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Glucose 6-phosphate dehydrogenase deficiency and its role in pathophysiology of essential hypertension

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Abstract

The main objective was to investigate the role of glucose 6-phosphate dehydrogenase deficiency in aetiology of essential hypertension. An analytical cross-sectional design was applied to 89 essential hypertensive participants and 89 healthy normotensive participants, making a total of 178. All the participants were aged between 35 and 65 years. Blood was collected for G6PD activity and levels of blood nitric oxide, glucose, creatinine, urea and electrolytes. In addition, routine urinalysis was done. A logistic regression was used to investigate the association of age, sex, nitric oxide levels, and G6PD deficiency with essential hypertension as the dependant variable. The G6PD deficiency was found in 14 (16%) participants with essential hypertension and 9 (10%) control participants. The difference however, in the G6PD deficiency prevalence rate was not statistically significant (*p= 0.13*). Logistic regression analysis revealed that G6PD deficiency was significantly associated with increased risk for essential hypertension. The analysis further showed a significant association of age and essential hypertension with participants in age groups 46-55 and 56-65 being at higher risk of developing essential hypertension than those in age group 35-45. The study also revealed no association between gender and essential hypertension. The study showed that states that there is no difference in G6PD deficiency prevalence between the essential hypertensive and normotensive adults. The findings also demonstrated a possible role of G6PD deficiency in the pathophysiology of essential hypertension.

Key words: Glucose 6-phosphate dehydrogenase, hypertension, NADPH, oxidative stress

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Introduction

Hypertension is one of the most prevalent non-communicable diseases in sub-Saharan Africa and elsewhere in people of sub-Saharan origin. Zambia being in the Sub-Saharan region has a very high prevalence of essential hypertension. Previous surveys carried out in several countries in sub-Saharan Africa showed that prevalence of hypertension in urban areas is higher than in rural areas[1-3]. No nationwide surveys have been carried out in Zambia but surveys carried out in Lusaka showed the prevalence for hypertension to be 34.8% (38.0% of males and 33.3% of females) and factors independently associated with hypertension were found to be age, sex, body mass index, alcohol consumption, sedentary lifestyle[4]. There were approximately 80 million adults with hypertension in sub-Saharan Africa in 2000 and projections based on current epidemiological data suggest that this figure will rise to 150 million by 2025[5].

Essential hypertension is caused by interplay of many factors; among them, at biochemical level is oxidative stress. Though oxidative stress is very much associated with hypertension it is not very clear whether oxidative stress is the cause of hypertension or whether oxidative stress is caused by hypertension[6]. Current experimental evidence

indicates that reactive oxygen species (ROS) play an important pathophysiological role in the development of hypertension due in part to superoxide anion ($\cdot O_2^-$) excess (oxidative stress) and decreased NO bioavailability in the vasculature and kidneys and to ROS-mediated cardiovascular remodeling [7, 8]. It is known that superoxide rapidly inactivates the endothelium derived NO, the most important endogenous vasodilator, thereby, promoting vasoconstriction [9]. Oxidative stress occurs when there is an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defence systems so that the latter become overwhelmed [10], a situation that likely contributes to the development of essential hypertension. Reduced antioxidant defence due to either decreased antioxidant activity (superoxide dismutase, catalase) or reduced levels of ROS scavengers (vitamin E, vitamin C, glutathione) can contribute to accumulation of excess superoxide anions resulting in oxidative stress [11, 12]. Superoxide anions form hydrogen peroxide, which in turn forms hydroxyl free radicals. It's the hydroxyl free radicals that cause more damage seen in oxidative stress. Glutathione, in reduced state, destroys hydrogen peroxide by reducing it to water, preventing the generation of more harmful hydroxyl radicals. Reduction of glutathione requires reducing power from NADPH which is formed mainly when glucose is oxidized through the pentose phosphate pathway. The first reaction of the pentose phosphate pathway catalysed by glucose 6-phosphate dehydrogenase is the committed step and NADPH is formed with this reaction. The third reaction of the pentose phosphate pathway catalysed by 6-phosphogluconate dehydrogenase is the second oxidative step which forms NADPH. Glucose 6-phosphate dehydrogenase deficiency can therefore result in reduced cellular generation of NADPH leading to decreased reduction of glutathione. A decrease in reduced glutathione would in turn decrease the rate of hydrogen peroxide elimination. The end result of this scenario would be reduced scavenging of reactive oxygen species, giving rise to oxidative stress.

