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RESEARCH ARTICLE

Evaluation of Some Biochemical Parameters in Glucose-6-Phosphate Dehydrogenase deficient subjects of Hausa and Fulani ethnics

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ABSTRACT

Glucose-6-phosphate dehydrogenase deficiency is a significant public health problem that is implicated in the pathogenesis of a number of common diseases via increased oxidative stress and a decrease in the generation of nitric oxide. There is little information about its impact on some organ, hence the need for this research. This was a case-control study carried out on Hausa and Fulani ethnics in Kano. Heparinized 5 ml venous blood specimen were collected from 140 individuals (70 deficient and 70 control) aged between 18-35 years selected for the study to determine the blood levels of some biochemical parameters using standard methods. There were significant increase in transaminases ($p<0.001$), but significant decrease concentrations of sodium ($p<0.05$), chloride ($p<0.001$), alkaline phosphatase ($p<0.001$) and total protein ($p<0.001$) whereas there was no statistically significant difference ($p>0.05$) in the plasma concentration of albumin, total bilirubin, conjugated bilirubin, urea, creatinine, potassium and bicarbonate ions. Our results demonstrate extremely significantly lower ($p<0.001$ for all) concentration in glutathione reductase, total antioxidants potential, copper, zinc and non-significant decrease ($p>0.05$) in manganese level of G-6-PD deficient patients compared to controls, whereas malondialdehyde level showed an increasing trend on contrary. However, there were correlations between G-6-PD activity and oxidative stress markers. The findings of the present study suggest that liver and kidneys functions were not altered among people living with G-6-PD deficiency but induce oxidative stress which is not capable of causing organ impairment.

Keywords: G-6-PD deficiency, oxidative stress, liver, kidneys, Hausa, Fulani, Kano-Nigeria.

1.0 Introduction

It is noteworthy that, unlike other cells types, RBCs do not contain mitochondria and therefore the PPP pathway is the only source of NADPH, which plays a key role in the protecting cells against oxidative damage due to reactive oxygen species [1]. Because the important function of NADPH is scavenging cellular ROS, NADPH is involved in at least three antioxidant pathways: the glutathione, thioredoxin, and glutaredoxin cycles. In the first pathway, the electron of NADPH passes to glutathione dimers (GSSG) during the reaction catalyzed by glutathione reductase enzyme that produces two reduced glutathione monomers (GSH) providing the first line of defense against ROS [2]. Moreover, glutathione peroxidase (GPX) removes peroxide from RBCs using GSH as substrate, while the NADPH is required to reduce GSSG oxidized and the sulfhydryl groups of some necessary proteins for the protection against oxidative stress. The RBCs that cannot eliminate this stress suffer haemolysis [3].

G-6-PD deficiency shows wide variety in its clinical expression which ranges from asymptomatic presentations to those cases with hemolytic anaemia being one of the most dangerous and severe neonatal hyperbilirubinaemia [4].

Liver plays a key role in many metabolic processes of not only itself but of other tissues as well[5], and it is one of the organ seems to be involved in frequent haemolytic episode that occur in G-6-PD deficient individuals [6]. Even though some believe that the breakdown of haemoglobin by the reticuloendothelial system causes increase in plasma bilirubin, others say that this increase is largely the result of an impairment of liver function caused by G-6-PD deficiency in the liver [7].

Kidneys are vital organs responsible for clearing waste products, salts and water from the body. Its regulate plasma Osmolarity by modulating the amount of water, solutes and electrolytes in the blood, thereby ensuring log term acid-base balance [8].

The kidneys have also been reportedly involved in the intravascular haemolytic episodes occurring in a G-6-PD deficiency. It seems that frequent experience of these haemolytic episodes can have adverse effects on kidneys. Severe and persistence haemolysis results in the accumulation of circulating haemoproteins, which increases iron delivery to kidney. In kidneys, haem-iron mediates oxidative injury inducing cell death and promoting acute kidney injury [6]. Intravascular haemolysis is the destruction of red blood cells in the circulation with the release of cell contents such as haemoglobin into plasma [9]. Then free plasma haemoglobin is filtered through the kidney and cause haemoglobinuria that is one of the most prominent clinical signs of excessive intravascular haemolysis and can cause renal failure [10].

