Review
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G6PD Deficiency: Exploring the Relationship with Different Medical Disorders

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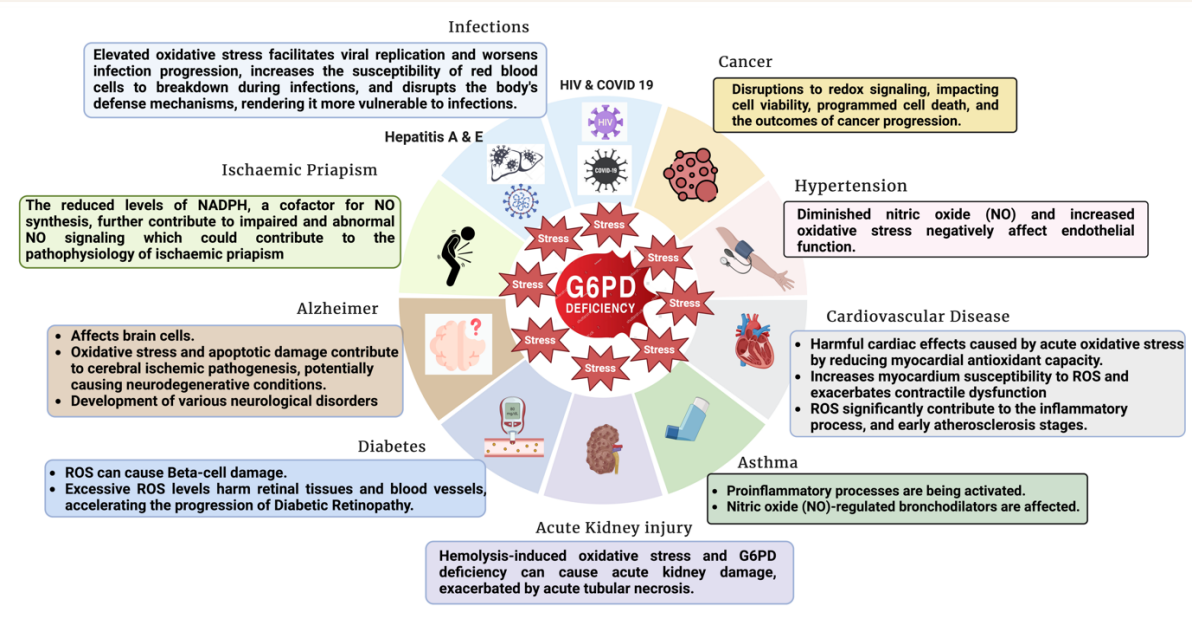
Abstract

G6PD deficiency (G6PDD) is associated with oxidative stress resulting from an imbalance between reactive oxygen species (ROS) production and the body's ability to counteract. In this review, we explore the adverse effects of G6PDD on diverse physiological processes and disease outcomes. Past studies have demonstrated the association between G6PDD and various other diseases, indicating a link between G6PDD to heightened oxidative stress by accelerating virus replication, worsening infection severity, and weakening the body's defense mechanisms. Such stress is critical in the destruction of red blood cells (RBCs) during infections and has a detrimental impact on redox signaling, ultimately impacting cell health and promoting cancer development. Furthermore, it impairs endothelial function by lowering the nitric oxide (NO) level and increasing stress, resulting in detrimental cardiac consequences and reduced myocardial antioxidant capacity. Because ROS contributes to inflammation, this imbalance causes conditions such as early atherosclerosis. It also compromises the functionality of NO-regulated bronchodilators and conditions such as G6PDD exacerbate the risks of kidney damage. Elevated ROS levels can also induce harm in retinal tissues, blood vessels, brain cells, and Beta-cells, hence quickening the progression of diseases like Diabetic Retinopathy. Furthermore, oxidative stress plays a significant role in cerebral ischemic pathogenesis, contributing to neurodegenerative disorders. Additionally, decreased NADPH level is vital for NO synthesis as it can impact blood vessel relaxation and can potentially lead to ischaemic priapism. Investigating the association between G6PDD and other medical conditions is crucial as it helps to identify possible approaches to mitigate oxidative stress, thereby preventing associated complications and diseases, particularly in situations where current treatment options are insufficient.

