Abstract

Aim. – Epidemiological data suggest that glucose-6-phosphate dehydrogenase (G6PD) deficiency may be a risk factor for diabetes. Also, the occurrence of haemolysis in the context of diabetes crises has been reported in patients with G6PD deficiency. A unifying hypothesis could explain these associations.

Methods. – We report two patients in whom haemolytic crises occurred soon after acute diabetes decompensation, and revealed G6PD deficiency. We have reviewed the mechanisms that may link the two diseases.

Results. – One patient was admitted for decompensated ketosis-prone type-2 diabetes (KPT2D), but no acidosis, and was treated with insulin, then metformin and glibenclamide. The second patient had type-1 diabetes and ketoacidosis treated with insulin. Haemolytic crises were recognized 8 and 4 days after admission, respectively, and G6PD deficiency was confirmed in both patients. These patients and the other published cases share, as a unique characteristic, the occurrence of haemolysis after diabetes decompensation, whatever the treatment or associated conditions. Experimental data show that hyperglycaemia can reduce expression of the $G6PD$ gene and activity of the enzyme. Conversely, G6PD deficiency can promote oxidative stress and impairment of insulin secretion by beta cells.

Conclusion. – In patients at risk of G6PD deficiency, the possibility of haemolysis should be explored in case of diabetes crisis. In African patients with KPT2D diabetes, potentially oxidative hypoglycaemic agents should be avoided in the remission phase of the disease. G6PD deficiency and diabetes can aggravate each other, and diabetes could be aetiologically associated with G6PD deficiency.

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1. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) catalyses the first step in the pentose phosphate pathway that produces reduced nicotinamide adenine dinucleotide (NADPH), the main reductant in all cell types. In red blood cells, the pentose phosphate pathway is the only source of NADPH, and defense mechanisms against oxidative damage are highly dependent on G6PD activity.

Mutations in the G6PD gene result in protein variants with different levels of enzyme activity, accounting for a wide spectrum of biochemical and clinical phenotypes. Although many individuals usually have no symptoms, G6PD deficiency can lead to haemolysis, particularly after exposure to oxidative stress, such as viral or bacterial infections, drugs, or the ingestion of fava beans [1].

The occurrence of acute haemolysis in patients with G6PD deficiency and diabetes has been reported and ascribed to various mechanisms [2–11]. Here, we report two patients with diabetes mellitus and G6PD deficiency revealed by haemolytic crisis, and we discuss the mechanisms that may link the two diseases.

2. Case reports

2.1. Case 1

A 44-year-old Congolese woman was admitted for acute decompensation that revealed diabetes. She was treated for arterial hypertension with bisoprolol, hydrochlorothiazide and valsartan, and for chronic headaches with amitriptyline. She complained of fatigue, polyuria, and blurred vision of eight days duration. She had lost no weight and her body mass index was 34 kg/m². Physical examination was unremarkable. Plasma glucose concentration was 34 mmol/L, and ketonuria was 2+. Arterial pH was 7.38, and bicarbonate plasma concentration was 4.3–5.7%. The diagnosis of ketosis-prone type-2 diabetes (KPD2) was made and oral fluids, potassium replacement, and subcutaneous insulin were started. On day 4 after admission, her blood glucose concentrations were normal. Metformin 850 mg b.i.d. and glibenclamide 5 mg t.i.d. were initiated, and good glycaemic control was maintained thereafter with diet and metformin. Blood counts and haemoglobin concentration returned to normal.

2.2. Case 2

A 36-year-old Laotian man, who had had type-1 diabetes for 12 years, was admitted for diabetic ketoacidosis (DKA). He had taken no drugs during the preceding weeks, but had omitted several insulin injections. Two days before admission, abdominal pain, nausea and vomiting occurred, and the patient stopped insulin therapy. Physical examination showed severe dehydration, lethargy, and tachypnoea. No precipitating factor other than omission of insulin injections was identified. Plasma glucose concentration was 24 mmol/L and ketonuria was +. Arterial pH was 7.02 and bicarbonates were 6 mmol/L. HbA1c was 9.4%.

The patient was treated with fluids and potassium replacement, and intravenous insulin. He rapidly recovered, and biological abnormalities resolved within 48 h. Subcutaneous insulin injections were resumed 72 h after admission, with good glycaemic control. On day 4 after admission, a haemolytic crisis occurred as shown by a drop of haematocrit and haemoglobin from 46% and 15.4 g/dL, after rehydration, to 26% and to 7.8 g/dL, respectively. Unconjugated bilirubinaemia increased from 15 µmol/L to 57 µmol/L, and haptoglobin was below 0.10 g/L. Schizocytes and Plasmodium falciparum were not detected on blood smears. Direct Coombs’ test was negative. Haemoglobin electrophoresis was normal. The patient’s condition improved after transfusion of two packed units of red blood cells. Glibenclamide was stopped, and good glycaemic control was maintained thereafter with diet and metformin. Blood counts and haemoglobin concentration returned to normal.

The diagnosis of G6PD deficiency was considered. G6PD activity was decreased to 27% of the lowest normal value. The patient was homozygous for the G6PD A− variant (Val68Met + Asn126Asp). After a 3-year follow-up, diabetes was well controlled (mean capillary blood glucose 5.4 mmol/L, HbA1c 5.3%) with diet and metformin 850 mg/day, and no relapses of haemolysis has occurred.