Oxidative stress is currently viewed as an imbalance between pro-oxidants and antioxidants in favor of the former, which implicates a loss of redox signaling. It can be triggered by excessive reactive oxygen species (ROS) production as well as by low antioxidant enzyme activities [11]. Under normal circumstances, the body is protected from such damage by a careful balance between pro-oxidants and antioxidants. In the erythrocytes of normal G-6-PD individual, NADPH generated from G-6-PD enzyme is required by cellular antioxidant systems to reduce reactive oxygen species [12].

The glutathione system requires NADPH to remove excess hydrogen peroxide (H_2O_2). In this system, glutathione reductase uses NADPH to convert oxidized glutathione (GSSG) to its reduced glutathione (GSH). Thus, NADPH fuels the removal of H_2O_2 by the glutathione [13]. Conversely, it is conceivable that G-6-PD deficient subjects suffer mild chronic haemolytic episode, due to insufficient levels of NADPH and GSH which ultimately lead to oxidative damage by continuous production of ROS-H_2O_2. This excessive production of ROS-H_2O_2 adversely affects cell function through damaging reactions with proteins, nucleotides, and peroxidation of membrane lipids causing intracellular haemolysis [14-16].

Few earlier studies indicated conflicting reports on the pattern of oxidative stressors in G-6-PD deficient subjects, although with a number of methodological differences for G-6-PD assessment A study by Ondei *et al.* [17] reported insignificant differences between Thiobarbituric acid reactive species (TBARS) and Trolox equivalent antioxidant capacity (TEAC) values for a specific A$^-$(202G>A) mutation of G-6-PD deficiency whereas a phenotypic assessment of suggest that G-6-PD deficient individuals may also be at the risk of developing oxidative stress induced diseases[18]. Similary, the study of Yasser *et al.* [19] reported that oxidative stress markers revealed significant changes in G-6-PD deficient cases among neonates. Since several studies have reported on G-6-PD deficiency with limited and unclear findings on the effect of G-6-PD deficiency on biochemical parameters, hence the need for this study.

2.0 Materials and methods

2.1 STUDY AREA

The study was conducted in Kano which is located at the extreme part of North Western Nigeria between longitude 3° and 7° east and between latitude 10° and 14° north of the equator. It shares borders with Jigawa State to the North- East, Katsina State to the North-West, Kaduna State to the South-West and Bauchi State to the South-East [20].

2.2 STUDY SUBJECTS

The study was approved by the ethical committees of Kano State Ministry of Health (NHREC/17/03//2018) and informed consent was obtained from each participant before subject's recruitment. Seventy (70) G-6-PD deficient individuals and seventy (70) individuals with normal G-6-D enzyme status that served as control were selected by random sampling techniques through random digits number without replacement in excel for the study to evaluate some biochemical indices in Kano. The target population was adults of Hausa and Fulani ethnics residing in Kano metropolis.

2.3 STUDY DESIGN

This was a case-control design.

2.4 BLOOD COLLECTION AND PROCESSING

Five (5 ml) of venous blood specimen was collected from the cubital vein in the forearm from each subjects and was dispensed into lithium heparin bottle. Specimens taken were transported in ice bags at a temperature range of 0°C–4°C to the laboratory designated for the study. The non-clotted blood was mixed gently and centrifuged at 3000 rpm for 5 min. The supernatant was aspirated (plasma) from lithium heparin container, divided into three aliquots each in cryovials and was stored frozen at -80 degrees Celsius until analyzed for micronutrients, oxidative stress markers, liver and renal function parameters.

2.5 METHODS

Total and conjugated bilirubin were estimated by Malloy and Evelyn [21], total protein and albumin by Biuret and Bromocresol Green (BCG) methods respectively; liver transaminases (AST, ALT) activities were determined using Reitman-Frankel method, alkaline phosphatase (ALP) by nitrophenyl phosphate method of Bassey *et al.* [22]. Lipid peroxidation was measured by plasma malondialdehyde estimation colorimetric method of Shah and Walker's [23] and total antioxidant potential by copper reducing antioxidant assay method of Sashindran *et al.* [24]. Glutathione reductase activity was measured spectrophometrically as described by method of Goldberg and Spooner [25] and in order to determine copper, zinc, manganese levels, a double lighted, deuterium sourced, background proof reading fire atomic spectrophotometer.