Graphical Abstract



Keywords: G6PD deficiency, oxidative stress, reactive oxygen species, medical disorders

Introduction

The human glucose-6-phosphate dehydrogenase (G6PD) enzyme plays a crucial role in red blood cells (RBCs), serving as the exclusive supplier of NADPH.[1] It maintains reduced Glutathione (GSH),[2] which helps neutralize harmful free radicals that could otherwise cause oxidative damage.[3] Consequently, this protective mechanism shields RBCs from the detrimental impact of reactive oxygen species (ROS). The occurrence of oxidative stress in biological systems arises from an excess of ROS, which is known as oxidants. Prolonged oxidative stress disturbs cellular structures and functions that are

normally regulated by essential oxidation-reduction (redox) pathways.[3] This will result in cell and tissue damage, leading to the development of the pathophysiology underlying various diseases.[4] In the event of a defective enzyme, RBCs become vulnerable to the cumulative effects of ROS and will result in hemolysis.[5,6] Conversely, genetic mutations in the G6PD gene will promote G6PD deficiency (G6PDD),[7,8] which is a globally prevalent enzymopathy impacting over 500 million people,[1,9] and 11 million infants every year.[10] Typically, individuals with G6PDD remain without symptoms for their entire lives unless they come into contact with certain medications or ingest specific foods like fava beans.[11] Despite the well-known link between G6PDD and oxidative stress, there is a crucial need to explore and investigate the intricate mechanisms underlying this relationship. Therefore, the present review was conducted as a comprehensive evaluation of clinical studies investigating the pharmacology and therapeutic aspects of G6PDD. This knowledge is of paramount importance for researchers and clinical pharmacologists seeking to unravel the complexities of G6PDD and its oxidative stress-related implications. It also has the potential to guide the development of targeted therapeutic interventions for G6PDD and enhance the overall quality of life for individuals affected by this condition, especially in the absence of new treatment options.

The Relationship Between G6PDD and Medical Disorders

Viral Infections

Individuals with G6PDD and severe enzymatic deficiency have been found to be more susceptible to infections.[12] The large decrease in G6PD activity is often connected to increased sensitivity, causing changes in the body's defense mechanisms and making them highly vulnerable to diseases.[12] Moreover, the presence of G6PDD leads to heightened oxidative stress levels that create a conducive environment for viral replication, thereby worsening the progression of the infection.[13] People with G6PDD are at a higher risk of experiencing RBCs breakdown during infections as the enzyme's role is to maintain sufficient GSH levels that can protect cells from damage caused by free radicals.[14] Furthermore, G6PDD has a significant impact on macrophage polarization and the synthesis of inflammatory cytokines in human monocytes.[15] Macrophage cells are crucial for innate immune defense against invading pathogens and contribute to acquired immune responses,[15] resulting in increased susceptibility to infections.[7,15]

Viral hepatitis can lead to serious complications like severe anemia, hemolysis, renal failure, hepatic encephalopathy, and potential fatality, particularly when it occurs alongside G6PDD.[16] In many cases, viral hepatitis results in a certain degree of hemolysis that can have more pronounced and severe impacts on individuals with G6PDD.[16]

Hepatitis A virus (HAV) is the most common form of viral hepatitis that presents a significant global public health concern due to its widespread prevalence and diverse clinical manifestations.[17] Occasionally, seemingly mild illnesses like hepatitis A can become complex when occurring alongside hidden medical conditions like G6PDD. In such cases, patients might experience multiorgan failure, leading to higher mortality rates. Therefore, it is advisable to investigate any previously undetected medical conditions if a patient displays unexpectedly severe clinical symptoms.[18] HAV is often a self-limiting condition; complications arise mainly when there is a secondary stress on RBCs.[18] Severe hemolysis can occur in individuals with severe hepatitis A, especially if they have underlying G6PDD.[18] Moreover, hepatitis E virus (HEV) is an infectious inflammation of the liver that commonly causes acute hepatitis and jaundice.[19] Past evidence suggests that G6PDD has been related to hematologic problems during acute HEV infections, with around 70% of acute HEV hepatitis patients displaying G6PD incidence.[12]

