**Clinical Significance of Glucose-6-Phosphate Dehydrogenase Deficiency**

**Abstract**

Glucose-6-phosphate dehydrogenase deficiency is a genetic disorder passed down the lineage and is associated with enzymatic defects that lead to premature destruction of the red blood cells during Haematopoiesis. This damage, termed as hemolytic, leads to the low supply of blood and oxygen to the tissues and other body systems since the red blood cells cannot function properly or their quantities is too small leading to hemolytic anemia. This condition manifests itself in many ways, thereby understanding the clinical significance associated with it could help patients and other caregivers save a life. These guide the need to undertake a systematic review of the clinical relevance of Glucose-6-phosphate dehydrogenase deficiency and its pathophysiology, and this could provide recent development made in understanding the disease and its management with the aim to improve care and better management by physicians. The study was accomplished through a systematic review of the peer-reviewed articles from the Science Direct, PubMed, and Scopus databases. Articles were selected using search terms “clinical significance of G6pd Deficiency” and limited to those published within the last six years. Findings show that patients with alleles are likely to experience episodes of hemolytic anemia when exposed to pharmacogenetics and foods with condition ranging from severe to mild. The G6PD and levels of enzyme deficiency determine the severity. Foods like fava beans or their pollens, malaria and, and chemical agents act as oxidative stressors and thereby predisposing patients with hemolytic anemia.  Low dosages of antimalarials, appropriate testing could improve patient outcomes.

*Keywords:* G6PD deficiency, risk factors, pharmacogenetics, testing, management

**Clinical Significance of Glucose-6-Phosphate Dehydrogenase Deficiency**

Evaluating the clinical significance of glucose-6-phosphate dehydrogenase deficiency provides existing and emerging approaches that could be adopted for an improved patient outcome. Patients with glucose-6-phosphate dehydrogenase deficiency could be exposed to life-threatening conditions because clinicians are likely to overlook a comprehensive assessment when administering medications for other conditions whose drugs could generate adverse effects on patients with G6PD deficiency. Several diseases and infections act as predisposing factors that potentiate the risks for the G6PD deficiency. For instance, reports indicate that some anti-malaria drugs and some food items may induce the breakdown of red blood cells and this could worsen the situation if patients with Glucose-6-phosphate dehydrogenase deficiency. Interestingly, the occurrence of G6PD deficiency is more prevalent in endemic malaria regions, which increases the risks for such patients. Clinicians need an evidence-based approach that could help save patients and improve the strategies for their outcome. Besides, lack of an appropriate diagnostic plan for the G6DP deficiency and poor handling of sample could make it difficult to manage the condition safely and efficiently. Reviewing existing literature on the therapeutics reported to have adverse effects on patients with G6DP deficiency and using appropriate testing could provide guidelines for recommending appropriate management strategies for guiding the practitioners when dealing with cases of G6DP deficiency.  Therefore, the review focuses on a systematic evaluation of the information relating to pharmacogenetics that could complicate the management of G6PD deficiency and evaluating the testing strategies for managing G6PD deficiency. This information is necessary to clinicians for it provides a roadmap for safe management of the condition based on clinical evidence. Besides, the finding could act as the guidelines for policy formulation when planning to roll out clinical trials in areas with high prevalence of G6PD deficiency.

**Methods**

The paper presents a systematic review, which involved sourcing for relevant articles from journals indexed in Science Direct, PubMed, or Scopus and using information that relates to the research search terms. These databases provide credible materials owing to the nature of review manuscripts undergo before acceptance for publications. Therefore, it was assumed that articles listed in these databases have undergone efficient peer review process and provide relevant information for this work. These items were selected based on the predetermined criterion, which included using key search words such as “Clinical Significance of G6PD Deficiency Pathophysiology.” Others terms used for the selection of appropriate papers included “G6pd enzyme deficiency.” Besides, the search was limited to include evidenced-based studies from clinical trials, case studies, or reviews of similar articles. Finally, the selection was based on previous studies reported within the last five years, with most recent ones given priority to ensure that the paper provides the latest information that could provide evidence for consideration.

