

High Frequency of Diabetes and Impaired Fasting Glucose in Patients with Glucose-6-Phosphate Dehydrogenase Deficiency in the Western Brazilian Amazon

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Abstract. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common human genetic abnormalities, and it has a significant prevalence in the male population (X chromosome linked). The purpose of this study was to estimate the frequency of impaired fasting glucose and diabetes among G6PD-deficient persons in Manaus, Brazil, an area in the Western Brazilian Amazon to which malaria is endemic. Glucose-6-phosphate dehydrogenase-deficient males had more impaired fasting glucose and diabetes. This feature could be used as a screening tool for G6PD-deficient persons who are unable to use primaquine for the radical cure of *Plasmodium vivax* malaria.

INTRODUCTION

The glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X chromosome-linked genetic disorder affecting approximately 400 million persons living mainly in tropical regions, which makes it the most common enzyme deficiency globally.¹ It has a prevalence of approximately 4.5% among the male population in the Amazon region.^{2,3}

Diabetes mellitus is a serious public health problem because of its high prevalence, severe morbidity and mortality; it is also widely distributed. Approximately 5.6% of the Brazilian population have been diagnosed with diabetes.⁴ Epidemiologic data suggest that G6PD deficiency may be a risk factor for diabetes. Several mechanisms may be involved in the association between diabetes and G6PD deficiency, especially in the genes controlling insulin secretion and G6PD activity.⁵ In addition, patients with diabetes and G6PD deficiency have a poorer prognosis.⁶ The present study aimed to estimate the frequency of diabetes mellitus among G6PD-deficient persons in Manaus, in the Western Brazilian Amazon, and compare them with matched controls. Findings could be useful in daily screening of G6PD in malaria patients, who are unable to use primaquine for radical cure of *Plasmodium vivax* malaria, considering that no standard rapid test for screening of G6PD deficiency is available worldwide.

MATERIALS AND METHODS

A group of 1,478 males (1–65 years of age) were randomly selected from peripheral areas in Manaus, Brazil (to which malaria is endemic) and screened for G6PD deficiency and plasma glucose levels during March 2009–March 2010. After persons completed a standard questionnaire and provided demographic data and medical history, 10 mL of blood was collected in vacuum EDTA tubes. Samples were stored at 2°C–8°C and processed within 48 hours for G6PD activity by using a specific test (Neolisa G6PD; Intercientífica Corporation, Hollywood, FL); G6PD status was categorized as deficient if its level was < 6.0 IU/gram of hemoglobin.

After G6PD phenotype testing, persons were contacted and told to fast for 8–12 hours. Blood (3 mL) was collected the next day into vacuum tubes that contained a gel separator to determine glucose dosage by using an automated enzymatic method (Cobas Mira; Roche, Basel, Switzerland). Samples from G6PD-deficient persons were subjected to molecular analysis by polymerase chain reaction–restriction fragment length polymorphism. For each G6PD-deficient person, two non-G6PD-deficient controls were randomly selected from the general population from the same study areas. Inclusion criteria for controls were the same as those for G6PD-deficient persons.

The study followed the guidelines of the International Conference for Harmonization of Technical Requirements and was approved by the Ethics Review Board of the Fundação de Medicina Tropical Heitor Vieira Dourado (approval no. 2399/2006 with amendment 304291/2013). Informed written consent was obtained from all participants. For children, guardians were instructed about the objectives of the study and also signed an informed consent form.

Persons with glucose levels ≤ 109 mg/dL were classified as having euglycemia, those with levels between 110 and 125 mg/dL as having impaired fasting glucose, and those with levels ≥ 126 mg/dL and/or with a history of known diabetes as having diabetes.⁷ Patients given a diagnosis of impaired fasting glucose or diabetes were referred to specialized treatment according to the guidelines of the Brazilian Ministry of Health. A chi-square test was used to estimate frequency differences, and logistic regression adjusted for age was performed. $P < 0.05$ was considered significant.

RESULTS

Mean \pm SD age was similar for persons with G6PD deficiency (35.9 ± 16.8 years of age, age range = 6–71 years) and persons without G6PD deficiency (31.2 ± 14.5 years of age, age range = 4–69 years) ($P = 0.276$). Sixty-six persons were detected as having G6PD deficiency in the phenotype screening, which resulted in an overall prevalence of 4.5% (95% confidence interval = 3.44–5.56%). Fifty-six (84.8%) persons were carriers of the African variant (202 G→A) of this deficiency, and 10 (15.2%) were genotyped as being carriers of the Mediterranean variant. One hundred thirty-two persons were enrolled as controls.

