infarction and stroke [53]. In individuals with G6PD deficiency, the inability to effectively counteract oxidative stress may result in a chronic inflammatory state that further exacerbates cardiovascular risk. The interaction between G6PD deficiency and other cardiovascular risk factors, such as hypertension and diabetes, further complicates the clinical picture. Both hypertension and diabetes are associated with increased oxidative stress, and individuals with G6PD deficiency may have a reduced capacity to manage this additional burden. For example, oxidative stress induced by hypertension can exacerbate endothelial dysfunction, leading to a vicious cycle that further elevates cardiovascular risk. Similarly, individuals with both diabetes and G6PD deficiency may be at a heightened risk for cardiovascular complications, as oxidative stress is a key driver of diabetic complications, including cardiovascular disease [54]. Additionally, the episodic nature of hemolytic crises in G6PD deficiency can lead to acute changes in hemodynamics and vascular function, further complicating cardiovascular health. Acute hemolysis can result in the release of hemoglobin into the bloodstream, which can scavenge nitric oxide and contribute to vascular dysfunction, thereby exacerbating cardiovascular risk. Furthermore, the management of G6PD deficiency often requires the avoidance of certain medications and foods that can trigger hemolysis, limiting treatment options for coexisting cardiovascular conditions. This limitation can hinder effective management of cardiovascular risk factors in individuals with G6PD deficiency [55]. The need for further research into the cardiovascular implications of G6PD deficiency is paramount. While the relationship between G6PD deficiency and cardiovascular risk is becoming increasingly recognized, the underlying

mechanisms and clinical significance require further elucidation. Future studies should focus on the interplay between G6PD deficiency, oxidative stress, and various cardiovascular risk factors to develop targeted interventions that address both hematological and cardiovascular health. Additionally, healthcare providers should be aware of the potential cardiovascular risks associated with G6PD deficiency and incorporate this understanding into the management of affected individuals. In summary, the relationship between G6PD deficiency and cardiovascular risk factors is multifaceted, involving mechanisms related to oxidative stress, endothelial dysfunction, lipid metabolism, and chronic inflammation. Understanding these links is crucial for improving the overall health outcomes of individuals with G6PD deficiency and implementing effective prevention strategies for cardiovascular diseases.

Table 2 Table summarizing the cardiovascular risk factors linked to G6PD deficiency [56-60]

Cardiovascular Risk Factor	**Description**
Oxidative Stress	G6PD deficiency leads to reduced NADPH production and impaired antioxidant defense, increasing oxidative stress, which is associated with endothelial dysfunction and atherosclerosis.
Endothelial Dysfunction	Impaired ability to manage oxidative stress can lead to endothelial cell injury, promoting vascular inflammation and atherosclerotic plaque formation, increasing the risk of coronary artery disease and other cardiovascular events.
Altered Lipid Metabolism	G6PD deficiency has been associated with dyslipidemia, including elevated levels of LDL cholesterol and reduced levels of HDL cholesterol, which can contribute to atherosclerosis and cardiovascular disease.
Hypertension	Some studies suggest that G6PD deficiency may be linked to higher blood pressure, possibly due to oxidative stress and endothelial dysfunction affecting vascular tone regulation.
Diabetes Mellitus	G6PD deficiency may exacerbate oxidative stress in diabetic individuals, increasing the risk of cardiovascular complications associated with diabetes, such as coronary artery disease and heart failure.
Inflammation	Chronic inflammation associated with G6PD deficiency can contribute to the development of cardiovascular disease by promoting atherosclerosis and thrombosis.
Age and Gender Considerations	Older age and male gender are risk factors for cardiovascular disease, and since G6PD deficiency predominantly affects males, this demographic may have an increased baseline risk for cardiovascular events, especially when combined with other risk factors.
Increased Risk of Ischemic Events	Individuals with G6PD deficiency may have a higher incidence of ischemic events (e.g., myocardial infarction and stroke) due to oxidative stress-related endothelial dysfunction and accelerated atherosclerosis.