**Review of Literature**

**Pharmacogenetics as a Predisposing Factor**

G6PD is an enzyme within the pentose phosphate pathway that produces NADPH, which provides cell protection against oxidative damages. The red blood cells lack mitochondria, nucleus and other organelles making the pentose pathway the single biochemical pathway involved in the reducing capacity (Luzzatto & Seneca 2013). Luzzatto and Seneca (2013) argued that pharmacogenetics has clinical implications for patients with G6PD. The primary challenge is that most clinicians may not have a picture of the entire health condition for each patient, which predisposes those with G6PD deficiency to potentially life-threatening conditions when exposed to some drugs that induces red blood cell destruction. According to Carter et al. (2011), G6PD deficiency is common in patients with malaria. The study terminated clinical trials on G6PD deficiency patients enrolled in Chlorproguanil-dapsone-artesunate treatment because of the increased risks associated with the hemolysis in such patients compared to the G6PD normal patients. The treatment with 8-aminoquinolines, which targets malaria, will remain the main problem to patients with G6PD deficiency. Interestingly, the study found that G6PD genotypes did not have the independent effect on malaria parasitemia, temperature, or baseline hemoglobin (Carter et al., 2011). The primary outcome of the study was the need for G6PD phenotyping and genotyping before using anti-malaria drugs to lower the risks to patients with G6PD deficiency.

A study by White et al. (2012) reports the lowest dose of 0.75 mg /kg of primaquine administered in a single dose to patients diagnosed with acute falciparum in regions with low episodes of malaria transmission. The finding agrees with a 0.25 mg/kg dose reported by Bancone et al. (2016). The dose was found to be safe and effective in combination with artemisinin combination treatment. White and the colleagues recommended the deployment of the prescription without necessarily testing for the G6PD deficiency among the patients in such population because the dose could not affect G6PD deficiency patients adversely. These findings agree with previous studies that modeled prevalence and correlated such information with the genetic variants so that one could predict the risks associated with hemolytic anemia resulting from G6PD deficiency (Howes et al., 2012; Seidlein et al., 2013). Such studies are essential in helping policymakers come with optimal strategies for safe deployment of drugs like primaquine, which could complicate condition of G6PD deficiency is testing is not readily available as reported previously (Seidlein et al., 2013). Other studies tried to elaborate the mechanism used by drugs like primaquine in the red blood cells of patients with G6PD deficiency by evaluating the eryptotic pathway (Ganesan et al., 2012).  The use of this drug is limited in malaria patient with G6PD deficiency, and this informed the need to evaluate how the drug induces hemolytic toxicity, which could inform clinical evaluation and planning the appropriate management strategies. The study found that mechanisms for eryptosis could not accelerate the removal of red blood cells associated with destruction by primaquine. However, increased oxidative stress could be used as a way of monitoring the responses from administering primaquine (Ganesan et al., 2012).

Kim et al. (2011) observed that the development of a rapid diagnosis kit that is easy to use and readily available is a pivotal step toward the management of G6PD deficiency. Such products may have application at the point of care making it possible to deploy some drugs like primaquine, which are associated with adverse reaction on patients with G6PD deficiency. The standard gold method for testing G6PD deficiency involves using standardized spectrophotometric approach, which was compared with the CareStarttm G6PD deficiency testing kit. Finding indicates that the kit had high sensitivity and specificity (68% and 100% respectively). However, 1.4% of the patients with G6PD deficiency were classified as normal, hence the need to lower false negative before its deployment. These developments are exciting since one could efficiently use such kits at the point of care without the need for sophisticated analysis.

**Complications of Management**

According to Najib et al. (2013), G6PD deficiency is a risk factor for the indirect occurrence of severe neonatal hyperbilirubinemia, and this could be contributing to the increasing cases of neonatal readmission. The risk factors were severe among the male, which subscribes to the prevalence of G6PD deficiency in most populations. G6PD deficiency resembles severe hyperbilirubinemia since both are based on family history. Although study associated G6PD deficiency as a risk factor for severe hyperbilirubinemia, their approach was limited and could not give any clinical relevance. However, it broadens our understanding of G6PD deficiency, which could predispose individuals to other conditions, which may mask G6PD deficiency thereby complicating management.