2.6 STATISTICAL ANALYSIS

GraphPad InStat Software was used to check for typographic errors, outliers and to carry out normality testing for continuous data. Statistical analyses of data obtained from this study were done using the statistical package for social science (SPSS) for Windows, version 26.0 (SPSS Inc., Chicago, IL, USA). Student's t-test was performed for comparisons of liver and kidneys parameters and oxidative stress status between deficient and non-deficient participants. Correlation of lipid peroxidation levels with antioxidants parameters was tested using Pearson chi-squared correlations. Continuous data were expressed as Mean ± SEM.

3.0 Results

3.1 LIVER FUNCTION INDICES IN G-6-PD DEFICIENT INDIVIDUALS

The pattern of liver function indices in G-6-PD deficient individuals are presented in Table 1. A significant increase ($p<0.001$) in plasma alanine transaminase (ALT) and aspartate transaminase (AST) activity among people living with G-6-PD deficiency compared to those with sufficient G-6-PD activity was noticed. The Alkaline phosphatase (ALP) activities of G-6-PD deficient subjects decreased significantly ($p<0.001$) compared to that of normal control group. There was no statistically significant difference ($p>0.05$) in plasma albumin, total bilirubin and conjugated bilirubin concentrations between the groups except total protein concentration were significantly reduced ($p<0.001$) in the G-6-PD deficient subjects compared to normal control group.

Table1: Liver Function Parameters in G-6-PD Deficient Subjects

G-6-PD Status	n	ALT (U/L)	AST (U/L)	ALP (U/L)	TP (g/L)	ALB (g/L)	DB (µmol/L)	TB (µmol/L)
Normal	70	3.97±0.18	2.43±0.29	192.13±18.44	69.68±1.10	39.9±0.82	3.18±0.08	14.67 ±0.32
Deficient	70	6.05±0.65**	3.53±0.17**	130.38±5.53**	65.90±0.76**	38.53±0.56	3.24±0.10	15. 82±0.27

Results are expressed as mean ± SEM using independent -t- test statistical tool for analysis. Superscripts (**) in the same column are significantly different at $p<0.001$. those values without superscript are not statistically insignificant at $p>0.05$. ALT=alanine transaminase AST=aspartate transaminase, ALP=alkaline phosphatase, TP=total protein, ALB=albumin, DB=direct bilirubin, TB=total bilirubin, G-6-PD= Glucose-6-Phosphate Dehydrogenase.

3.2 KIDNEY FUNCTION PARAMETERS IN G-6-PD DEFICIENT INDIVIDUALS

Table 2 shows the plasma concentrations of urea, creatinine and electrolytes (Na^+ Cl^- K^+, HCO^{3-}) of G-6-PD deficient individuals. The urea and creatinine plasma concentrations of G-6-PD deficient group did not show any statistically significant different ($p>0.05$) compared to normal control group. A significant decrease ($p\leq0.05$) existed in sodium and chloride concentrations of G-6-PD deficient individuals in comparison to non G-6-PD deficient group. Conversely, potassium (K^+) and bicarbonate (HCO_3^-) ions concentration revealed non-significant difference ($p>0.05$) between the groups.

Table 2: Kidney Function Parameters in G-6-PD Deficient Individuals

		Parameters (mmol/L)					
G-6-PD Status	n	Urea	Creatinine	Na^+	K^+	Cl^-	HCO^{3-}
Normal	70	4.57±0.16	1.01±0.02	139.62±0.37	4.12±0.05	103.26±0.29	28.20±0.43
Deficient	70	4.51±0.15	0. 99±0.02	138.80±0.22*	4.18±0.05	101.46±0.28**	28.68±0.42

Results are expressed as mean ± SEM using independent -t- test statistical tool for analysis. (**) Superscripts in the same column are significantly different at $p<0.001$. (*) Superscripts in the same column are significantly different at $p<0.05$.Those values without superscript are not statistically significant at $p>0.05$. Na^+ =sodium ion, K^+=potassium ion, Cl^- =chloride ion, HCO^{3-}=Bicarbonate ions, G-6-PD= Glucose-6-Phosphate Dehydrogenase, L=litre.