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3. Discussion

The occurrence of acute haemolysis in patients with diabetes and G6PD deficiency has long been reported. For example, G6PD deficiency was revealed after DKA in a male patient with KPDT2 [11]. In an African-American male patient, three episodes of severe haemolysis occurred following relapsing DKA before G6PD deficiency was diagnosed [9]. In a series of 15 patients with the Mediterranean variant of G6PD deficiency who had been admitted for a total of 36 episodes of DKA, ten haemolytic crises occurred. Since in all cases there was evidence of either concurrent bacterial infection or ingestion of drugs, the authors claimed that DKA should not be regarded as a risk factor for haemolysis [12]. These authors, and others, have also suggested that iatrogenic hypoglycaemia [2,8,10], or a decrease of glucose availability after correction of hyperglycaemia [4,6], could trigger haemolysis in patients with G6PD deficiency. Many drugs are also suspected to induce haemolysis in G6PD-deficient individuals, including oral hypoglycaemic agents. Two cases of acute haemolysis occurring a few days after the introduction of glibenclamide for type-2 diabetes have been reported [3,7]. In another patient, acute haemolysis occurred seven days after introduction of metformin and repaglinide. Haemoglobin concentration normalized after metformin was stopped [13].

Thus, many circumstances have been associated with acute haemolysis in individuals with diabetes and G6PD deficiency, and no unifying hypothesis has been proposed to explain this association. The two patients we have reported shared several characteristics including a high degree of hyperglycaemia, treatment with insulin and the absence of detectable infection or drug exposure before admission. However, they differed in several other aspects. The first patient had KPDT2. She had no metabolic acidosis on admission, and haemolysis was detected after glibenclamide and metformin were introduced. The second patient had type-1 diabetes and DKA, and was treated only with insulin.

Thus, the unique characteristic shared by all reported cases is that haemolysis occurred after admission for a decompensated hyperglycaemic state. We suggest that, in patients with G6PD deficiency, severe hyperglycaemia could further decrease G6PD activity and trigger haemolysis per se, whatever the treatment and associated conditions. This may be also facilitated by the erythrocyte depletion in glutathione, a critical antioxidant that is observed in patients with diabetes [14].

The hypothesis that hyperglycemia can lead to a decrease of G6PD activity is supported by experimental observations. In bovine endothelial aortic cells cultured at high-glucose concentration, activation of protein kinase A led to the phosphorylation of G6PD and to a decrease in its activity. The same results were observed in the kidney cortex of diabetic rats, and were reversed with insulin treatment [15]. Both post-translational mechanisms and decreased gene expression appear to be involved in the decrease of G6PD activity, that was observed after exposure to high levels of hyperglycemia (20–30 mmol/L). Recently, it has been shown that high glucose also decreased G6PD expression and activity in human islets [16]. Although a decreased G6PD activity, not related to G6PD mutations, was reported in patients with KPDT2, no correlation was observed between chronic hyperglycaemia and G6PD activity [17]. However, individual data were not given, and decreased G6PD activity might be observed only in patients with very poor diabetes control. Given the variability of G6PD activity, partly due to gene polymorphisms, population studies may also miss correlations with diabetes control. Therefore, it would be interesting to test this hypothesis by measuring G6PD activity longitudinally in the same patients at various degrees of diabetes control.

The reverse hypothesis – that G6PD deficiency could be a risk factor for the occurrence of diabetes – has also been raised. In several populations, systematic screening of G6PD activity suggested an increased prevalence of G6PD deficiency in individuals with diabetes, compared with the background rate of the general population [18–23]. Moreover, glucose intolerance and abnormal first-phase insulin secretion in response to intravenous glucose have been reported in G6PD-deficient subjects [24–26]. However, in these studies, only G6PD activity was measured, and no data were given to confirm a genetic defect. In West African patients with KPDT2, an inverse correlation between insulin secretion in response to intravenous glucagon and G6PD activity was observed [17]. It has been recently shown that inhibition of G6PD increased oxidative stress and apoptosis, and decreased insulin secretion in the MIN6 beta-cell line. Conversely, overexpression of G6PD in the cell line improved insulin secretion in response to high-glucose concentrations. Moreover, G6PD-deficient mice had reduced beta-cell mass, insulin secretion, and impaired glucose tolerance [16]. Similarly, catalase deficiency, which leads to an increased oxidative stress, may damage beta cells and impair insulin secretion, and is associated with diabetes [27].

Altogether, these observations have suggested that a vicious circle could occur, in which G6PD deficiency and diabetes aggravate each other [16]. Thus, G6PD may play a central role in the so-called “glucose toxicity”, as already shown in other pathways of chronic oxidative stress [28].

4. Conclusion

G6PD deficiency affects over 400 millions people worldwide. The occurrence of KPDT2 has been reported in patients from African origin, who are potentially affected by the most frequent G6PD variant A−. We suggest that, in patients at risk for G6PD deficiency, the possibility of haemolysis should be explored in the few days following diabetes decompensation. Haemolysis may be underdiagnosed, since a drop in haematocrit and haemoglobin levels may be regarded as the result of rehydration, and because haemolysis may be self-limiting in many patients [1]. Moreover, since sulfonylureas are potentially oxidative drugs, metformin may be preferable for maintaining remission of insulin dependency in patients with KPDT2. Finally, converging arguments suggest that G6PD deficiency and diabetes may be aetiologically linked.
Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

References