Global surveys have shown that there is high prevalence of glucose 6-phosphate dehydrogenase deficiency in malaria endemic areas, probably a protective measure against malaria infection[13]**.** Surveys have also shown that there is higher prevalence of hypertension among the black population[14]**.** While glucose 6-phosphate dehydrogenase deficiency may offer protection against malaria, it is also possible that the oxidative stress induced by deficiency of this enzyme could be responsible for essential hypertension. It may be the reason why hypertension is more prevalent among the black population because they mainly originate from malaria endemic areas where they are likely to have various degrees of glucose 6-phosphate dehydrogenase deficiency for protection against malaria but at the same time risk developing hypertension. The aim of the study was to investigate the link between glucose 6-phosphate dehydrogenase deficiency and essential hypertension.

Materials and methods

The study was conducted at the University Teaching Hospital (UTH). This hospital is the largest hospital in the country (Zambia), and is a referral for all the hospitals around the country. It provides treatment services and medical check-ups for most of the population in Lusaka. An analytical cross-sectional study design was used. The study population included all the hypertensive patients coming to filter clinic to be attended to, and controls were mainly participants who were coming to the hospital with minor ailments or for medical check-ups. All participants had to undergo a thorough medical examination to rule out any chronic diseases. Any client who was between 35 years and 65 years inclusive and willing to participate was recruited. Those who were pregnant, obese, had other chronic conditions or with secondary causes of hypertension were excluded. The systematic random sampling method was employed; where every 3rd person was selected for the study. This was done after a thorough medical examination by the medical doctor on duty. Venous blood amounting to 4mls was collected from the anticubital vein for the purposes of determining levels of nitric oxide, glucose, creatinine, urea, electrolytes and glucose-6-phosphate dehydrogenase activity. Based on an expected prevalence of essential hypertension of 50%; and 6% G6PD deficiency in normotensives, we enrolled 89 participants from each group in order to have 80% power to detect a 14% difference in G6PD deficiency prevalence (20%) in hypertensive patients, using α=0.05.

Glucose 6-phosphate dehydrogenase activity was measured using the quantitative spectrophotometric method as outlined elsewhere[15]. In brief the method relies on the fact that nicotinamide adenine dinucleotide phosphate ($NADP^+$) is reduced to NADPH by glucose 6-phosphate dehydrogenase in the presence of glucose

6-phosphate. The rate of formation of NADPH is proportional to the activity of glucose 6-phosphate dehydrogenase and is measured spectrophotometrically as in increase in the absorbance at 340 nm. Production of the second molar equivalent of NADPH by erythrocyte 6-phosphogluconate dehydrogenase (6-PGDH) according to the reaction:

$$6\text{-PG} + NADP^{+} \longrightarrow \text{Ribulose-5-Phosphate} + NADPH + H^{+} + CO_2$$

is prevented by use of maleimide, an inhibitor of 6-phosphogluconate dehydrogenase. The activity of glucose 6-phosphate dehydrogenase is determined in terms of U/g haemoglobin (Hb) or as $U/10^{12}$ erythrocyte (RBC). Therefore Hb concentration had to be determined prior to the performance of the glucose 6-phosphate dehydrogenase assay.

The measurement of G6PD activity was compared to the standard reference system with a normal value of 12.1 ± 2.09 U/g Hb. Decreased activity or G6PD deficiency was taken as any level of enzyme activity less than 10.01 U/g haemoglobin, (pointe scientific, Inc.2000).

Statistical analysis: Data was analysed using STATA® Version 12 (STATA Corporation, College Station, Texas). The first step in this section dealt with summary statistics for continuous variables for both groups (study and control groups). Means and standard of deviations were used to come up with the descriptive statistics for continuous variables. The continuous and categorical variables were compared using the student t-test and chi-square respectively. The second step involved using frequency tables to establish the prevalence of G6PD deficiency in both groups i.e, study group and the control group. This was followed by three way cross tabulations to establish the prevalence distribution of G6PD deficiency among different age groups and gender (male and female) in both groups (study and control group).