Additionally, oxidative stress occurs continuously among HIV-infected people.[4] This oxidative stress is thought to contribute to various aspects of HIV disease progression, including viral replication, inflammatory responses, impaired immune cell proliferation, immune function loss, apoptosis, chronic weight loss, and heightened susceptibility to drug toxicities.[4] GSH might play a role in these processes, particularly as reduced GSH levels have been discovered in the tissue analysis of HIV-infected patients who are asymptomatic and experiencing oxidative stress early in the course of the disease.[4,14] COVID-19 is another viral infection associated with an unbalanced redox condition that can generate hyperinflammation and cytokine storm, leading to cell death. Individuals with G6PDD are at a higher risk of contracting COVID-19 compared to those with normal G6PD levels due to their impaired immune response to viral infections.[20] Traditionally, chloroquine and hydroxychloroquine have been used to kill malarial parasites by inducing oxidative stress. Both medications were utilized to treat COVID-19 infections due to their capacity to raise endosomal pH, hence inhibiting the fusion of COVID-19 and the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell membrane. Moreover, the mechanism of these medications generates increased systemic oxidative stress, making their usage in individuals with G6PDD entirely inappropriate. In several case studies, hydroxychloroquine therapy for COVID-19 for G6PD-deficient individuals demonstrated a significant reduction in hemoglobin and haptoglobin, indicating erythrocyte destruction.[21] Understanding the intricate relationship between G6PDD and viral infections is essential for developing targeted approaches to manage infections and minimize complications.

Cancer

Cancer is a prevalent cause of global mortality with complex underlying factors. Although the origins of cancer vary, shared characteristics are found across several different types, including the reprogramming of energy metabolism.[22] A relationship between G6PDD and cancer has been proposed owing to pentose phosphate pathway (PPP) downregulation. PPP is a major glucose metabolic pathway and protein dysregulation in its system may play a role in cancer development.[22] Cancer cells generally prefer PPP because it produces high levels of NADPH, which is required for fast development. G6PD, the first rate-limiting enzyme of PPP, is also involved in the development of cancer.[22] It causes redox signaling abnormalities, which influence cell survival and apoptosis and have been linked to the progression and outcomes of numerous cancer types.[23]

Invasive fungal diseases (IFDs) are a major source of morbidity and death among individuals with hematologic

cancers.[24] Those with acute myeloid leukemia (AML) who are receiving remission induction chemotherapy or undergoing hematopoietic stem cell transplantation are at a greater risk of IFD.[24] Furthermore, G6PD activity was found to impact the chance of developing IFDs. G6PD enzyme deficiency, in particular, appears to greatly increase the risk of Candida sepsis and mold infections in patients with acute myeloid leukemia.[24] Moreover, there is an elevation of G6PD expression in numerous cancer types.[22] Elevated G6PD levels have also been associated with several facets of cancer advancement, including tumor size, depth of invasion, involvement of lymph nodes, and the presence of distant metastases, as indicated by the tumor node metastasis (TNM) stage and overall survival rate.[22]

Hypertension

G6PD is also involved in the production of endogenous antioxidants. A decrease in G6PD activity leads to higher levels of ROS or oxidative stress within the cell.[25] Aldosterone, a mineralocorticoid hormone, is released by the outer layer (zona glomerulosa) of the adrenal cortex. An overproduction of aldosterone is known as hyperaldosteronism. This condition may manifest as mild to severe with occasional treatment-resistant and hypertension, making it challenging to detect in some cases [[26]. Hyperaldosteronism is linked to compromised vascular reactivity and it has been demonstrated that aldosterone causes G6PDD, leading to impaired endothelial function. However, both aldosterone antagonism and G6PD gene transfer have been shown to enhance vascular reactivity.[7] Endothelial dysfunction is identified by a reduction in the availability of nitric oxide (NO), which controls the adherence of white blood cells (WBCS) to the endothelial lining. Studies have shown that boosting G6PD expression reduces the buildup of ROS while simultaneously enhancing nitric oxide synthetase (NOS) activity and the amount of available NO in vascular endothelial cells.[7] G6PDD also results in reduced NADPH levels, which is crucial for the synthesis of NO.[7] Consequently, G6PD-deficient endothelial cells display diminished expression of endothelial NO synthase, lower levels of NO, as well as a reduction in GSH. The decline in NO and the rise in oxidative stress levels negatively impact endothelial function and contribute to the development of hypertension, atherosclerosis, stroke, and various other vascular disorders.[7]

