Original Article

ERYTHROCYTIC GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY IN DIABETIC PATIENTS

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ABSTRACT

Background and objectives: Diabetes mellitus is a common and complicated disease. Studies imply blood glucose and its oxidant derivatives have a key role in pathogenesis of diabetes mellitus. Activity of enzyme "glucose-6-phosphate dehydrogenase" (G6PD), an anti-oxidant system, is important in preventing its complications. Unsuitable control of blood glucose decreases G6PD activity and increases diabetes mellitus complications. This study evaluated the difference of G6PD activity among diabetic and non diabetic patients, and the impact of hyperglycemia on the G6PD activity.

Methodology: One hundred diabetic and one hundred non diabetic subjects were selected from patients 30 to 60 years old. Demographic data including gender, age, height, weight, duration of diabetes mellitus, type and duration of treatment, medical history (especially favism) were recorded. Blood pressure and body mass index were also measured. One blood sample was taken from each subject and 5 elements including G6PD presence and activity, fasting plasma glucose, plasma triglyceride and plasma high density lipoprotein were measured.

Results: G6PD activity was significantly higher in non diabetic subjects ($P<0.01$). Within diabetics, G6PD mean activity was significantly higher in non dyslipidemic group ($P<0.05$) and in subjects with BMI < 25 ($P<0.05$). G6PD mean activity was significantly higher in non diabetics than dyslipidemic ($P<0.01$) and non dyslipidemic diabetics ($P<0.05$).

Conclusion: Diabetic hyperglycemia may lead to serious complications and decrease G6PD activity. This issue itself aggravates diabetic injury due to inappropriate antioxidation process. Simultaneous dyslipidemia and obesity may intensify the effect of hyperglycemia and oxidative stress.

KEYWORDS: Glucose-6-phosphate dehydrogenase, Diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is a common and complicated disease with increasing prevalence especially in developing countries.[1,2] Complications of DM impose heavy health and financial burden on society.[1,3] Almost, 75-80% diabetics die of cardiovascular disease,[2] the risk of coronary heart disease, cerebrovascular and peripheral vascular diseases is significantly higher among diabetic patients.[2]

Recent studies imply concentration of blood glucose and its oxidant derivatives have a key

role in pathogenesis of DM.[4,5] Activity of enzyme "glucose-6-phosphate dehydrogenase" (G6PD), an anti-oxidant system, is important in preventing or postponing complications of DM.[6,7] Since poor control of blood glucose decreases G6PD activity and increases DM complications,[4-7] the study of impact of poorly controlled higher blood glucose levels on G6PD activity seems useful for better understanding of DM pathogenesis and also prediction of its complication based on G6PD activity.

The aim of the present study was to evaluate the difference of G6PD activity among diabetic and non diabetic patients, and the impact of higher blood glucose on the activity of this enzyme.

