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THE IMPACT OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY ON LIVER FUNCTION AND ENZYMATIC ANTIOXIDANTS IN PATIENTS FROM BASRAH PROVINCE[a]

EL IMPACTO DE LA DEFICIENCIA DE GLUCOSA-6-FOSFATO DESHIDROGENASA EN LA FUNCIÓN HEPÁTICA Y LOS ANTIOXIDANTES ENZIMÁTICOS EN PACIENTES DE LA PROVINCIA DE BASORA

BUSHRA A. M ABDUL AZEEZ AL SALEM[b], ZAINAB SHAKIR ABDULLAH AL ALI[b*]

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ABSTRACT: Glucose-6-phosphate dehydrogenase (G6PD) is an X-linked genetic disorder that represents the majority frequent enzymatic flaw worldwide, affecting approximately 400 million people, primarily of Asian, African and Middle Eastern descent. Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme that protects red blood cells and acts as an antioxidant. In other words, it protects red blood cells from oxidative damage in cases of stress in the event of a deficiency of the enzyme G6PD; this causes the breakdown of red blood cells before they mature, and this causes what is known as hemolysis, which in turn may cause hemolytic anemia. G6PD deficiency can result in hyperbilirubinemia, hemolysis and/or jaundice in neonates, but these symptoms are typically reversible with medical intervention. The objectives of this study were an attempt to evaluate and compare some enzymatic antioxidants and biochemical parameters of liver function in patients with G6PD enzyme deficiency. This study includes 58 subjects ages 1-15 years (30) patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) and (28) controls from healthy people who have normal activity of the G6PD enzyme. Samples were collected from Ibn Ghazwan Hospital in Basrah governorate from July to October 2023. The results of the study showed a significant increase in the concentration of serum AST, ($P < 0.01$), ALT and ALP ($P < 0.05$) in patients in G6PD deficient showed a significant increase in the concentration of serum AST ($P < 0.01$), ALT and ALP ($P < 0.05$) in patients in G6PD deficient group in comparison with the controls group was found a significant decrease in the activity of plasma (GPX, and SOD) in the patients' group in comparison with controls group($P < 0.001$). These results confirm that oxidative stress markers are potential new markers for the risk assessment of G6PD deficiency. The results indicated a nonsignificant positive correlation among G6PD (GPX and ALP). In contrast, a negative correlation was found among G6PD and (SOD, AST and ALT). Conclusion, Our findings are indicative of an association between abnormal G6PD levels and enzymatic antioxidants and liver functions. This indicates that the deficiency of G6PD may cause liver failure in the future.

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[b]University of Basrah, Basrah, Department of Chemistry, College of Science, Iraq
[*]Corresponding Author zainab.abdulah@uobasrah.edu.iq

KEYWORDS: Liver functions; G6PD; antioxidants enzyme.

RESUMEN: La glucosa-6-fosfato deshidrogenasa (G6PD) es un trastorno genético ligado al cromosoma X que representa la falla enzimática más frecuente en todo el mundo, afectando aproximadamente a 400 millones de personas, principalmente de ascendencia asiática, africana y de Oriente Medio. La glucosa-6-fosfato deshidrogenasa (G6PD) es una enzima que protege a los glóbulos rojos y actúa como antioxidante. En otras palabras, protege a los glóbulos rojos del daño oxidativo en casos de estrés en caso de deficiencia de la enzima G6PD; esto provoca la degradación de los glóbulos rojos antes de que maduren, y esto causa lo que se conoce como hemólisis, que a su vez puede causar anemia hemolítica. La deficiencia de G6PD puede resultar en hiperbilirrubinemia, hemólisis y/o ictericia en neonatos, pero estos síntomas suelen ser reversibles con intervención médica. Los objetivos de este estudio fueron un intento de evaluar y comparar algunos antioxidantes enzimáticos y parámetros bioquímicos de la función hepática en pacientes con deficiencia de la enzima G6PD. Este estudio incluye 58 sujetos de entre 1 y 15 años (30) pacientes con deficiencia de glucosa-6-fosfato deshidrogenasa (G6PD) y (28) controles de personas sanas que tienen una actividad normal de la enzima G6PD. Las muestras se recogieron en el Hospital Ibn Ghazwan de la gobernación de Basora de julio a octubre de 2023. Los resultados del estudio mostraron un aumento significativo en la concentración sérica de AST ($P < 0,01$), ALT y ALP ($P < 0,05$) en pacientes con deficiencia de G6PD mostraron un aumento significativo en la concentración sérica de AST ($P < 0,01$), ALT y ALP ($P < 0,05$) en pacientes en el grupo deficiente de G6PD en comparación con el grupo de controles se encontró una disminución significativa en la actividad del plasma (GPX y SOD) en el grupo de pacientes en comparación con el grupo de controles ($P < 0,001$). Estos resultados confirman que los marcadores de estrés oxidativo son nuevos marcadores potenciales para la evaluación del riesgo de deficiencia de G6PD. Los resultados indicaron una correlación positiva no significativa entre G6PD (GPX y ALP). En cambio, se encontró una correlación negativa entre G6PD y (SOD, AST y ALT). Conclusión: Nuestros hallazgos son indicativos de una asociación entre los niveles anormales de G6PD y los antioxidantes enzimáticos y las funciones hepáticas. Esto indica que la deficiencia de G6PD puede causar insuficiencia hepática en el futuro.

