Original Article

Glucose-6-phosphate dehydrogenase enzyme deficiency as a diagnostic factor of diabetes mellitus: An original study

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Abstract

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common genetic disorders affecting approximately 400 million people worldwide. Several recent studies have reported a relationship between G6PD deficiency and the incidence of diabetes.

Objectives: The aim of the present study was to evaluate and compare levels of G6PD deficiency in diabetes mellitus patients.

Materials and Methods: G6PD activity and fasting glucose levels were measured in blood samples of 49 diabetic patients and 21 healthy controls.

Results: G6PD activity was decreased in patients with diabetes mellitus as compared to healthy controls and showed that overall G6PD deficiency was significantly associated with diabetes mellitus as compared to nondiabetics.

Conclusion: The study concluded that G6PD deficiency is noted in diabetics than in nondiabetics and can be a biomarker of oxidative stress and poor glycemic control in diabetes mellitus.

Keywords: Diabetes mellitus, G6PD deficiency, glucose-6-phosphate dehydrogenase

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BACKGROUND

Diabetes Mellitus is a metabolic disease characterized by hyperglycemia (elevated blood glucose levels) due to defects in insulin metabolism. In a state of hyperglycemia, glucose is known to generate free radicals through several mechanisms. In the long term, damage, dysfunction, and failure of different organs, notably the eyes, kidneys, nerves, heart, and blood vessels can be caused if hyperglycemia is not managed properly.[1] There is an observation of increased oxidative stress in diabetic patients, which may be due to an increase in oxidants production processes or a decrease in the antioxidant defense mechanisms.[2]

The rate-limiting enzyme of the pentose phosphate pathway is the Glucose-6-phosphate. It is required for the antioxidant defense because it produces nicotinamide adenine dinucleotide phosphate (NADPH), the main cellular reductant and the fuel for glutathione recycling within the cells.[3] G6PD is essential for cell metabolism and has been linked to the pathophysiology of numerous disorders, including cancer, diabetes, and endothelial dysfunction

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brought on by aldosterone. The primary function of G6PD is to serve as a main source of NADPH, a hydrogen carrier needed by numerous vital cellular processes, including glutathione recycling and nitric oxide generation.[4] There is growing evidence that G6PD activity, rather than ribose synthesis, is crucial for the creation of NADPH, which is a protection against oxidative stress.[5] It was discovered that diabetes mellitus, hyperglycemia, and high glucose levels limit the action of G6PD by increasing adenylate cyclase activity, which then raises cyclic adenosine mono phosphate (cAMP) levels inside the cell.[6]

A risk factor for diabetes could be the deficiency of G6PD enzyme. Impaired G6PD activity by high glucose concentrations in endothelial and kidney cells is associated with increased reactive oxygen species (ROS) production and decreased cell survival.[7] Persons with G6PD deficiency are more likely to have impaired fasting glucose and diabetes.

OBJECTIVES

The study was carried out to evaluate and compare the levels of G6PD in patients with diabetes mellitus and in normal healthy individuals and to correlate the relationship between G6PD and diabetes mellitus.

MATERIALS AND METHODS

Seventy patients who consented to participation in the study were randomly selected and screened for G6PD deficiency and plasma glucose levels in the Oral Pathology department of a Dental Institute in Vadodara, Gujarat. A total of 49 patients were taken as subjects. Twenty one patients coming for routine hematological investigations like Complete Blood Count and giving history of no other systemic diseases were taken as controls.

In total, 33 males (21 diabetic and 12 nondiabetic) and 37 females (28 diabetic and nine nondiabetic) were considered for the study. All subjects were advised no medications on the morning before blood sample collection. Fasting blood was obtained from the antecubital vein after an overnight fasting period (10-12 hours). The collected samples were divided into three parts:

The first sample was collected in a plain vacuum tube for the estimation of complete blood count, using Accurex Acculab CBC 330 cell counter, which reads according to the parameters and calculates the complete blood count.

Haemoglobin (Hb) values: 14.0-18.0 g/dL and 12.0-16.0 g/dL were considered normal for men and women, respectively.[8]

The second sample was collected in a vacuum tube with fluoride for the estimation of Fasting blood glucose level using Mindray BA 88A semi-automatic biochemical analyzer. A Liquizyme Glucose GOD/POD method reagent kit was used.

Blood sugar levels between 70-110 mg/dL and PPBS up to 130 mg/dL were considered normal, values above that were considered as high and the patient was diagnosed as diabetic (according to GOD/POD method).