METHODOLOGY

Study Population: This study was conducted in "Zahedan University of Medical Science", Zahedan, Iran during October 2006. Using a simple non-probability sampling, one hundred diabetic subjects were selected from patients 30 to 60 years old who were referred to "Diabetes Mellitus Clinic" in Zahedan, and one hundred non diabetic subjects were selected from patients 30 to 60 years old who were referred to "Zahedan Reference Laboratory". Demographic data including gender, age, height, weight, duration of DM, type of treatment, duration of treatment, medical history (especially history of favism) were recorded for all subjects. Diabetes mellitus was defined as fasting plasma glucose (FPG)³ 126 mg/dL or 2-hour postprandial glucose³ 200 mg/dL.[1,8] Non diabetics were defined as FGP < 100 mg/dL without history of DM or any other major disease. Dyslipidemia and body mass index (BMI) were also measured. Dyslipidemia was defined as fasting plasma triglyceride (TG) ³ 250 mg/dL or fasting plasma high density lipoprotein (HDL) £ 35 mg/dL.[9] Since BMI ³ 25 is a risk factor for DM type 2,[1] the subjects were classified into two groups: BMI³ 25, and BMI < 25. Hypertension, as comorbidity, was defined as systolic blood pressure³ 140 mmHg or diastolic blood pressure³ 90 mmHg.[10] One blood sample was taken from each subject and 5 elements were measured including G6PD presence and activity, FPG, TG, HDL. G6PD activity was analyzed with kinetic method and spectrophotometer (Eppendorf ECOM-P4 153). G6PD spot test fluorescencse was used for G6PD qualitative measurement (Chem. Enzyme Lab Kit; Iran). If G6PD level were normal, its place would be visible, in a way that the more the enzyme is, the more visible fluorescence will be. At first, each blood sample underwent "spot test". In case of the negative results, the subject was excluded; but when the result was positive, "Chem Enzyme" kit was used for G6PD quantitative measurement. The more active G6PD is the more light it absorbed in spectrophotometer. Since beta-thalassemia (an important confounder for hemoglobin concentration) is rare in Zahedan, it was not taken into account by the researcher(s).

Statistical Analysis: "Independent student t-test" was used for comparison of significant difference between two independent groups (diabetics and non diabetics). Then, "Levene test" was used for comparison of similarity of variances. In addition, "one sample Kolmogov-Smironov test" was used to observe whether data conformed to normal distribution.

RESULTS

There were 100 non diabetic patients (70 women, 30 men). There were 100 diabetic patients (60 women, 40 men) with mean age 51.9 (± 8.5) years. Mean of DM duration was 82 months. Mean of HbA1c was 7.5 (±2.2) at beginning of study.

Seven subjects used insulin injection, 81 subjects used oral anti-diabetics tablets and 12 subjects used both insulin and oral-antibiotics. Among diabetics 27 subjects had a history of hypertension. Within diabetic group, 37 subjects had history of diseases including cardiovascular disease in 12 subjects, respiratory disease in 7 subjects, ocular disease in 5 subjects, gastrointestinal disease in three subjects, hyperthyroidism in two subjects and cerebro vascular disease in one subject.

Comparison of G6PD mean activity between diabetics and non diabetics showed that the

enzyme activity was significantly higher in non diabetic subjects (P<0.01) (Fig-1). Then, diabetic subjects were divided into two subgroups: dyslipidemic and non dyslipidemic. There were 31 dyslipidemic subjects within diabetics. Analysis showed that G6PD mean activity was significantly higher in non dyslipidemic group (P<0.05) (Table-I). Comparison of G6PD mean activity between non diabetics and dyslipidemic diabetics indicated that enzyme activity was significantly higher in non diabetics (P<0.01) (Table-I). Moreover, comparison of G6PD mean activity between non diabetics and non dyslipidemic diabetics indicated that enzyme activity was significantly higher in non diabetics (P<0.05) (Table-I).

At last, G6PD mean activity between diabetic subjects with BMI ³ 25 and BMI < 25 was compared. It showed G6PD mean activity is significantly higher in subjects with BMI <25 (P<0.05).

DISCUSSION

In the present study, we found that G6PD mean activity in diabetics is significantly lower than non diabetics. Since mean of DM duration was 82 months, it was long enough to induce hyperglycemic adverse effect. Various studies have concluded that reduced activity of G6PD is a risk factor for DM.[11-16]

A study conducted by Wan and colleagues, measured G6PD activity in 237 diabetic and 656 healthy persons, and indicated that G6PD activity was significantly decreased in diabetics.[6] In a case-control study, Xu and colleagues showed G6PD activity, NADPH production and glutathione reduction was decreased in diabetic rats, and administration of insulin and correction of hyperglycemia improved enzyme activity.[15] It implies that diabetic hyperglycemia was the cause of reduced G6PD activity. In a similar survey, Gupta and colleagues showed that erythrocytic G6PD activity was lower in diabetic rats compared to healthy rats. They showed the enzyme activity rose to normal limit after insulin administration.[17] It again suggests that diabetic hyperglycemia is the cause of reduced G6PD activity.