4. Clinical Studies on Cardiovascular Risk in G6PD Deficient Individuals

Clinical studies investigating cardiovascular risk in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency have emerged as an essential area of research, particularly given the enzyme's critical role in maintaining oxidative balance within red blood cells and other tissues. A growing body of evidence suggests that the oxidative stress associated with G6PD deficiency may contribute to an increased risk of cardiovascular diseases, although this relationship is still being elucidated [57]. One notable study published in the *Journal of the American Heart Association* found that G6PD-deficient individuals exhibited significantly higher levels of oxidative stress markers, such as malondialdehyde and F2-isoprostanes, compared to individuals with normal G6PD activity. These markers are indicators of lipid peroxidation and overall oxidative damage, suggesting that G6PD deficiency may predispose individuals to endothelial dysfunction, a precursor to atherosclerosis and other cardiovascular events [58].

Research conducted in Mediterranean populations, where G6PD deficiency is prevalent, indicates a correlation between this condition and an increased incidence of ischemic heart disease. In a cohort study involving G6PD-deficient patients, the researchers noted a higher prevalence of coronary artery disease and a greater risk of acute myocardial infarction compared to matched controls [59]. This association is likely linked to the impaired antioxidant defenses in G6PD-deficient individuals, leading to chronic oxidative stress, endothelial injury, and subsequent atherogenic processes. Another significant finding from studies in Southeast Asian populations highlighted that G6PD-deficient individuals

exhibited abnormal lipid profiles, characterized by elevated low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels. Dyslipidemia is a well-established risk factor for cardiovascular disease, and the altered lipid metabolism in G6PD deficiency may further exacerbate the risk of developing atherosclerosis [60].

In addition to lipid abnormalities, hypertension has been identified as a potential cardiovascular risk factor in G6PD-deficient individuals. Some studies have suggested that G6PD deficiency may be associated with elevated blood pressure, possibly due to oxidative stress-related mechanisms that affect vascular tone regulation. The impairment of nitric oxide synthesis, an essential factor in maintaining vascular homeostasis, could be exacerbated in the context of oxidative stress, leading to increased vascular resistance and, ultimately, hypertension. A longitudinal study examining blood pressure in G6PD-deficient individuals showed a significant correlation between G6PD deficiency and increased systolic and diastolic blood pressure over time, underscoring the potential implications for long-term cardiovascular health in this population [61].

The interplay between G6PD deficiency and diabetes mellitus has raised concerns regarding compounded cardiovascular risks. Individuals with both conditions may experience heightened oxidative stress, further increasing their susceptibility to cardiovascular complications. Studies have shown that G6PD deficiency can lead to worse glycemic control and greater oxidative stress in diabetic patients, thereby enhancing the risk of adverse cardiovascular events, including heart failure and myocardial infarction. A cross-sectional analysis involving diabetic patients revealed that those with G6PD deficiency had significantly higher rates of cardiovascular events compared to their G6PD-normal counterparts, suggesting that the combination of these conditions could synergistically contribute to cardiovascular morbidity [62].

Inflammation is another critical aspect that connects G6PD deficiency to cardiovascular risk. Chronic inflammation is a known contributor to atherosclerosis, and individuals with G6PD deficiency may exhibit elevated levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) [63]. These inflammatory markers have been associated with an increased risk of cardiovascular events, further supporting the notion that G6PD deficiency could play a role in the pathogenesis of cardiovascular diseases through an inflammatory pathway. A study found that G6PD-deficient individuals had higher baseline levels of CRP, correlating with a higher incidence of cardiovascular events, highlighting the inflammatory component of the disease process [64]. Despite these findings, it is important to note that not all studies agree on the extent of cardiovascular risk associated with G6PD deficiency, and some research has produced mixed results. Variability in study populations, differences in G6PD mutation types, and confounding factors such as age, gender, and comorbidities can influence outcomes. Moreover, much of the existing research has focused on populations with high prevalence rates of G6PD deficiency, which may not fully represent the global population. Future longitudinal studies and meta-analyses are needed to clarify these associations further and to explore the underlying mechanisms connecting G6PD deficiency to cardiovascular risk [65].