The G6PD deficiency could be an independent indicator of poor prognosis in some conditions like cancer. According to Wang et al. (2012), G6PD is associated with the progression of gastric cancer. The study identified over-expression of G6PD among the patients presenting with clinical gastric cancer, and these findings correlate significantly with the size of the tumor, survival rate, stage, distant metastasis, lymph node metastasis and the depth of invasion (Wang et al., 2012).

Ingestion of fava bean or its pollen has been documented to induce severe acute hemolysis, which manifests in the symptomatic methemoglobinemia as previously demonstrated by Odievre et al. (2011). The study emphasizes the need to screen G6PD deficiency in the symptomatic methemoglobinemia especially on the young boys if the association relates with the intravascular hemolysis (Odievre et al., 2011). This study presents the role played by other factors in the induction of G6PD deficiency, which could help keep patients safe from complications associated with the ingestion of molecules that induces hemolytic anemia.

**Testing Strategies Could Enhance Safe Management**

The study by Domingo et al. (2013) builds on the realization that testing of G6PD deficiency is a vital step toward safe management of the condition. The testing is paramount in lowering the risks to positive patients when deciding appropriate treatment regimes for other diseases associated with G6PD deficiency. The study recommends the need to test G6PD deficiency at the level of the individual to ensure appropriate and safe management. Besides, testing at the population level could give an indication to guide the risk mapping for making policies (Domingo et al., 2013).

The primary pathology in G6PD deficiency is hemolysis, which describes the breakdown of erythrocytes in blood. During the collection of blood specimen for analysis, this hemolysis can take place if a phlebotomist fails to follow appropriate procedures during collection, handling, and storage of sample (Lippi et al., 2011). These pre-analytical problems are of particular concerns to the emergency departments since hemolysed blood may indicate hemolytic anemia even if it is from poor laboratory practices. This issue leads to poor clinical and organization association between the clinicians working in the laboratory and those in the emergency departments (Lippi et al., 2011). Therefore, the development of parameters that identifies suitable specimens such as hemolysis index, differentiation between in vivo and in vitro hemolysis was proposed as the best alternative for this problem. These strategies are appropriate for other clinicians when making diagnosis.

According to Pamba et al. (2012), G6PD A- type, which occurs when mutations occur in N12D and V68M, ought not to be regarded as a mild condition since such clinicians may enroll patients to medications with life-threatening episode. For instance, the clinical trial undertaken by Pamba and others indicate that the treatment of patients with dapsone (2.5 mg/kg for three days once a day) led to the decline of hemoglobin concentration to 11%, which required blood transfusion. Although dosages and nature of drug influences the acute hemolytic anemia, G6PD A- deficiency should be regarded as potentially life threatening when deciding on the treatment regimes for such patients.  The report subscribes to a recent study by Olusanya et al. (2014), which aimed to address the burden of neonatal hyperbilirubinemia in patients with G6PD deficiency. The study found that G6PD deficiency is a risk factor for neonatal hyperbilirubinemia and led to increased neurodevelopment disorders, neonatal mortality and jaundice related morbidity. Some of the burdens identified in the study were lack of devices for monitoring and measuring bilirubin and the lack of clinical G6PD deficiency investigation, and these were linked to prohibitive prices for the appropriate tools for undertaking measurements. Besides, routine screening of blood before transfusion to infants is necessary to avoid the exchange of blood from donors with G6PD deficiency, which could prolong phototherapy sessions (Olusanya et al. 2014).

**Discussion**

Findings show that the prevalence of G6PD deficiency is high in areas with high malaria transmission dynamics. These observations are in tandem with other studies that associated G6PD deficiency with treatment regimes. For instance, previously Luzzatto and Seneca (2013) showed that some pharmacogenetics has clinical implications for patients with G6PD. Examples of these drugs include the Chlorproguanil-dapsone-artesunate treatment and 8-aminoquinolines (Carter et al., 2011). These studies show that these drugs increase the risks of red blood cells hemolysis. However, White et al.’s (2012) findings indicate that the lower dosages of primaquine when administered once could be safe and effective in combination with artemisinin combination treatment in patients with G6PD deficiency. The most important aspect for consideration is the pathophysiological implication of drugs that could deteriorate conditions of patients with G6PD deficiency. Clinicians ought to discriminate medications that worsen the condition of such patients.