PALABRAS CLAVE: Funciones hepáticas; G6PD; enzima antioxidante.

1. INTRODUCTION

Glucose-6-Phosphat-Dehydrogenase (G6PD) (E.C.1.1.1.49) is an essential enzyme in the pentose phosphate pathway (Shetty *et al.*, 2023). It contributes to the generation of pentose carbohydrates, which are indispensable for the process of nucleic acid synthesis. However, pentose can also be generated via the alternative transketolase-transaldolase pathway (Dorgalaleh *et al.*, 2013). G6PD is an important controlling enzyme in the exosome phosphate valving mechanism that catalyzes the oxidation of glucose-6-phosphate to 6-phosphogluconolactone (Park *et al.*, 2017).Every cell has a cytosol that contains the human G6PD enzyme. It catalyses the pentose phosphate pathway's first step, supplying the nicotinamide adenine dinucleotide dinucleotide phosphate (NADP+/NADPH) and ribose-5-phosphate required for DNA synthesis (Pes & Dore, 2022). Through the pentose phosphate pathway, Glucose-6-phosphate dehydrogenase (G6PD) controls the production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) (Matsui *et al.*, 2005). NADPH is the major cellular reducer involved as a redox couple system, the equilibrium between

oxidised glutathione (GSSG) and reduced glutathione (GSH) essential for protection against oxidative damage (Aydemir & Ulusu, 2020).

NADPH, also known as its coenzyme, is created by G6PD and serves as an electron donor in activities necessary for the biosynthesis of fatty acids, steroids and deoxyribonucleotides. It is also a cofactor of cytochrome P450, an enzyme crucial to the metabolism of many medicines and other xenobiotics (Luzzatto *et al.*, 2020). There are more than 442 known variants of human G6PD. Numerous individuals suffer from anaemia, which results from an impairment in the ability of erythrocytes to respond to toxic stress (Dorgalaleh *et al.*, 2013).

The most prevalent enzymopathy in humans is G6PD deficiency, which was originally identified in people by Marks and Gross in 1959 (Marks & Gross, 1959). Globally, 400 million people have a G6PD gene mutation that results in an enzyme deficiency. The enzyme glucose-6-phosphate dehydrogenase (G6PD) guards the red blood cells and keeps them from becoming hurt. People who lack G6PD can typically experience normal health. However, they may have acute hemolysis if they have a serious infection or are exposed to oxidant stress from specific medications or toxins. When red blood cells undergo acute hemolysis, bilirubin will be generated, which causes jaundice (Govindarajan *et al.*, 2022). In the event of G6PD deficiency, the presence of oxidizing substances causes the sulfhydryl bridges between sections of the hemoglobin molecule to be oxidized, which reduces the solubility of hemoglobin and results in hemolysis (van den Broek *et al.*, 2016).

Reactive oxygen species (ROS) are overproduced in oxidative stress (OS), which is characterized by an imbalance between oxidants and antioxidants (Ji & Yeo, 2021). Oxidation products are produced and endogenous antioxidants are depleted as a result of oxidative stress. Excessive ROS harms macromolecules and cellular structures, causing malfunction and cell death (Manisha *et al.*, 2017). Intravascular hemolysis occurs with extravascular hemolysis, the disease's characteristic manifestation. Haemoglobin is released into plasma during intravascular hemolysis, which destroys red blood cells. The kidney filters the free plasma hemoglobin, which results in hemoglobinuria, among the greatest obvious clinical indications of excessive intravascular hemolysis and a risk factor for renal failure. Additionally, favism is characterised by extravascular hemolysis takes place when oxidatively damaged altered RBCs are phagocytized by macrophages in the bone marrow, liver, and spleen, as a result, free hemoglobin is not released into the plasma. Although some people think that the reticuloendothelial system's breakdown of hemoglobin is what causes a rise in plasma bilirubin, this increase is primarily the result of the liver's inability to function normally due to a G6PD deficiency (Dorgalaleh *et al.*, 2013).G6PD deficiency is typically asymptomatic in the majority of cases. However, exposure to oxidative stress can swiftly alter this result. More frequently In newborn neonates, G6PD deficiency includes persistent and rapid-onset neonatal jaundice, which, if not detected early, remains one of the primary causes of kernicterus or bilirubin-induced neurologic dysfunction(BIND). These oxidative triggers are less common in the newborn period than in elder children and adults who consume fava beans or medications that make them susceptible to acute hemolytic anaemia (Valaes, 1994; Kaplan &

