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Is Glucose-6-Phosphate Dehydrogenase Deficiency a Risk Factor for Proliferative Diabetic Retinopathy in Male Patients with Type 1 Diabetes Mellitus in Basrah?

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Abstract
Background: *Diabetes Mellitus is a chronic and common disease with diabetic retinopathy a frequent long-term complication.Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent human enzyme defect. Both of these conditions are very common in our locality with many burdens on the patients' quality of life and health care services.*
Aim: *To search for any significant association between G6PD deficiency and the development of proliferative diabetic retinopathy (PDR) among male patient with type 1 diabetes mellitus (T1DM).*
Method: *A case-control study was conducted onNinety-four adult male patients with T1DM in Al Faiha Diabetes, Endocrine and Metabolism Center over a two-year period from October 2012 to October 2014. All patients are submitted to both funduscopicexaminations of their eyes and G6PD assay.*
Results: *PDR is found among 7.6% of those who were G6PD sufficient in comparison to 42.9% of G6PD deficient (p-value<0.001).*
Conclusion: *There is a significant association between G6PD deficiency status and the development of PDR in male patients with T1DM.*
Keywords: *type 1 diabetes mellitus, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, and proliferative diabetic retinopathy.*

Introduction

Type 1 diabetes mellitus (T1DM) is a chronic medical condition in which genetically susceptible subjects had their pancreatic β-cells destructed by autoimmune process which results in absolute insulin deficiency. This disease is diagnosed between infancy and adulthood and is clinically manifested by polyuria, polydipsia, and weight loss associated with glycosuria and ketonuria.[1]

T1DM is the usual type of diabetes in youth, accounting for morethan85% of all diabetes cases in youth< 20 years of age worldwide.[2,3,4,] In general, the incidence rate increases from birth and peaks between the ages of 10–14 years during puberty.[5,6,7] The increasing incidence of T1DM throughout the world is especially marked in young children.[6,8]

Diabetic retinopathy is a microvascular complication of diabetes with a considerable risk of blindness. Global population-based data indicate that it is the fifth most common cause of blindness in the world, accounting for approximately 4.8% of global blindnessand considered as a leading cause of blindness in industrialized countries, [9]and its significance is likely to increase with increasing frequency of diabetes. [10]

The strong relationship between chronic hyperglycemia and the development and progression of diabetic retinopathy had been confirmed by the Diabetes Control, and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) clinical trialsbut the exact underlying mechanism that is responsible for the development of microvascular disease as a result of hyperglycemia remains unclear.[11,12]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent enzyme deficiency in the world, with an estimated >400 million people with G6PD deficiency. G6PD deficiency is common throughout sub-Saharan Africa, regions in the Mediterranean, and parts of Southeast Asia.[13,14]

The relationship between diabetes and G6PD deficiency is still a matter of debate. The theory that chronic hyperglycemia can cause a decrease in G6PD activity is supported by experimental observations. [15] On the other hand, the reverse theoryin that G6PD deficiency could be a risk factor for the occurrence of diabetes has also been raised. In several populations, individuals with diabetes had increased prevalence of G6PD deficiency compared with the background rate of the general population.[15]

Evidence indicates that patients with aG6PD deficiency are protected against ischemic heart disease, cerebrovascular disease, nonarteritic anterior ischemic optic neuropathy and retinal vein occlusion. [16,17,18] On the other hand, an increased prevalence of proliferative diabetic retinopathy (PDR) in patients with G6PD deficiency and type 1 diabetes has recently been reported in a small study, raising the idea that G6PD deficiency accelerates the microvascular retinalcomplications of diabetes.[19]

In a recent study, it was found that in diabetic men with PDR the prevalence of G6PD deficiency was lower than in age-matched non-diabetic controls and that G6PD deficiency showed a tendency for protection against PDR in diabetic individuals, but the results were not statistically significant. [20]

As diabetes mellitus become a global pandemic, especially in middle eastern countries, [21,22,23] together with the rapid increase in the incidence of T1DM, [6,7,8,24] it is curious to find the various associations with that disease. As G6PD was the commonest enzyme deficiency, [13,14] then it was important to see the association between these two common implications for the human being.

Aim of the study

To search for any significant association between G6PD deficiency and the development of PDR among male patients with T1DM.

Patients and Methods

Ninety-four male patientsare enrolled in this Case-Control study, who were regular attendants atthe Al Faiha Endocrine, Diabetes and Metabolism Center for both G6PD assay and concomitant funduscopic eye examination during the time intervalbetween October 2012 andOctober 2014.

The ethical committee of the Basrah College of Medicine approved the study, and verbal informed consent was taken from patients.

The general characteristics of the (case and control groups) were assessed for: age of the patient, duration of T1DM, Level and number of glycosylated hemoglobin (HbA1c) measurements over the last three years, Systolic and diastolic

pressures, intraocular pressures in both eyes and the prevalence of complications in terms of albuminuria, diabetic retinopathy, PDR, and maculopathy.