As shown in Table 1, G6PD-deficient persons are more prone to having impaired fasting glucose and diabetes. When

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TABLE 1
Association between G6PD deficiency and impaired fasting glucose or diabetes, Western Brazilian Amazon*

Glucose	G6PD normal	G6PD deficient	Total	Adjusted OR (95% CI)†	P‡
Normal (≤ 109 mg/dL)	115 (82.1%)	25 (17.9%)	140		
Impaired fasting glucose (110–125 mg/dL)	9 (25.7%)	26 (74.3%)	35	11.4 (4.6–29.8)	< 0.001
Diabetes (≥ 126 mg/dL)	8 (34.8%)	15 (65.2%)	23	6.8 (3.0–20.5)	< 0.001
Impaired fasting glucose or diabetes	17 (29.3%)	41 (70.7%)	58	8.7 (5.5–18.4)	< 0.001
Total	132	66	198		

* G6PD = glucose-6-phosphate dehydrogenase; OR = odds ratio; CI = confidence interval.

† Adjusted by age.

‡ By Mantel-Haenszel test.

the two variants were analyzed individually, the same association was found. Similar frequencies of impaired fasting glucose and diabetes were found among carriers of the African (30 of 56, 53.6%) and Mediterranean variants (7 of 10, 70.0%) ($P = 0.269$). A medical history compatible with hemolytic crisis (jaundice, need for blood transfusion, and/or dark urine) during antimalarial treatment with primaquine was self-reported by 21 (31.8%) of 66 G6PD-deficient persons. The same medical history was reported by 19 (14.4%) of 132 persons without a G6PD deficiency ($P = 0.021$). Patients with diabetes and impaired fasting glucose patients had similar frequencies of hemolysis during past antimalarial treatments (15 of 58, 25.9%) as patients with euglycemia (26 of 140, 18.5%) ($P = 0.254$).

DISCUSSION

Persons with G6PD deficiency are more likely to have impaired fasting glucose and diabetes; this is observed in carriers of the African and Mediterranean variants. This result is consistent with those of previous reports of hyperglycemia⁸ and higher risk of diabetes⁹ in persons with G6PD deficiency. Concurrence of these two factors may result in important clinical repercussions. There is an increased prevalence of proliferative retinopathy in patients with type 1 diabetes who have G6PD deficiency,^{10,11} which suggests that G6PD deficiency accelerates microvascular complications of diabetes. Mechanisms are not clear, but one hypothesis suggests availability of nitrous oxide and endothelial dysfunction.⁶ The same authors reported an increased frequency of microalbuminuria among patients with G6PD deficiency and diabetes, and a higher percentage of increased HbA1c levels was found among patients with G6PD deficiency and diabetes compared with patients who did not have a G6PD deficiency.⁶ Diabetic acidosis can induce hemolysis in G6PD-deficient patients, and may also be enhanced by hypoglycemic drugs, such as glibenclamide.¹²

Major limitations of the present study were lack of differentiation between type 1 and type 2 diabetes, as well as the lack of an HbA1c dosage. Further prospective studies are needed to describe complications of malaria in persons with diabetes.

In summary, we have found a high prevalence of impaired fasting glucose and diabetes in persons with G6PD deficiency. In most of the countries to which *P. vivax* malaria is endemic, the standard radical cure regimen with chloroquine plus primaquine is prescribed without the proper screening for G6PD deficiency, which might predispose persons to severe hemolysis triggered by primaquine. Our data indicate that patients with a history of diabetes or impaired fasting glucose detected by a rapid glucose test in the primary health system

could be systematically screened for G6PD deficiency or referred to tertiary care centers, thus avoiding further clinical complications.

Received January 17, 2013. Accepted for publication March 13, 2014.

Published online May 27, 2014.

Acknowledgments: We thank the health agents from the Foundation of Health Surveillance for technical support; Gloria Lima, Elizabeth Santos Galusso, Evalino Ferreira Itapirema, and all undergraduate students from Centro Universitário do Norte and Universidade do Estado do Amazonas for assistance; and José Alves Maciel, Jr. for help with field and laboratory activities.

Financial support: The study was supported by the Fundação de Amparo à Pesquisa and Programa de Pesquisa para o Sistema Único de Saúde. Marcus V. G. Lacerda was supported by a level 2 fellowship from the Conselho Nacional de Desenvolvimento Científico e Tecnológico.

Disclosure: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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