Hammerman, 1998).

The objective of the present investigation was to examine the connection between serum of 30 patients with glucose-6-phosphate dehydrogenase deficiency, aged 1 to 15 years, and to assess any potential relationships between the activity of antioxidant enzymes and liver functions and glucose-6-phosphate dehydrogenase deficiency.

2. MATERIALS AND METHODS

2.1. Subjects

This study comprises 58 subjects (30 patients and 28 controls), and samples were collected from Ibn Ghazwan Hospital in Basrah governorate during the period from July to October, 2023 the patients aged 1- 15 years.

Blood samples were collected in EDTA containers and either analysed immediately or refrigerated at 4 °C until analysis. Each sample was analysed within 48 hours. Participants' written informed assent was obtained. The study protocol was evaluated and endorsed by our institution's Ethics Committee. No medical suggestions or prescriptions were compromised by the research protocol.

2.2. Samples Collection and Laboratory Tests

Five mL of blood sample was extracted from both the control group and the sick group. The samples were partitioned into two distinct segments. The initial volume of 3 ml was added into EDTA tubes and subjected to gentle agitation to quantify the activity of G6PD. This was achieved by employing the G6PDHU.V. kinetic technique (REF97089) kit provided by Biolabo Business, France. The absorbance of the sample was determined using a Cecil spectrophotometer 1000S from England. The residual whole blood underwent centrifugation at a speed of 3000 revolutions per minute for a duration of 20 minutes. The plasma samples were isolated from the remaining samples and thereafter kept at a temperature of -20 °C until they could be further analysed. The second portion (2ml) was transferred to a standard tube without anticoagulant, facilitating coagulation at ambient temperature. Subsequently, centrifugation was performed at a speed of 3000 revolutions per minute for a duration of 20 minutes. The serum samples were separated and afterwards kept at a temperature of -20 °C to measure biochemical parameters at a later time unless they were utilised immediately. The evaluation of serum Aspartate transaminase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) was conducted on all patients. Liver enzyme measurements were conducted utilising a chem 200 apparatus manufactured by Gesan production, located in Campobello Di Mazara, Italy. Before analysing the real samples, a calibration, standard, and control were constructed and subsequently measured. AST, ALT and ALP enzyme levels were determined in all samples using the analyser computed system.

The activity of plasma enzymatic antioxidants (superoxide dismutase (SOD), glutathione peroxidase (GPX)) was measured using enzyme-linked immunosorbent assay (ELISA), using the diagnostic kit provided by the sun long company (number: SL3490Hu, SL2786Hu), respectively.

2.3. Statistical Analysis

The data were analysed using SPSS software version 26.0. Data were expressed as *mean* $\pm$ *SD*. All examined groups' parameters were compared using a t-test for independent samples. P-values were considered ($P-value \leq 0.05$).

3. RESULT AND DISCUSSION

Thirty individuals with a deficiency in glucose-6-phosphate dehydrogenase (G6PD) had a mean age of 8 ± 3.58 years, with 16 (53.7 %) male and 14 (46.7 %) female, and 28 healthy had a normal activity of G6PD in the control group, 14 (50.0 %) were male and 14 (50.0 %) female with a mean age of 9.071 ± 3.090 years, and there were no significant differences in each (age and sex). The activity of G6PD decreased significantly (p<0.001) between the patients' group (47.466 ± 6.404 IU/ml) and the control group (299.392 ± 22.696 IU/ml) in the present study. G6PD deficiency is an X-linked disorder caused mainly by diverse point mutations (Karadsheh *et al.*, 2021). Although few G6PD variants cause chronic hemolysis, the most common clinical manifestation of its deficiency is polymorphic and may range from erythroblastosis fetalis, chronic hemolysis, acute hemolysis, and hyperbilirubinemia. Acute hemolytic crises are usually caused by medications, systemic infections, or fava bean consumption and may induce severe anemia (Zaimi *et al.*, 2021). There was a significant increase in the concentration of serum AST, ($P < 0.01$), ALT and ALP ($P < 0.05$) in the patients group in comparison with the controls group, as shown in Table 1.