Type 1 diabetes was defined by time of diagnosisless than 40 years, C-peptide less than or equal to 0.3 nmol/L or starting insulin treatment within one year of diagnosis if C-peptide was not measured andpositive anti-glutamate decarbox-ylase antibody (anti-GAD), islet cell or insulin antibodies. [25,26,27]

The inclusion criteria are being male with T1DM with duration of more than ten years.

Those patients with chronic kidney disease, age below 16 years, duration of diabetes less than ten years, and those who are smokers were excluded from the study.

The (cases) are male patients who had T1DM of more than or equal to10 years and are G6PD deficient while the (controls) are male patients who had T1DM of more than or equal to 10years and are G6PD sufficient.

The G6PD assay method that was used in this study is the old traditional colorimetric assay in which RBCs were treated with nitrite and so converting oxyhemoglobin [red] into methemog-lobin [brown], then examining the rate of NADPH-dependent methemoglobin reduction in the presence glucose as a substrate and an appropriate radix catalyst (Nile blue or methylene blue).[28,29]

The funduscopic eye examination was conducted at (Al Faiha Ophthalmology Consultation Clinic) with both direct and indirect ophthalmoscope done by the consultant ophthalmologist according to the 2011 Scottish Diabetic Retinopathy Grading Scheme.[30] (Appendix)

Statistical Analysis

The data obtained from this study were analyzed using the Statistical Package for Social Sciences (SPSS) software version 20.0, descriptive analysis was done using (mean ± standard deviation), (frequency) and (percentage of each value), with the (p-value of less than 0.05) to be considered as significant.

Results

Ninety-four patients with T1DMwere enrolled with a mean age of (27.66 ± 8.69 years), and a mean duration of T1DM (15.3 ± 3.32 years). Among them, the number of patients who were G6PD deficient was 28 patients (29.8%).

The general characteristics of the (case and control groups) in terms of age, duration of diabetes, level and number of HbA1c measurements over the last 3 years, systolic and diastolic pressures and intraocular pressures in both eyes together with the prevalence of complications in terms of albuminuria, diabetic retinopathy, PDR and maculopathy are shown in (Table 1).

In the studiedgroup, diabetic retinopathy was seen in 38 patients (40.4%), and those who had normal retinal examination were56 patients (59.6%).

Of those 66 patients who were G6PD sufficient (Table 2, Fig. 1), 40 (60.6%) had no retinopathy in comparison to 26 (39.4%) had retinopathy, while among those 28 patientswho were G6PD deficient,it was found that 16 (57.1%) had no retinopathy in comparison to 12 (42.9%) patients had retinopathy (p-value = 0.820).

Table 3 (Fig.2) illustrated the association of G6PD deficiency with the prevalence of PDR. Among the 66 patients who were(G6PD sufficient), there were five patients (7.6%) had proliferative retinopathy, while 61 patients (92.4%) had no evidence of proliferative retinopathy. On the other side,among the28 patients whowere(G6PD deficient), 16 patients (57.1%) had no prolifera-tive retinopathy in comparison to 12 (42.9%) had evidence of proliferative retinopathy (p-value<0.001).

Table 1-Characteristics of the male diabetic patients studied and prevalence of complications

Characteristic	T1DM, G6PD Sufficient *n*=66	TIDM, G6PD deficient *n*=28	P-value
Age (years) Mean ± SD	29.0±9.3	26.5±6.1	0.119
Duration of diabetes (years) Mean ± SD	15.6±3.5	14.8±2.9	0.313
HbA1c Measurements (n) Mean ± SD	3.4±1.9	4.3±3.0	0.136
HbA1c (%) Mean ± SD	10.7±2.3	9.7±1.8	0.122
Blood Pressure, Systolic (mm Hg) means ± SD	119.5±14.6	114.3±14.8	0.120
Blood Pressure, Diastolic (mmHg) mean ± SD	73.8±12.3	73.4±12.6	0.889
Intraocular Pressure R (mmHg) mean ± SD	14.5±1.1	14.2±0.9	0.157
Intraocular Pressure L (mmHg) mean ± SD	14.6±1.1	14.2±0.9	0.112
Albuminuria, n (%)	48 (72.8)	18 (64.3)	0.419
Retinopathy, any n (%)	26 (39.4)	12 (42.9)	0.820
Retinopathy, Proliferative (%)	5 (7.6)	12 (42.9)	0.001
Maculopathy n (%)	1 (1.5)	7 (25)	0.010

Table 2-Association between diabetic retinopathy and G6PD deficiency

		Retinopathy *n* (%)		Total *n* (%)
		No	Yes	
G6PD Deficiency	No	40 (60.6)	26 (39.4)	66 (70.2)
	Yes	16 (57.1)	12 (42.9)	28 (29.8)
Total		56 (59.4)	38 (40.6)	94
p value =0.820				