5. Mechanistic Insights from Animal and Cell Models

Research utilizing animal and cell models has provided valuable mechanistic insights into the pathophysiology of glucose-6-phosphate dehydrogenase (G6PD) deficiency, particularly regarding its effects on oxidative stress and cardiovascular risk. Animal models, such as G6PD-deficient mice, have been instrumental in demonstrating the consequences of impaired G6PD activity on redox homeostasis. These studies have shown that G6PD-deficient mice exhibit significantly elevated levels of reactive oxygen species (ROS) and reduced antioxidant capacity, leading to oxidative stress that affects multiple organ systems. In these models, the absence of G6PD results in compromised endothelial function, as evidenced by increased arterial stiffness and impaired vasodilation, highlighting the role of oxidative stress in cardiovascular pathophysiology [66].

Cell culture studies have also provided insights into the mechanisms underlying oxidative stress in G6PD deficiency [67]. For instance, human endothelial cells exposed to oxidative stressors demonstrate increased cell death and dysfunction when G6PD activity is inhibited. This finding suggests that G6PD plays a crucial protective role in endothelial cells, where it helps maintain NADPH levels necessary for the regeneration of glutathione, thus mitigating oxidative damage. Furthermore, studies on red blood cells derived from G6PD-deficient patients have shown an increased propensity for hemolysis in response to oxidative agents, underscoring the vulnerability of these cells due to their impaired ability to detoxify ROS. Together, these animal and cell model studies elucidate the critical role of G6PD in managing oxidative stress, providing a foundation for understanding the increased cardiovascular risks associated with G6PD deficiency [68].

Table 3 Animal Models and findings [69-75]

Model Type	Findings
Animal Models	G6PD-deficient mice show elevated ROS levels and oxidative stress, leading to impaired endothelial function and increased arterial stiffness.
Cell Models	Endothelial cells with inhibited G6PD activity exhibit increased cell death and dysfunction under oxidative stress, emphasizing G6PD's protective role.
Red Blood Cells	G6PD-deficient RBCs are more susceptible to hemolysis when exposed to oxidative agents, highlighting their vulnerability due to impaired ROS detoxification.

6. Potential Therapeutic Interventions

The management of glucose-6-phosphate dehydrogenase (G6PD) deficiency presents unique challenges, particularly given the condition's propensity for oxidative stress and associated complications, including hemolytic anemia and increased cardiovascular risk. While there is currently no definitive cure for G6PD deficiency, several potential therapeutic interventions aim to mitigate oxidative stress and improve the overall health of affected individuals. One promising approach involves the use of antioxidants, which can help restore redox balance in G6PD-deficient patients. Compounds such as N-acetylcysteine (NAC), a precursor of glutathione, have been studied for their ability to replenish intracellular glutathione levels. By enhancing the antioxidant defenses of red blood cells, NAC may help reduce hemolysis and oxidative damage, particularly during episodes triggered by infections or exposure to oxidative stressors [76].

Another area of research focuses on dietary interventions. The inclusion of antioxidant-rich foods, such as fruits and vegetables, may help bolster the body's natural defenses against oxidative stress. For instance, foods high in vitamin C and vitamin E could provide additional support to combat oxidative damage, although specific dietary recommendations need further exploration in G6PD-deficient individuals to avoid adverse reactions to certain foods, like fava beans, which can trigger hemolysis. Furthermore, the identification of specific dietary patterns that minimize oxidative exposure while providing essential nutrients can be an important aspect of managing G6PD deficiency [77]. Pharmacological strategies targeting the underlying oxidative stress mechanisms are also under investigation. For instance, the use of pharmacological agents that upregulate endogenous antioxidant pathways could represent a viable approach. Research into drugs that stimulate the expression of antioxidant enzymes, such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD), could enhance the ability of G6PD-deficient cells to cope with oxidative stress. Additionally, compounds like metformin, commonly used in diabetes management, have shown promise in modulating oxidative stress and inflammation, potentially providing dual benefits for individuals with both diabetes and G6PD deficiency [78]. Gene therapy offers another potential avenue for therapeutic intervention, particularly as advancements in genetic engineering continue to evolve. Targeting the G6PD gene directly to correct mutations or enhance its expression could provide a long-term solution to the deficiency. Recent advances in CRISPR-Cas9 technology hold promise for precise gene editing, enabling the correction of specific mutations responsible for G6PD deficiency. While still in its infancy, this approach has the potential to revolutionize the management of genetic disorders, including G6PD deficiency, by restoring normal enzyme function and alleviating the associated symptoms and risks [79].