These parameters have been demonstrated to be straightforward indicators for assessing the severity and outcome of liver failure patients. The majority of these prognostic indicators, however, are focused on decreased liver function and have high specificity but low sensitivity. G6PD deficiency is generally a manageable disease because most afflicted individuals do not experience any negative symptoms except for when they are stimulated by viral infections, certain medications, and fava beans. These stimuli cause significant oxida-

Table 1: Activity of G6PD, AST, ALT and ALP in patients and control groups

	Groups		
Parameters	$Patients(Mean \pm SD)$ $(No. = 30)$	$Controls(Mean \pm SD)$ $(No. = 28)$	p-value
G6PD (IU/ml)	47.466 ± 6.404	299.392 ± 22.696	<0.001
AST (U/L)	47.433 ± 8.787	39.857 ± 8.072	<0.01
ALT (U/L)	42.266 ± 7.182	38.571 ± 3.775	<0.05
ALP (U/L)	111.133 ± 10.156	105.821 ± 6.70	<0.05

Table 2: Activity of enzymatic antioxidants GPX and SOD in patients and controls groups. Where GPX: Glutathione peroxidase, SOD: Superoxide Dismutase.

	Groups		
Parameters	$Patients(Mean \pm SD)$ $(No. = 30)$	$Controls(Mean \pm SD)$ $(No. = 28)$	p-value
GPX(pmol/ml)	0.185 ±0.074	0.924 ± 0.077	< 0.001
SOD(ng/ml)	1.569±0.982	0.723 ±0.37	<0.01

tive damage to the red blood cells resulting in hemolytic anemia, which is the basis for the major medical complications of G6PD deficiency. This study also agreed with a study that showed high levels of AST and ALT in G6PD deficient patients (Dorgalaleh *et al.*, 2013),some other studies such as Alavi *et al.* (2005) that reported elevated levels of AST in the majority and ALT in some favism patients. Severe cases of G6PD deficiency can cause damage to the kidneys and liver, but the mechanism underlying the liver damage is poorly understood (Shah & Gopalareddy, 2022).

Occurrence of frequent mild or severe episodes of hemolysis can, over time, lead to more serious complications, particularly in the liver and kidney as the two main organs involved in the hemolytic process. Elevated liver enzymes can result from the occurrence of recurrent hemolytic episodes that involve the liver because a part of this hemolytic process can be extravascular. Moreover, G6PD deficiency in the liver can be a probable cause of liver complications in these patients (Dorgalaleh *et al.*, 2013).

Table 2 shows enzymatic antioxidant activity. It was found a significant decrease in the activity of plasma (GPX, and SOD) in the patients' group in comparison with the control group ($P < 0.001$ and $P < 0.01$). These results confirm that markers of oxidative stress are potential new markers for the risk assessment of G6PD deficiency. Oxidative stress is produced when there is an increased production of Reactive oxygen species (ROS) including (Singlet oxygen, Superoxide, hydroxyl radical, hydrogen peroxide, hydroperoxyl radical, ozone etc) and decreased level of antioxidants in the body (Manisha *et al.*, 2017). Antioxidants are substances that prevent, reduce, or delay the oxidation of materials that may be exposed to oxidation such as proteins, lipids, carbohydrates, and DNA in living cells, and this is called antioxidant defence. There are two types of Antioxidants in the human body enzymatic antioxidants and nonenzymatic antioxidants. Enzymatic antioxidants are superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX), and nonenzymatic antioxidants are vitamin E, vitamin C, vitamin A, selenium (Se), transferrin, and lactoferrin. Antioxidants are often intracellular and sometimes extracellular (Hussain & Kayani, 2020).

Glutathione peroxidase catalyzed by the reaction catalyzed by the reduced form of glutathione (GSH) by reacting with hydrogen peroxide or lipid peroxides while playing a role in the detoxification of these molecules by creating a glutathione bridge with another glutathione molecule (GSSG) form (Flohé *et al.*, 2022). H_2O_2 is detoxified by catalase and glutathione peroxidase (Sadi *et al.*, 2014).