3.3 OXIDATIVE STRESS BIOMARKERS IN G-6-PD DEFICIENT INDIVIDUALS

As shown in table 3, the activity of glutathione Reductase (GR) and Total Antioxidants potential (TAP) levels of G-6-PD deficient subjects was extremely significantly lower ($p<0.001$ for all) compared to participants in control group. Moreover, the concentration of malondialdehyde (MDA) were found to be significantly increased in G-6-PD deficient subjects compared to subjects in control groups ($p<0.001$). The plasma levels of antioxidant minerals (copper and zinc) in G-6-PD deficient subjects indicated a significantly lower ($p<0.001$) values than those of control and a non-significant decrease ($p>0.05$) in manganese level was observed among G-6-PD deficient subjects when compared to normal group.

Table 4 depicted a non-significants correlation analysis showing a non-significant ($p>0.05$) between lipid peroxidations (MDA) and antioxidants parameters (glutathione reductase, Total antioxidant potential, copper, manganese and zinc) in people with G-6-PD deficient subjects. However, there were correlations between the parameters measured as shown in Table 5. The Glutathione Reductase (GR) correlated with the G-6-PD activity ($r=0.18$, $P<0.012$), the TAP correlated with the G-6-PD activity ($r=0.22$, $P<0.028$). In addition, they were significant correlations between G-6-PD activity and Zn^{2+} ($r=0.41$, $P<0.01$), Cu^{2+} ($r=0.36$, $P<0.0001$), Mn^{2+} ($r=0.21$, $P<0.024$).

Table 3: Antioxidants Indices in G-6-PD Deficient Individuals

G-6-PD enzyme	n	MDA (nmol/L)	GR (U/L)	TAP (µM CRE)	Cu^{2+} (mg/L)	Zn^{2+} (mg/L)	Mn^{2+} (mg/L)
Normal	70	7.70±0.60	49.51±3.69	35.66±0.89	2.77±0.04	1.63±0.19	2.45±0.22
Deficient	70	15.60±0.45**	37.89±2.29**	31.95±0.63**	2.22±0.12**	0.87±0.08**	1.96±0.17

Results are expressed as mean ± SEM using independent -t- test statistical tool for analysis. (**) = Superscripts in the same column are significantly different at $p<0.001$. Those values without superscript are not statistically significant ($p>0.05$). Cu^{2+} =Copper (II) ion, Zn^{2+}=Zinc ion, Mn^{2+} =manganese ion, CRE=copper reducing equivalents. GR= Glutathione Reductase, MDA= Malondialdehyde, G-6-PD= Glucose-6-Phosphate Dehydrogenase, mg= milligram, L: Litre

Table 4: Correlation between MDA and Antioxidant Indices

Correlation between parameters	r-value	p-value
MDA and GR	- 0.027	0.787
MDA and TAP	- 0.045	0.758
MDA and Zn^{2+}	0.177	0.142
MDA and Cu^{2+}	- 0.102	0.405
MDA and Mn^{2+}	0.003	0.981

MDA= Malondialdehyde, GR= Glutathione Reductase, TAP= Total antioxidant Potential, Zn^{2+}= Zinc ion, Cu^{2+} =copper ion, Mn^{2+} =Manganese ion

Table 5: Correlation between G-6-PD Activities with Antioxidant Indices

Correlation between parameters	r-value	p-value
GR	0.18	0.012
TAP	0.22	0.028
Zn^{2+}	0.42	0.01
Cu^{2+}	0.36	0.001
Mn^{2+}	0.21	0.002

GR= Glutathione Reductase, MDA= Malondialdehyde, MDA= Malondialdehyde, Zn^{2+}= Zinc ion, Cu^{2+} =copper ion, Mn^{2+} = Manganese ion

4.0 Discussion

4.1 LIVER FUNCTIONS STUDIES

Liver is one of the largest organs in human body and the chief site for intense metabolism and excretion [26]. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction [27]. Therefore, maintenance of a healthy liver is essential for the overall well being of an individual.