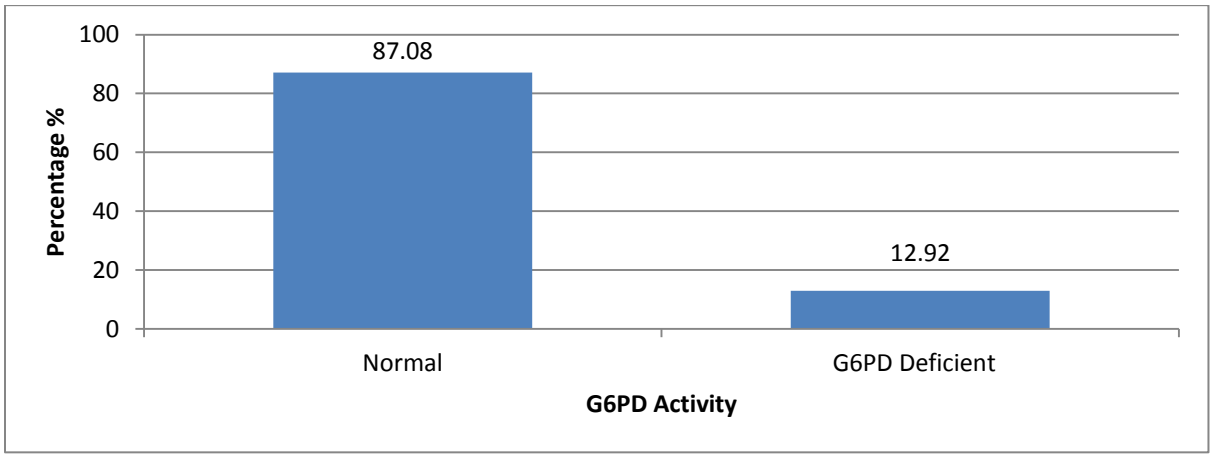
A core set of background variables that are believed to influence essential hypertension such as gender, age, G6PD deficiency and nitric oxide levels were defined. Then the significance of these factors was first tested using a bivariate logistic regression to determine the effect of each independent variable on the dependant variable (essential hypertension), then a multivariate logistic regression was performed to establish the effect of the independent variables (G6PD deficiency, gender, nitric oxide levels and age) on the dependent variable (essential hypertension). The odds ratios were used to establish the degree of association.

Results

Table 1: Descriptive statistics for essential hypertensive patients and control participants.

Parameter	Essential hypertensive Patients (study group) (n=89)		Normotensive (control group) (n=89)		P-values (cases vs. controls)
	Mean	Standard deviation	Mean	Standard deviation	
Age (Years)	52.1	10.4	43.8	9.0	<0.000
Nitric Oxide (uM)	70.0	39.9	96.5	48.6	<0.001
pH	6.6	0.3	6.6	0.3	0.25
Specific Gravity	1.0	0.0	1.0	0.0	0.07
Glucose (Blood)(mmol/L)	5.2	0.8	5.0	0.9	0.03
Urea (mmol/L)	3.8	1.1	3.6	0.9	0.08
Creatinine (mg/dl)	0.7	0.1	0.7	0.2	0.05
Sodium (mmol)	136.6	1.5	137.1	2.3	0.03
Potassium (mmols)	3.7	0.2	3.7	0.2	0.40
Chloride (mmols)	100.0	2.6	100.2	3.0	0.39
G6PD deficiency, n (%)	14 (15.7)		9 (10.11)		0.13

Fig. 1 Percentage distribution of G6PD Deficiency in the participants (n=178)



The study group consisted of 89 hypertensive patients with a mean age of 52.6 ± 10.4 which was greater than that in the control group (43.8 ± 9.0 years) and the difference was significant (*P<0.0000*). The data also indicated a higher prevalence of G6PD deficiency (16%) in the study group compared to the control (10%), though the difference was not statistically significant (*P = 0.13*). Other variables whose means came out to be significant at 5% include serum glucose, creatinine and sodium levels all with p-values less 0.05 (Table 1).

Out of the 178 participants (both hypertensives and normotensives) who took part in the study 23 participants were G6PD deficient; representing a prevalence rate in the whole group of 13%; and 155 participants had normal activity of the enzyme G6PD; representing 87% (Fig. 1).

Out of all those that were G6PD deficient in the study group, 50% belonged to the age group of 35-45, 42.86% belonged to 46-55 age group, and 7.14% belonged to 56-65 age group, while all the participants in the control group who were G6PD deficient belonged to 35-45 age group (Table 2).

Table 2: The distribution of G6PD deficiency by age category

	Study Group		**Control Group**	
	G6PD deficiency	Normal G6PD activity	G6PD deficiency	Normal G6PD activity
Age category	----------%----------			
35-45	50	30.67	100	62.5
46-55	42.86	16		20
56-65	7.14	53.33		17.5
TOTAL	100	100	100	100

G6PD deficiency was found to be more prevalent in males than in females as can be seen both in the study and control groups although the prevalence rate in the former (93%) is greater than in the latter (67%) (Table 3). A bivariate logistic regression was performed to determine the effect of each independent variable on the dependent variable (essential hypertension), after which a multivariate logistic regression was done to control for potential confounders.