Table 3-Association between proliferative retinopathy and G6PD deficiency

		Proliferative Retinopathy *n* (%)		Total *n* (%)
		No	Yes	
G6PD Deficiency	No	61 (92.4)	5 (7.6)	66 (70.2)
	Yes	16 (57.1)	12 (42.9)	28 (29.8)
Total		77 (81.9)	17 (18.1)	94
p value =0.001				

Figure 1-Association between diabetic retinopathy and G6PD deficiency

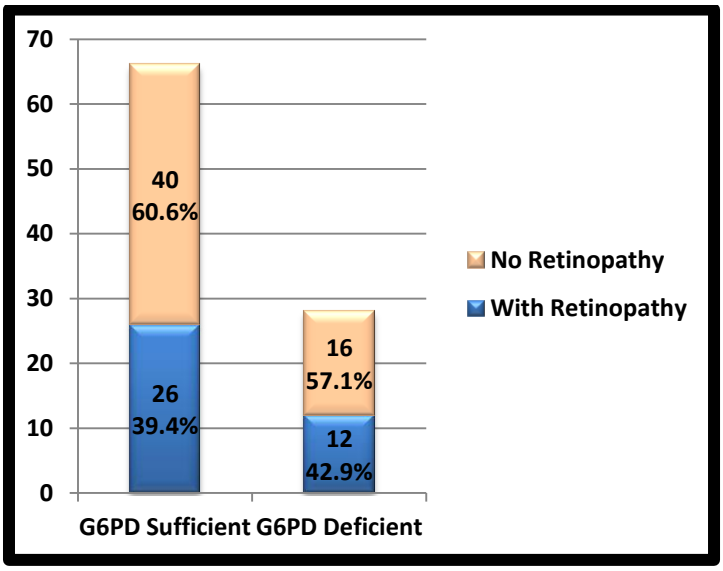
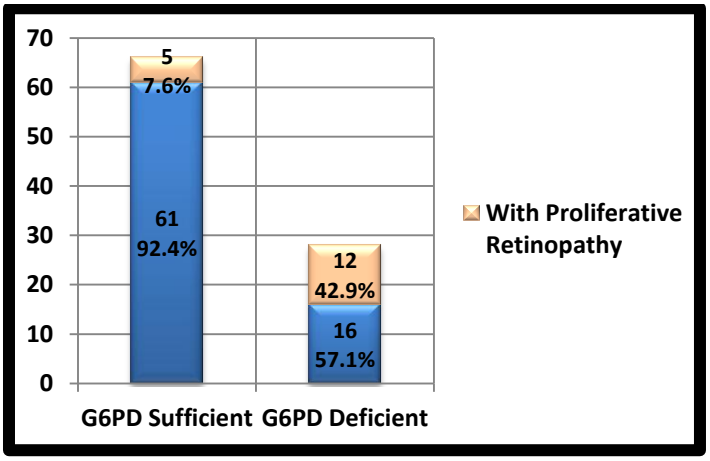


Figure 2-Association between proliferative retinopathy and G6PD deficiency



Discussion

The prevalence of G6PD deficiency among Iraqi people was 7-9.9%, according to World Health Organization data, [14] However, inthisstudy G6PD deficiency was seen in 29.8%because its highly selective study with a limited number of patients and thus did not reflect the exact prevalence of G6PD among Iraqi people.

During the last 20 years, many studies had published on the effect of G6PD deficiency on many of the human diseases, including malaria[31], cardiovascular disease[18,32,] and retinal vein occlusion. [17]This study did notfind an increased prevalence of diabetic retinopathy among patients who are G6PD deficient (p-value of 0.820).

A significant association was seen between G6PD deficiency and the development of PDR (p-value< 0.001) which is similar to Cappai et al, who studiedpatients with G6PDdeficiency or sufficiency with more than fifteen years history of T1DM for whom HbA1c records were available for at least the previous three years,smoking and renal failure were exclusion criteriaand they find that PDR was onlyfounded in individuals with G6PD deficiency.[19]

On the other hand, Pinna A etal., hadconcluded that the prevalence of G6PD deficiency in diabetic males with PDR was lower than in age-matched non-diabetic controls, and G6PD deficiency showed a tendency for protection against PDR in diabetic individuals, but the results were not statistically significant,and they enrolled type 1 and type 2 patients with age more than 50 years.[20]

The main study limitation was the non-availability of the field colored photographs for retinal examination for the standardization purposes. With the method that was used for the G6PD assay was a crude qualitative method. And it's a single-center study with a small number of patients.

Conclusion

No associationwas found between the prevalence of diabetic retinopathy and G6PD status, but once retinopathy developed there is a significant association with the development of PDR among those who are G6PD deficient indicating that G6PD deficiency is a risk factor for the development of PDR in male patients with T1DM. G6PD could be measured inmales with T1DM, as it may be a marker of subsequent proliferative retinopathy.

Conflict of interest: *None declared*

Author Contributions: *Both authors contributed equally to the study.*

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