Other studies by Howes et al. (2012) and Seidlein et al. (2013) propose the need to model the prevalence and correlate such information with the genetic variants so that clinicians could predict the risks associated with hemolytic anemia resulting from G6PD deficiency. It is important to note that prevalence correlates with the genetic variants, and one could predict the risks associated with hemolytic anemia resulting from G6PD deficiency. However, such approaches could only give the basis for undertaking further studies that identifies the individuals in the population with the G6PD deficiency. Using prediction could be nonspecific for some patients since they may not provide appropriate indication of the G6PD deficiency. Therefore, it is not appropriate to use such information to help policy makers come with optimal strategies for safe deployment of drugs like primaquine, which could complicate condition of G6PD deficiency. What the policymakers ought to do is to fund additional studies that build on the findings from the modeled prevalence and the genetic variants.

Ganesan et al. (2012) articulated the need to use the increase in oxidative stress when monitoring the responses from administering primaquine. However, it is prudent to understand that any occurrence of hemolytic anemia may not relate to G6PD deficiency. Perhaps, this could only be appropriate in mild to moderate conditions, which are also difficult to identify, and could be life threatening in severe conditions.  One would tend to think that G6PD deficiency is induced by other factors like fava food, which could also lead to increased oxidative stress hence making it difficult to use this parameter for monitoring purposes. The study by Odievre et al. (2011) provides necessary information associated with the food items that could complicate situations on patients with G6PD deficiency. Although the survey majored on symptomatic methemoglobinemia, it gives an alternative perspective for managing patients with G6PD deficiency by emphasizing the need to screen for G6PD deficiency since some food items could induce severe acute hemolysis.

The most appropriate strategy that could help clinicians manage G6PD deficiency is to use a rapid diagnosis kit that is easy to use and readily available, as described by Kim et al. (2011). Designing test strategies are essential for discriminating patients with the condition to avoid exposing those with G6PD deficiency to drugs that could worsen their conditions. The diagnosis, especially in malaria-endemic regions, could be the best approach for clinicians toward effective management of G6PD deficiency since it provides first-hand information on positive patients. Although most of the evaluated kits reported false negative, the levels of such reports are low and could be evaluated further using the randomized approach on increased sample size to underpin its sensitivity and specificity on a larger scale so that their deployment is evidence-based.

The study classifying severe hyperbilirubinemia as a risk factor for the G6PD deficiency examined factors that associate with the cases of neonatal readmissions (Najib et al., 2013). The study associates G6PD deficiency with severe hyperbilirubinemia because both are inherited within the family line. However, this finding may be limited for clinical application. Although it broadens our knowledge of the G6PD deficiency and its associated factors, it does not associate the treatment strategies used for severe hyperbilirubinemia as a possible factor that could complicate the management of G6PD deficiency. Besides, the study by Wang et al., (2012) pointed that G6PD deficiency is the independent indicator for poor prognosis in cancer, but the study did not examine the interaction of the two conditions at the treatment levels. Such information is relevant since it helps clinicians understand the pathophysiological changes that could take place when one treatment regimen is administered, thereby providing evidence on the most appropriate way of management.

The initial testing that guides the appropriate treatment regime is the G6PD phenotyping and genotyping. These kinds of tests are necessary before using anti-malaria drugs to lower the risks to patients with G6PD deficiency. Selection of appropriate testing strategy is vital for the safe management of patients. However, most of these testing strategies are too expensive to undertake. The gold standard testing procedure, which is based on spectrophotometric approach, requires instrumentation and this may not be utilized in areas with low resources where the prevalence of G6PD deficiency is high. Development of alternative testing methods that use kits could help clinicians manage the condition better since such tests could be used outside of the clinical environment like the fields as previously illustrated (Kim et al., 2011).  New developments should focus on these ready to use kits to hasten clinicians approach in clinical assessment. Besides, handling of specimens for testing could complicate the expected results if appropriate handling procedures are not met during the collection and analysis of the laboratory specimen. Soon, it would be important for clinicians to have indices that differentiate hemolysed samples based on the causes to lower the prospect of associating any degradation with G6PD deficiency.