The results for the unadjusted odds ratio for the bivariate logistic regression indicate that age had a significant effect on hypertension at 5% significance level. More specifically, participants in 46-55 age group were 2.2 (95% CI 0.99-4.96) times more likely to develop essential hypertension than those in 35-45 age group; and those in 56-65 age group were 5.7 (95% CI 2.72-12.21) times more likely to develop essential hypertension than participants in 35-45 age group (Table 4).

Logistic regression for predictors of development of essential hypertension among 35-65 year olds screened at UTH shows that advancing age and G6PD deficiency all are positively and significantly associated with increased risk of hypertension. The participants in 46-55 age group were 2.4 (95% CI 1.05-5.54) times more likely to develop essential hypertension than those in 35-45 age group; and participants in 56-65 age group were 7.3 (95% CI 3.22-16.61) times more likely to develop essential hypertension than those in 35-45 age group. The results further indicate that participants with G6PD deficiency were 2.92 (95% CI 1.07-7.95) times more likely to develop hypertension than those without the G6PD deficiency (Table 5).

Table 3: G6PD deficiency by gender

	Study Group		**Control Group**	
	G6PD deficiency	No G6PD deficiency	G6PD deficiency	No G6PD deficiency
Gender	----------%----------.			
Female	7.14	54.67	33.33	45
Male	92.86	45.33	66.67	55
TOTAL	100	100	100	100

Table 4: Bivariate logistic regression with Essential Hypertension as the dependent variable with unadjusted odds ratios (Number of cases =89; Number of controls=89)

Variables		**P-Value**	**Unadjusted OR (95% CI)**
G6PD	Not deficient	0.27	1.00
	Deficient		1.66 (0.68-4.07)
Age category(in years)	35-45	0.05	1.00
	46-55		2.21 (0.99-4.96)
	56-65		5.76 (2.72-12.21)
Gender	Female	0.65	1.00
	Male		0.87 (0.48-1.58)
NO levels (uM)	-	0.00	0.98 (0.98-0.99)

Table 5: Logistic regression for predictors of development of essential hypertension among 35-65 year olds screened at UTH.

Variables		**Found with essential hypertension after screening.**		**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
		Yes n (%)	No n (%)		
G6PD	Not deficient	75(84.3)	80(89.9)	1.00	1.00
	Deficient	14(15.7)	9(10.1)	1.66 (0.68-4.07)	2.92 (1.07-7.95)
Age category(in years)	35-45	30(33.7)	59(66)	1.00	1.00
	46-55	18(20.2)	16(18)	2.21 (0.99-4.96)	2.41 (1.05-5.54)
	56-65	41(46.1)	14(15.7)	5.76(2.72-12.21)	7.31 (3.22-16.61)
Gender	Female	42(47.2)	39(43.8)	1.00	1.00
	Male	47(52.8)	50(56.2)	0.87 (0.48-1.58)	0.79 (0.39-1.60)
NO levels (uM)	-	-	-	0.98 (0.98-0.99)	0.98 (0.97-0.99)

Discussion

The study explored the prevalence of G6PD deficiency in essential hypertensive and normotensive adults aged between 35 and 65 years and its association wih essential hypertension. This section provides answers to the objective of this study.

When this study was conducted to establish the prevalence rates of G6PD deficiency in the two groups namely; essential hypertensive (study group) and normotensive adults (control group), it was found that G6PD deficiency prevalence was at 16% in the study group, which translated to 14 participants out of 89 recruited participants in this group. While in the control group, the prevalence was at 10% translating to 9 participants out of 89. Although there seems to be a difference of 6%, the p-value indicated no statistical significance (*p=0.13*). Comparing the study group's prevalence rates of 16% to other studies, there are similarities in the rates with other findings[16] where Egesie et al.,2008 reported a 20% prevalence of G6PD deficiency in health individuals, and WHO (2008) found a 15-26% deficiency in individuals without any condition but in malaria endemic zones. From this, we can establish that the findings are in line with what other authors have established.

Our findings also suggest that there is no significant difference in prevalence of glucose 6-phosphate dehydrogenase deficiency between essential hypertensive and normotensive adults. But what may differ is probably the susceptibility to certain conditions when one is G6PD deficient. We further proceeded to look at the association between G6PD deficiency and essential hypertension.