Since diabetic patients, simultaneously, suffer from other endocrine problems like dyslipidemia, it is worthy to evaluate the impact of such associated abnormalities on G6PD activity. Comparing G6PD activity between dyslipidemic and non dyslipidemic patients within diabetics and comparing G6PD activity between non diabetic and dyslipidemic diabetic patients, the researcher(s) showed that its activity was significantly lower in dyslipidemic patients. There is no similar survey which compares G6PD activity in dyslipidemic connection. Since quantitative cholesterol levels were not available, we were not able to detect any relationship between G6PD activity and cholesterol concentration. In addition, measurement of glycated hemoglobin A_1 (HbA_{1c}) was impossible. Thus, the similar correlation was impossible to detect.

Table-I: Comparison of G6PD mean activity between diabetic and non diabetic patients

Patients	*G6PD* mean activity (IU/gHb)(mean±SD)*
Non diabetic	12.3± 3.1
Diabetic	9.4±2.6
Dyslipidemic	7.3 ± 1.9
Non dyslipidemic	10.7 ± 2.3
BMI† ³ 25	8.21 ± 1.9
BMI < 25	12.4 ± 1.6

*G6PD, glucose-6-phosphate dehydrogenase; ¶ IU/gHb, international unit per gram of hemoglobin; † BMI, body mass index, all values are shown as value (± standard deviation)

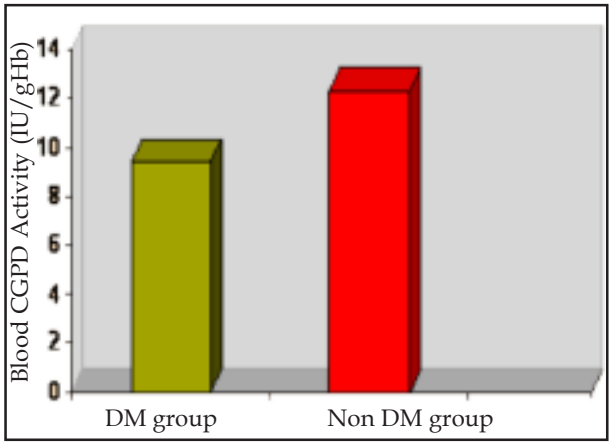

Fig-1: Comparison of G6PD activity between diabetes and non-diabetes groups.

Several surveys have concluded that obesity resulted in resistance to insulin, which in turn leads to increase of CAMP. This may activate protein kinase A, which itself reduces G6PD activity.[7,15] In the present study, G6PD activity was significantly lower in obese patients (BMI[3] 25) than slim patients.

As shown above, diabetic hyperglycemia results in remarkable decrease in G6PD activity and augments oxidative stress. Several associated endocrinopathies like dyslipidemia can aggravate decreasing G6PD activity. Thus, it is possible to use G6PD activity for evaluation of intensity of diabetic complications and even prediction of future complications with appropriate investigations.

Limitations of the study: In our study mean of HbA_{1c} (at beginning of study) had shown poorly controlled blood glucose. Assay of HbA_{1c} during this study, was necessary to evaluate correlation between G6PD activity level and concentrations of HbA1C. Moreover, G6PD activity needs to be evaluated in presence of dyslipidemia. Moreover since it is not a population based study, its results cannot be generalized.

CONCLUSION

Diabetic hyperglycemia may lead to serious complications and decrease G6PD activity through glycation process and oxidative stress. This issue itself aggravates diabetic injury due to inappropriate antioxidation process. Simultaneous dyslipidemia and obesity may intensify the effect of hyperglycemia and oxidative stress. Thus, the G6PD activity level can reflect the glycemic control, and even predict subsequent complications while they are not present.

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