**Limitations**

The main limitation in the selected articles is the number of sample size reported. For instance, Odievre et al. (2011) used a boy to draw information that could be applied in a clinical setting or a population.  The sample size in White et al. (2012), which was based on recommending a lower dose of 0.75 mg /kg primaquine as the safest and effective drug for malaria patients with G6PD deficiency, may not be representative. Perhaps, they could have to undertake a similar study on a broader set of a population to draw meaningful conclusions. It would have been appropriate for the researcher to have a more extensive sample size to make such findings. Patients may have different tolerant to the predisposing factors, and in such situations, the nursing professionals would need to use their experiences during assessments. The study that recommended the alternative dose for primaquine used patients in regions with low episodes of malaria transmission, it is not clear if the same finding could be applied in regions with high rates of transmission. The study by Wang et al. (2012), could have sought to unravel whether administration of cancer therapy influenced the outcome of G6PD deficiency so that clinicians could have an understanding of the effects of other medications used in cancer treatment on the G6PD deficient patients. Besides, Howes et al. (2012) and Seidlein et al. (2013) proposed the need to use modeled prevalence by correlating it with the genetic variants to guide prediction of the risks associated with hemolytic anemia. These assumptions could only be appropriate in undertaking further experiments as opposed to using such to roll out mass treatment. Using the increase in oxidative stress to monitor response to administering primaquine, as demonstrated by Ganesan et al. (2012), could be limited since it could expose some patients to severe acute hemolysis, which may be life-threatening hence the need for alternative monitoring strategies. Although fava is the main food associated with adverse effects on the induction of severe acute hemolysis, nursing professionals need to watch for patients who develop adverse conditions to other potential food items. The best approach is by taking history of the patients and their diet regimes, since most clinicians fail to undertake such assessment.

**Conclusion**

The findings show that apart from genetics, pharmacological agents against diseases like malaria act as the primary predisposing factor that could complicate patients’ outcome. Patients suffering from malaria have a high prevalence of G6PD deficiency, and the treatment of such patients may lead to life-threatening episodes for G6PD deficiency patients. Other factors include the fava food, which acts as an inducer for acute severe hemolysis. The main challenges facing the caregivers are proper diagnosis and the selection of appropriate medication for such patients. The information is relevant because it provides existing challenges, which could help the caregivers come up with alternative strategies to improve patient outcome through appropriate identification of the condition and design appropriate drug regimes. These realizations have led to research the lowest dosages of the adverse drugs that could lower adverse outcome and improve patient’s conditions. Although genotyping and phenotyping diagnostic approach could be expensive and may not be readily available for all clinical settings, they provide the standardized approach for selecting appropriate drugs. However, recent developments in the manufacture of kits could improve the caregivers’ effort in the management strategies, though some of the kits reported low sensitivity, they could be improved. Besides, a multi disciplinary approach that take on board specialists from fields like modeling could play a role in identifying parameters of predisposition to guide specific and more targeted research. The testing of G6PD deficiency and appropriate handling of the samples play a significant role in the management by clinicians.

**Summary**

Recent studies on glucose-6-phosphate dehydrogenase deficiency have majored on the risk factors, testing strategies, and appropriate ways of management. The Glucose-6-phosphate dehydrogenase deficiency is associated with the destruction of erythrocytes rendering them non-functional. Patients present with different symptoms ranging from paleness to jaundice as well as rapid heart rate, shortness of breath and fatigue. The realization that this condition is prevalent in the areas with high malaria transmission and that some anti-malaria drugs complicate the episodes of glucose-6-phosphate dehydrogenase deficiency has informed the evaluation of some drugs and their effects on patients with the condition. This study involved a systematic review of the previous and recent literature on the predisposing factors, testing strategies, and appropriate management approaches that could guide clinicians undertake safe management of the patients. The study involved searching articles from Scopus, PubMed and science direct, which were selected based on search terms and the relevance to the study. The finding shows that pharmacogenetics is the primary predisposing factor and this could guide clinician select appropriate medication that lowers adverse effects on patients. Besides, easy to use testing kits with high sensitivity and specificity could help clinicians manage the condition. The kits that do not require sophisticated instrumental analysis could help clinicians improve the approaches for managing G6PD deficiency and its associated pathophysiology. Some food items could also increase the hemolysis, and clinicians ought to discriminate foodstuffs that predispose patients to hemolytic anemia. These findings are relevant since they guide practitioners on the best strategies for handling patients with the G6PD deficiency for the improved clinical outcome.

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