A multiple logistic regression was performed to determine the effect of G6PD deficiency on essential hypertension as the dependent variable. Using the odds ratio (OR), our results indicated a positive association between the G6PD deficiency and essential hypertension. We found that a G6PD deficient individual was 2.9 times more likely to have essential hypertension than a non-G6PD deficient individual. Our results are consistent with other studies which suggested that G6PD deficiency predisposes to development of higher blood pressure[17, 18].

This is also in agreement with what Luzatto et al [19]states about oxidative stress. The author writes to say that, oxidative stress, which is a major contributor to essential hypertension, maybe as a result of G6PD deficiency since the reduction of hydrogen peroxide, removal of free radicals and other forms of oxidative stress to a large extent depend on G6PD enzyme for the generation of NADPH. In a study conducted by Gaskin et al (2001), the author also states that people with X-linked chromosome defects of G6PD deficiency are at risk of getting essential hypertension[20]. Rodrigo et al (2003), in his studies, pointed out that the reduction of anti-oxidant enzymes such as G6PD enzyme leads to the generation of oxidative stress that is likely to increase the risk of having essential hypertension[21, 22]. It can therefore be concluded from the findings of this study that, G6PD deficiency has a possible role in the development of essential hypertension.

There is still a huge debate as to how deficiency of glucose 6-phosphate dehydrogenase might be linked to the aetiology of essential hypertension. One possible explanation is that the deficiency of the enzyme leads to deficiency of NADPH which results in deficiency of reduced glutathione. As a result cells cannot reduce hydrogen peroxide and this invariably leads to increased oxidative stress. Deficiency of NADPH would slow the formation of nitric oxide vital for relaxation of vascular smooth muscles because NADPH is a cofactor in formation of nitric oxide from arginine by nitric oxide synthase[23]. It's this relaxation of vascular smooth muscles that is vital for lowering blood pressure[24].

Other studies have actually found that high levels of NADPH tend to promote the formation of reactive oxygen species in vascular smooth muscles[25]. This is because NADPH oxidase generates superoxide by transferring electrons from NADPH inside the cell across the membrane and coupling these to molecular oxygen to produce superoxide anion, a reactive free-radical. The vascular NAD(P)H oxidases have been found to be essential in the physiological response of vascular cells, including growth, migration, and modification of the extracellular matrix and they have also been linked to hypertension and to pathological states such as atherosclerosis[26]. G6PD deficiency may reduce vascular superoxide anion production by limiting production of the substrate for NADPH oxidase, thereby inhibiting oxidant-mediated Ang II-induced signaling pathways that contribute to hypertension and smooth muscle hypertrophy[27]. This seems to contradict the observation that increased NADPH

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increases the production of NO which leads to vascular smooth muscle relaxation and reduction in blood pressure. Perhaps what determines the blood pressure at the end is a balance between vascular smooth muscle relaxation as a result of NADPH facilitated production of NO and vascular smooth muscle contraction as a result NADPH mediated reactive oxygen species production by NADPH oxidase followed by activation of oxidant-mediated angiotensin II- induced signalling which could contribute to essential hypertension.

In our study, age was also found to have a positive association with essential hypertension, with the participants in 45-55 age group being 2.4 times more likely to have essential hypertension than those in 35-45 age group; on the other hand, participants in 56-65 age group are 7.3 times more likely to have essential hypertension than those in 35-45 age group. This shows that an increase in age is associated with higher odds of essential hypertension. This is supported by a previous study, on the prevalence of hypertension and its correlates in Lusaka Urban District of Zambia, where it was found that age and sex (gender) were associated with hypertension[4]. In this study, however, we found that gender had no association with essential hypertension [OR]=0.79, [CI]=0.39-1.60 (*P=0.6*).

Conclusion

In conclusion our study established that G6PD deficiency prevalence in the essential hypertensive adults (study group) and in normotensive adults (control group) was 15.7% (16%), and 10.1% (10%) respectively. However, there was no statistical difference in the prevalence of G6PD deficiency between the two groups (*p=0.13*). Therefore we concluded that there was no significant difference in G6PD deficiency prevalence between essential hypertensive and normotensive adults. We also found that there was an association between G6PD deficiency and its possible role in the pathophysiology of essential hypertension. Based on our findings we conclude that G6PD deficiency is associated with increased risk of developing essential hypertension.

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