Monitoring and preventative strategies are also critical in the management of G6PD deficiency. Educating patients and caregivers about potential triggers of hemolytic episodes—such as certain medications, infections, and dietary factors—can empower individuals to make informed choices that minimize oxidative stress. Healthcare providers should be vigilant in screening for and managing conditions that could exacerbate oxidative stress, such as infections or chronic inflammatory diseases. Furthermore, regular monitoring of hemoglobin levels and renal function is essential in patients with G6PD deficiency to detect potential complications early [80].

The development of novel biomarkers to assess oxidative stress levels in G6PD-deficient individuals could provide insights into their risk for cardiovascular disease and help tailor interventions more effectively. For instance, measuring levels of oxidized glutathione, malondialdehyde, or other oxidative stress markers could serve as valuable tools for evaluating disease progression and treatment efficacy [81].

Collaboration among healthcare professionals, researchers, and patient advocacy groups is vital in advancing the understanding and management of G6PD deficiency. Multidisciplinary approaches that involve hematologists,

cardiologists, nutritionists, and geneticists can help create comprehensive care plans that address the diverse needs of affected individuals. As research continues to evolve, novel therapeutic strategies that target the multifaceted nature of G6PD deficiency will be essential in improving patient outcomes and enhancing quality of life [82-87].

7. Conclusion

In conclusion, glucose-6-phosphate dehydrogenase (G6PD) deficiency represents a significant public health concern due to its implications for oxidative stress and the increased risk of various health complications, including hemolytic anemia and cardiovascular disease. The condition, primarily inherited in an X-linked recessive pattern, affects millions globally, particularly in regions with high prevalence rates. Understanding the underlying pathophysiology, including the critical role of G6PD in maintaining redox homeostasis, is essential for developing effective management strategies. Clinical studies have demonstrated the association between G6PD deficiency and heightened oxidative stress, leading to endothelial dysfunction and dyslipidemia, which are key contributors to cardiovascular risk. This relationship underscores the necessity of targeted interventions aimed at reducing oxidative stress, such as the use of antioxidants, dietary modifications, and pharmacological therapies that enhance the body's natural antioxidant defenses. Additionally, advancements in gene therapy present promising avenues for future treatment options that could potentially correct the genetic basis of the deficiency itself. Furthermore, the importance of patient education cannot be overstated; empowering individuals with knowledge about potential triggers for hemolytic crises, such as certain medications and foods, plays a crucial role in preventing complications. Monitoring and preventative strategies, including regular assessments of hemoglobin levels and renal function, are vital for managing the long-term health of individuals with G6PD deficiency. As research progresses, the development of novel biomarkers to evaluate oxidative stress levels and cardiovascular risk will facilitate more personalized and effective therapeutic approaches. The collaborative efforts among healthcare professionals, researchers, and patient advocacy groups will be essential in advancing the understanding and management of G6PD deficiency, ultimately leading to improved health outcomes and quality of life for affected individuals. In summary, while the challenges posed by G6PD deficiency are multifaceted, a comprehensive and integrated approach that encompasses education, dietary interventions, pharmacological therapies, and ongoing research holds great promise for mitigating the risks associated with this condition and enhancing the well-being of those impacted. Continued dedication to exploring therapeutic options and optimizing care strategies will be crucial in addressing the complexities of G6PD deficiency and its far-reaching effects on individuals' health and quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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