Cardiovascular Diseases

Cardiovascular diseases (CVDs) are widespread and remain the primary cause of global mortality, with atherosclerosis accounting for the majority of CVD cases. The development of plaque and subsequent thrombosis in atherosclerosis is an ongoing process affected by multiple risk factors, including hypertension, diabetes, dyslipidemia, obesity, smoking, inflammation, and a sedentary lifestyle.[27] Due to its impact on reducing myocardial antioxidant capacity, G6PDD can potentially worsen the detrimental cardiac effects caused by acute oxidative stress, such as in the case of ischemia-reperfusion injury. Furthermore, G6PDD increases the myocardium's susceptibility to ROS and worsens contractile dysfunction when faced with oxidative damage.[28] Atherosclerosis primarily develops due to chronic inflammation of the blood vessel wall, which is largely influenced by the innate immune response[28] ROS plays a crucial role in the inflammatory process and an imbalance in ROS production or neutralization contributes significantly to the early stages of atherosclerosis. In both *in vitro* and *ex vivo* studies, G6PDD has been found to have extensive and detrimental effects on inflammatory response, cell adhesion mechanisms, and fibrogenesis.[29] One of the prominent consequences of impaired inflammatory response in G6PDD is reduced bactericidal activity by phagocytic cells, resulting from the inhibition of the respiratory burst.[30] This leads to an increased vulnerability to pyogenic infections.[31] Conversely, the alleged reduction in ROS production caused by G6PDD is believed to enhance susceptibility to various viral infections.[32] Interestingly, viral infections have been associated with a higher incidence of ischemic heart disease and cardiomyopathy.[27]

Asthma

Asthma is a chronic inflammatory respiratory condition that globally impacts more than 300 million individuals.[33] Certain asthma patients continue to have inadequate control with traditional treatments and face a higher risk of severe exacerbations.[33] Chronic inflammation, which is primarily influenced by the innate immune response, is the main underlying cause of asthma. ROS stands as an effective mediator of this inflammatory process and an imbalance in the levels of ROS production and neutralization is a key factor in the development of asthma.[34] Moreover, G6PDD leads to a reduction in NO levels.[34] NO serves as a significant signaling molecule and a free radical, exhibiting a dual role: at low levels, it primarily relaxes the airway muscles, while at high levels, it triggers proinflammatory processes. As a result, the impact of NO depletion in asthma is intricate, including in severe cases of G6PDD. It is possible that the continuous depletion of NO, resulting from G6PDD, may affect the normal bronchodilator function regulated by this molecule.[35] This effect becomes particularly notable in the elderly where antioxidant mechanisms tend to progressively decline.[36,34]

Acute Kidney Injury

Acute kidney injury is characterized by an abrupt decrease of excretory renal function. It is one of the several ailments grouped together as acute kidney diseases and disorders, in which progressive degradation of kidney function or persistent renal dysfunction is linked with irreversible loss of kidney cells and nephrons that can potentially lead to chronic kidney disease.[36] Acute hemolytic anemia puts a significant load on several tissues, notably the kidneys. Acute kidney damage caused by hemolysis is regarded as a serious and dangerous consequence, particularly in severe hemolysis.[37] Apart from its role in hemolytic disorders, G6PD, a crucial component of antioxidant defense, is implicated in the pathogenesis of other diseases, including unexplained kidney diseases. Increased oxidative stress that is observed in various diseases linked to renal damage may also contribute to this association. Past studies demonstrated that children with unexplained chronic kidney disease have a higher prevalence of G6PDD, suggesting that G6PDD-induced anemia could be a significant factor in the development of chronic kidney disease.[37] Additionally, massive intravascular hemolysis in severe G6PDD cases can

lead to acute renal failure and there is a possibility of acute tubular necrosis complicating the severe hemolytic episode.[37]

Diabetes Mellitus

Diabetes mellitus (DM) is a complex disease commonly influenced by multiple factors, including increased oxidative stress.[38-42] This, in turn, leads to the development of diabetes-related complications.[38] The balance between ROS and antioxidants determines the oxidative status of cells. Despite the stable level of GSH in diabetic patients, which is likely sustained by NADPH supplied by normal G6PD, hyperglycemia can lead to the buildup of ROS.[42] This is caused by the activation of various metabolic pathways, such as an increase in glucose flow through the polyol pathway, elevated formation of advanced glycation end products, activation of protein kinase C, and an increase in hexosamine pathway flux. These activated biochemical pathways generate excessive ROS, resulting in oxidative stress and damage to proteins and lipids.[42]

Furthermore, individuals with G6PDD are at a higher risk of developing type 2 diabetes[43] compared to those without such deficiency. Several factors contribute to the susceptibility of G6PDD patients to diabetes mellitus.[39] Primarily, the PPP of G6PDD patients fails to produce enough NADPH to reduce oxidized GSH, resulting in altered glucose tolerance. This leads to decreased levels of GSH and increased oxidative stress, which in turn elevates the risk of diabetes.[39] The beta-cells in the islets of Langerhans in the pancreas are highly sensitive to ROS, making them susceptible to damage by increased free radicals observed in the G6PDD status. These findings explain why G6PDD patients are more prone to developing diabetes mellitus.[39]