In G-6-PD deficiency, liver is one of the main organs involved in the haemolytic processes-typically extra vascular in nature, however, intravascular haemolysis also occurs [28]. This extra vascular haemolysis in favism occurs when altered RBCs during oxidative damage are phagocytized by macrophages in the spleen, liver and bone marrow; therefore, free haemoglobin is not released into plasma [29]. Even though some believe that the breakdown of haemoglobin by the reticuloendothelial system causes increase in plasma bilirubin, others say that this increase is largely the result of an impairment of liver function caused by G-6-PD deficiency in the liver [7].

From this study, all the values obtained for liver function indices of G-6-PD deficient individuals were within the reference range; hence the synthetic and conjugating ability and excretory functions of the liver amongst people living with G-6-PD deficiency were preserved. This value agrees with the study of Oduola *et al.* [18], but however disagrees with the values reported from the Mediterraneans region by Anees *et al.* [30], Alavis and Hoseini [31], Akbar *et al.* [6]. Favism is a disease prevalent in Mediterranean countries resultant from ingestion of fava beans implicating a hemolytic source for this enzyme. The typical features of the disease are jaundice, haematuria and acutes haemolytic anaemia [6]. These discrepancies in the elevated liver enzymes can be attributable to high cultivation of fava bean in the study area which is a trigger of haemolytic episodes that involve liver because a part of this haemolytic process can be extravascular [32]. In the same vein, transaminases on the other hand are not only specific for liver damages as they are

found in erythrocytes, cardiac and skeletal muscles [33]. Thus, the elevated liver enzyme could be due to AST and ALT of erythrocytes origin; an erythrocyte iso-form released into circulation during haemolysis. The significant decrease observed in alkaline phosphatase (ALP) level amongst G-6-PD deficient group whose values that falls within normal ranges may implicate effects of haemolytic episodes on liver or gallbladder as blood cell haemolysis reduces the activity of ALP through Magnesium ions inhibitory action when released from the red blood cells due to haemolysis[34].

The results show a significantly ($p<0.05$) reduced total protein and a non-significantly ($p>0.05$) reduced pattern of albumin except conjugated bilirubin and total bilirubin that shows a slight increase among G-6-PD deficient individuals compared to control group, but all the values were within normal physiological ranges. This value agrees with the findings reported by Oduola *et al.*[18] and may further support the fact that the synthetic function of the liver is not impaired among G-6-PD deficient subjects but may be an indication that they suffer from an increased risk of *Toxoplasmosis* and bacterial infections[35-36] which in turns precipitate acute haemolytic episodes.

Although, the slight increase in bilirubins concentration could be due to continues release of newly synthesis bilirubin through intravascular haemolysis of red blood cells in deficient individuals.

4.2 KIDNEYS FUNCTIONS STUDIES

The kidneys have also been reportedly involved in the intravascular haemolytic episodes occurring in a G-6-PD deficiency. It seems that frequent experience of these haemolytic episodes can have adverse effects on kidneys. Severe and persistence haemolysis results in the accumulation of circulating haemoproteins, which increases iron delivery to kidney in kidneys, haem-iron mediates oxidative injury inducing cell death and promoting acute kidney injury [6]. Intravascular haemolysis is the destruction of red blood cells in the circulation with the release of cell contents such as haemoglobin into plasma [9]. Then free plasma haemoglobin is filtered through the kidney and cause haemoglobinuria that is one of the most prominent clinical signs of excessive intravascular haemolysis and can cause renal failure [10].

The values obtained in the kidney function indices shows a non significant decrease ($p>0.05$) in the concentrations of urea and creatinine in G-6-PD deficient group. These decreased values in urea and creatinine concentrations of G-6-PD deficient group falls within normal values and it emphasized non-dysfunction of the excretory role of the kidneys, as urea and creatinine are synthesized in the liver and excreted by the kidneys. The results of this study corroborates the findings of Akbar *et al.* [6] and Oduola *et al.* [18] but disagrees with the study of Anees *et al.* [30] who reported elevated values of these parameters. This increase in the urea and creatinine concentrations is probably because of blood sampling that was collected during acute haemolytic crisis.

On the other hand, sodium and chloride concentrations showed a significant increase ($p<0.05$) in G-6-PD deficient individuals in comparison to non G-6-PD deficient group. Conversely, potassium (K^+) and bicarbonate ($HCO3^-$) ions concentration revealed non-significant difference ($p>0.05$) between the groups. The values reported in this present study are in tandem with the reports of Oduola *et al.* [18].