The third sample was for estimating the level of G6PD, using LiquiMAX G6PDH (quantitative/kinetic method) test kit manufactured by Avecon Healthcare Pvt. Ltd., Saha.

First, the hemolysate preparation was done by adding 1 mL lysing reagent to10 μL of whole blood which was mixed well and incubated for 10 minutes. After 10 minutes, 0.5 mL of buffer and 0.5 mL of the substrate were added to 0.5 mL hemolysate prepared above and was mixed well. This mixture was aspirated and according to the parameters set, G6PD activity was measured with the semi-auto analyzer.

Values between 4.6 and 15.0 U/g Hb were considered as normal values of G6PDH activity (according to LiquiMAX G6PDH test kit).

RESULTS

A distribution of study subjects based on gender and G6PD levels is shown in Table 1 and Graph 1. Of the total study population, 33 study subjects were males. Among them, 21 (63.64%) study subjects were G6PD deficient, whereas 37 study subjects were females. Among

Table 1: Distribution of study subjects based on gender and G6PD levels

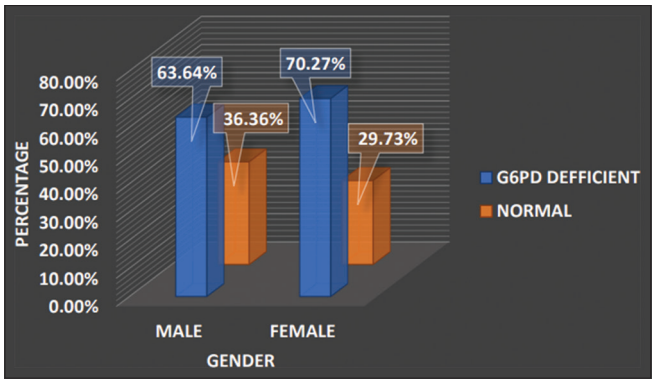
Gender	Deficient N (%)	Normal N (%)	Total N (%)	P value
Male	21 (63.64%)	12 (36.36%)	33 (100%)	≥ 0.05**
Female	26 (70.27%)	11 (29.73%)	37 (100%)	
Total	47 (67.14%)	23 (32.86%)	70 (100%)	

Pearson chi-square value= 0.306, Level of significance ≤ 0.05, * Significant Result, ** Non-Significant Result

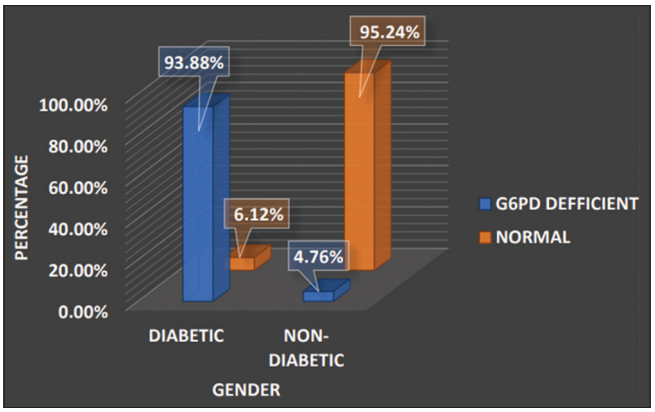
Table 2: Distribution of study subjects based on diabetes mellitus and G6PD levels

Status	Deficient N (%)	Normal N (%)	Total N (%)	P value
Diabetic	46 (93.88%)	3 (6.12%)	49 (100%)	≤ 0.05*
Non-Diabetic	1 (4.76%)	20 (95.24%)	21 (100%)	
Total	47 (67.14%)	23 (32.86%)	70 (100%)	

Pearson chi-square value= 0.00, Level of significance ≤ 0.05, * Significant Result, ** Non-Significant Result



Graph 1: Distribution of study subjects based on gender and presence of diabetes mellitus



Graph 2: Distribution of study subjects based on diabetes mellitus and G6PD levels

them, 26 (70.27%) study subjects were G6PD deficient and statistically no significant result was observed among genders with regard to G6PD levels.

Distribution of study subjects based on diabetes mellitus and G6PD levels is shown in Table 2 and Graph 2. Of the total study population, 49 study subjects were diabetic. Among them, 46 (93.88%) study subjects were G6PD deficient and three (6.12%) study subjects were normal. Whereas 21 study subjects were nondiabetic. Among them, one (4.76%) study subject was G6PD deficient and 20 (95.24%) study 0.00% 20.00% 40.00% 60.00% 80.00% 100.00% DIABETIC NONDIABETIC 93.88% 4.76% 6.12% 95.24% PERCENTAGE GENDER G6PD DEFFICIENT NORMAL subjects were normal and statistically significant difference was observed among genders with regard to G6PD levels.