Another study demonstrated that an increase in G6PD activity can protect beta cells from cell death, confirming the role of G6PD in the pathogenesis of type 2 diabetes mellitus.[42] Moreover, multiple converging pieces of evidence suggest a potential genetic link between diabetes and G6PDD as its prevalence is higher among individuals with diabetes compared to the general population.[42] Diabetic retinopathy (DR) is classified as a microvascular complication of diabetes and poses a significant risk to vision.[44] It is widely recognized as the primary cause of visual impairment or blindness in working-age adults and elderly individuals worldwide.[38] The development of DR is strongly influenced by oxidative stress as an overabundance of ROS can cause damage to the retinal tissues and surrounding blood vessels, ultimately leading to the condition. Hyperglycemia-induced oxidative damage in the retina is associated with four primary metabolic abnormalities: activation of the protein kinase C pathway, polyol pathway flux, activation of the hexosamine pathway, and intracellular formation of advanced glycation end-products.[42]

Alzheimer's Disease

Alzheimer's disease (AD) is a complex degenerative condition that affects the brain and causes gradual cognitive decline in older individuals. It is characterized by the accumulation of two abnormal protein aggregates, amyloid-β and phosphorylated tau, in the brain.[45] The presence of amyloid-beta in the central nervous system triggers a series of molecular events that lead to neurodegeneration and the progression of AD.[46] Oxidative stress and apoptotic damage are significant contributors to the development of cerebral ischemic pathogenesis and could be potential targets for treatment.[46] Increased G6PD enzyme activity is also recorded in the blood of individuals with AD, which is about twice the normal level.[47] Increased G6PD enzymatic activity may serve as a protective mechanism against oxidative stress. G6PD activation redirects the glycolytic pathway to the pentose phosphate pathway, leading to the production of more NADPH. The elevated NADPH level helps to maintain reduced GSH level, which plays a vital role in scavenging ROS, thereby protecting brain cells from oxidative damage.[46] However, G6PDD compromises the protective mechanism provided by the G6PD enzyme, making the brain cells more vulnerable to oxidative damage. If the mechanisms that defend against oxidative stress are ineffective, brain cells are at a higher risk of being harmed by ROS and other factors inducing oxidative stress. The increased vulnerability may contribute to the onset or progression of various neurological disorders and conditions. Furthermore, previous research suggested that the aging process can lead to changes in the kinetic behavior of the G6PD enzyme.[46]

Ischaemic Priapism

Ischaemic priapism is a severe urological condition with the potential to cause permanent erectile dysfunction.[48] G6PDD was discovered during evaluation for priapism that can lead to increased oxidative stress, and ultimately priapism.[48] Therefore, it is important to include G6PDD screening in the assessment of idiopathic causes of the disorder. In individuals with G6PDD, weakened antioxidant defenses result in oxidative stress, leading to hemolysis, endothelial injury, and depletion of NO.[48] The reduced level of NADPH, which is a cofactor for NO synthesis, further contributes to impaired and abnormal NO signaling that can contribute to the pathophysiology of ischaemic priapism.[48] Additionally, the mechanism behind recurrent priapism without a clear cause could be related to hemolytic anemia stemming from G6PDD.[49] There are several potential explanations for this connection, including hyperviscosity, direct endothelial dysfunction caused by hemoglobin vasculotoxicity, and relative NO deficiency, subsequently causing vasoconstriction and vascular smooth muscle proliferation.[49] Early identification and management of G6PDD in patients with priapism may offer potential avenues for preventing or minimizing the risk of permanent erectile dysfunction.

Conclusion

In conclusion, G6PDD is a genetic disorder characterized by heightened oxidative stress levels, affecting multiple physiological processes and disease outcomes. The impact of G6PDD extends to viral replication, cancer progression, endothelial function, myocardial antioxidant capacity, bronchodilation, and severe hemolysis. The altered PPP also contributes to glucose metabolism changes and an increased risk of diabetes. The damaging effects on pancreatic beta-cells underscore the crucial importance of early detection and intervention. Having thorough research on G6PD mutations can unveil factors influencing disease severity and propose strategies to increase enzyme activity, reduce oxidative stress, and prevent related

complications. These significant discoveries could lead to the development of personalized drugs tailored to individuals with G6PDD, not only to treat the condition effectively but also to improve their quality of life, particularly in cases where current treatment options are insufficient.

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