4.3 IN-VITRO ANTIOXIDANTS STUDIES

Oxidative stress is an inevitable side-effect of aerobic life. The requirement for oxygen leads to the formation of reactive oxygen species (ROS) during the respiration process [37] Aerobic organisms therefore need mechanisms to protect themselves from oxidative damage and have developed efficient protective networks based on a wide variety of antioxidants. In the erythrocytes of normal G-6-PD individual, NADPH generated from G-6-PD enzyme is required by cellular antioxidant systems to reduce reactive oxygen species (ROS) [12]. The glutathione system requires NADPH to remove excess hydrogen peroxide (H_2O_2). In this system, glutathione reductase (GR) uses NADPH to convert oxidized glutathione (GSSG) to its reduced glutathione (GSH). Thus NADPH fuels the removal of H_2O_2 by the glutathione [13]. Conversely, it is conceivable that G-6-PD deficient subjects suffer mild chronic haemolytic episode, due to insufficient levels of NADPH and GSH which ultimately lead to oxidative damage by continuous production of ROS-H_2O_2. This excessive production of ROS-H_2O_2 adversely affect cell function through damaging reactions with proteins, nucleotides, and peroxidation of membrane lipids causing intracellular haemolysis [14-16].

Regarding markers of oxidative stress, the results of the present research indicated significantly higher concentrations of serum MDA and reduced TAP, GR activity, antioxidant minerals (copper, zinc, and iron except manganese) in G-6PD deficient participants compared to the subjects in control groups. These results supported the findings of Oduola *et al.* [18] and Yasser *et al.* [19] who reported significant

elevation in the concentrations of MDA in participants with G-6-PD deficiency compared to people with normal G-6-PD status ($p<0.05$). There are a few biochemical mechanisms that explain the reason for such a rise of MDA. The increase in the blood free fatty acid levels in G-6-PD deficiency depending on the degree of lipolysis, which results in an increase in MDA production. Moreover, the increased MDA levels of G-6-PD deficient individuals may take origin from the peroxidative damage of the membrane lipids. Since MDA is a byproduct of lipid peroxidation which play a major role in the formation of vascular tissue damage, it is suggested that an increase in MDA in G-6-PD deficient individuals is a cause for many disease pathogenesis such as diabetes angiopathy, hypertension, retinopathy [38]. In this study, plasma malondialdehyde concentrations increase significantly may signify the nature and extends of cellular damage. This increase could signify damage, from lipid peroxidation. Some studies have reported reduced levels of total antioxidant potentials, which corroborates with the present study whereas a study by Ondei *et al.* [17] reported insignificant differences between Thiobarbituric acid reactive species (TBARS) and Trolox equivalent antioxidant capacity (TEAC) values for a specific A-(202G>A) mutation of G-6-PD deficiency. This study contrasts the findings of the current study. This specific mutation of G-6-PD deficiency studied in the previous study, patients are unlikely not to be on antioxidants supplements might be the reason for the observed differences.

In this study, plasma Cu and Zn levels were significantly decreased ($p<0.001$) and insignificant decrease ($p>0.05$) in Mn level among G-6-PD deficient patients compared to those with G-6-PD status. The study of Karunanithy *et al.* [39] has reported decreased copper and zinc levels in G-6-PD deficiency. Since G-6-PD acts as a guardian of cellular redox potential during oxidative stress, G-6-PD deficient individuals may be prone to oxidative stress induced disorders and as such might be consumed in neutralizing oxidative process, and this may be why we observed low values.

It is however important to note that there is a significant positive correlation between the G-6-PD activity and all the antioxidants markers investigated thus implying that depletion of G-6-PD activity could affect antioxidant system. Further work need to be done to authenticate this.

Conflict of interest

None

Conclusion

The liver and kidneys parameters were not altered among people living with G-6-PD deficiency and that G-6-PD deficiency induce oxidative stress which is capable of forming vascular tissue damage, an indication for many disease pathogenesis. One of this study's limitations was the small size of the study group. The other limitation was that our in ability to estimate transaminases of erythrocyte-origin as differential diagnosis to the level of enzyme in the plasma.

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