DISCUSSION

The cytoplasmic enzyme G6PD, which is connected to the X chromosome, works to promote free radical detoxification to protect cells from oxidative damage. An intracellularly balanced oxidative environment is ensured by this metabolic route, which also results in the formation of NADPH, a compound involved in the glutathione cycle. All tissues express G6PD; however, in red blood cells, this biochemical activity is significantly diminished when the enzyme is unusually low or insufficient, making these cells more sensitive to oxidative stress.[9]

In most cells of the human body, NADPH is the key electron donor required for many biosynthetic processes, including several reactions in the pathways of fatty acid synthesis, cholesterol, and steroid hormone synthesis, as well as in the formation from ribose of deoxyribose required for DNA synthesis.[10]

Epidemiological data suggest that G6PD deficiency may be a risk factor for diabetes. Several pathways, including those involving the genes regulating insulin secretion and G6PD activity, may play a role in the relationship between diabetes and G6PD impairment. The prognosis is worse for those who have both diabetes and G6PD impairment.[11]

G6PD appears to be of unique importance to many cellular processes that use NADPH, as inhibition of G6PD impairs many cellular processes that are dependent on NADPH. Hence, the other enzymes do not provide a sufficient amount of NADPH to maintain many of these processes at normal levels.

The most prevalent enzymatic disease affecting red blood cells in humans is G6PD deficiency. It is estimated that about 400 million people are affected by this deficiency.[12]

Numerous observations have demonstrated highly significant decreases in G6PD activity due to hyperglycemia or diabetes in liver, kidney, brain, endothelial cells, red blood cells, and other cells and tissues.

In the study by Heymann AD *et al.*,[13] patients aged 45-64 years with G6PD deficiency had a 1.44 times higher prevalence of diabetes compared to those without G6PD deficiency at this age group which was similarly noted in other studies which observed that G6PD enzyme activities were consistently reported to be lower among patients with diabetes compared to normal controls. The present study confirmed the finding where among 70 patients, 46 patients (>65%) with diabetes mellitus showed lower levels of G6PD activity.

Similarly, in Adinortey MB *et al.*'s study,[14] the prevalence of G6PD deficiency was higher in diabetics (50.7%) compared to normal controls (22.3%). The relative risk of developing diabetes was 1.61 times higher. Niazi GA *et al.*'s[15] study showed significantly higher prevalence of G6PD deficiency

among patients with diabetes mellitus (12.4%) compared to healthy population control (2.0%).

Saha N's[16] study estimated higher prevalence of G6PD deficiency in Chinese and Indian patients with diabetes. In Festus OO *et al*.'s study,[17] patients with diabetes had lower G6PD enzyme activity compared to healthy controls. This was similar to the studies by Mahmoud AA and Nor El Din AK,'[18] Rashidi H *et al*.,[19] and Wan GH *et al*.[20]

Male predominance for G6PD deficiency was observed like in a study conducted by Saeed TK *et al*.,[21] where higher prevalence of G6PD deficiency among diabetic patients (19.6%) compared to controls (10.4%). The number of patients with G6PD deficiency was higher in men with longer duration of diabetes while female predominance was observed in the study conducted by Akter N *et al*.;[22] female patients with type 2 diabetes had lower G6PD enzyme activity compared to healthy controls. The present study observed statistically no significant difference among genders over G6PD deficiency concluding that G6PD deficiency can be observed in both the genders.

G6PD is a sex-linked genetic disorder which when present manifests from birth and therefore not age-dependent. The results showed that the overall prevalence of G6PD deficiency in the study population was significantly higher among type 2 diabetics as compared to nondiabetics. With the established role of oxidative stress in the development and progression of diabetes mellitus, it has been suggested that G6PD-induced oxidative stress may be a key link for association between diabetes and enzymopathy. However, smaller sample size in the present study would not be legitimate to confirm the findings which remain the limitation of the study.

CONCLUSION

The study revealed that G6PD deficiency is more prevalent among diabetics than among nondiabetics. The study also concludes that diabetes is independently associated with G6PD deficiency in males and females both without any gender predilection. Further studies using a larger sample size and designed to identify potential causal link between the two conditions will go a long way in elucidating this observed relationship between the two conditions. G6PD activity can be taken as a biomarker of oxidative stress and poor glycemic control in type 2 diabetes mellitus patients.

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Conflicts of interest
There are no conflicts of interest.

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