The G6PD enzyme is constitutively expressed in cells and plays an essential role in the pentose phosphate pathway. Importantly, G6PD regenerates the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH). NADPH acts as a cofactor and reducing agent for enzymes such as glutathione reductase and thioredoxin reductase, catalyzing the reduction of glutathione (GSH) and thioredoxin (Trx), respectively (Lee *et al.*, 2022) reduced Trx participates in the reduction of peroxiredoxins, which, together with GSH, form the main antioxidants of the red blood cell (RBC) (Low *et al.*, 2008; Forman *et al.*, 2009). These antioxidants reduce hydrogen peroxide and in doing so protect the RBC against oxidative damage. Perhaps the two more recognized clinical manifestations of G6PD deficiency are blackwater fever and favism, syndromes consequent to acute and massive hemolysis. The hemolysis of G6PD-deficient RBCs in favism arises because the cells cannot generate sufficient NADPH to detoxify excessive hydrogen peroxide and other reactive oxidants. In red cells with normal G6PD activity, hydrogen peroxide is detoxified by catalase and by glutathione peroxidase (Luzzatto & Arese, 2018).

SOD is an enzyme that catalyzes the dismutation of two superoxide anions ($O_2{}^{\cdot -}$) into hydrogen peroxide and molecular oxygen. It protects the tissue to a certain degree from the harmful effects of superoxide radicals. GPX catalyses the reduction of hydroperoxides using glutathione (GSH). Glutathione metabolism is one of the most essential antioxidative defence mechanisms (Yalcin *et al.*, 2020).

G6PD catalyzes the rate-limiting step in the pentose phosphate pathway (PPP), which provides the precursors of nucleotide synthesis for DNA replication as well as reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is involved in the detoxification of cellular reactive oxygen species (ROS) and de novo lipid synthesis. There is an association between increased PPP activity and the stimulation of cell growth that has been reported in different tissues including the skeletal muscle, liver, and kidney. Across all forms of life, NADPH donates high-energy electrons for reductive biosynthesis and antioxidant defence. One of the main functions of NADPH in our cells is in the maintenance of redox homeostasis (Nóbrega-Pereira *et al.*, 2016).

NADPH is the electron donor for the antioxidant enzymes glutathione reductase (GR) and thioredoxin reductases (TrxR). Reduced glutathione (GSH) and reduced thioredoxin ($Trx(SH)2$) provide reducing equivalents for glutathione peroxidase (GPx), glutaredoxins (Grx), and peroxiredoxins (Prx). Thus, NADPH is located at the core of the antioxidant defence (García-Domínguez *et al.*, 2022).

NADPH is produced by G6PD via PPP and the limiting substrate for glutathione reductase activity catalysing the reaction of converting glutathione disulfide (GSSG) to glutathione(GSH). GSH is oxidized to GSSG during oxidative stress metabolism via the GPx enzyme and reduced to back GSH by GR enzyme to maintain GSH/GSSG balance by NADPH-dependent mechanism in both cytosol and mitochondria. Both Intracellular GSH levels and GSH/ GSSG ratio are key players of the defence mechanism against oxidative stress regulated by glutathione-dependent enzymes including GPx, GR and glutathione S-transferase (GST),

Table 3: Correlation among G6PD, enzymatic antioxidants AST, ALT and ALP. Where *r*=Coefficient with *G6PD* Pearson Correlation.

G6PD with	r	p-value	Result
GPX	0.025	0.894	Insignificant positive correlation
SOD	0.016	0.932	Insignificant positive correlation
AST	-0.150	0.428	Insignificant positive correlation
ALT	-0.028	0.882	Insignificant positive correlation
ALP	0.100	0.598	Insignificant positive correlation

therefore cells exposed to elevated levels of oxidative stress need high activity (Aydemir & Ulusu, 2020).

Applying Pearson's correlation (*r*) to explain the correlation among G6PD, enzymatic antioxidants, AST, ALT and ALP. Table 3 was show a positive correlation between G6PD and (GPX, SOD and ALP). In contrast, a negative correlation was found among G6PD, and (AST and ALT).

4. CONCLUSION

Our results suggest a connection between aberrant G6PD levels and liver functions and enzymatic antioxidants. This suggests that liver failure could result from a G6PD deficiency in the future.

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Author's Contributions

The study was conceived, designed, collected samples, and did all lab work by both BA and ZS. BA wrote and interpreted the manuscript's findings. All authors participated in all manuscript requirements to create a final version that was approved by all parties after it was read.

Author's Declaration

Conflicts of interest: None. Informed consent: All participants in this investigation, or their legal custodians, gave their informed consent. Ethical approval: All participants gave written informed consent before enrollment following the guidelines of the local ethics committee.

Ethical Clearance

The authors declare that all experiments were done according to the ethical committee's permission from the University of Basrah.

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