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RAPID COMMUNICATION:

High Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency without Gene Mutation Suggests a Novel Genetic Mechanism Predisposing to Ketosis-Prone Diabetes

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Abstract

Context: Ketosis-prone diabetes (KPD) is mostly observed in males of West African descent and is characterized by phasic or permanent insulin dependence without apparent autoimmune process.

Objective: KPD subjects display a propensity to hyperglycemia-induced acute insulin deficiency, suggesting that they exhibit a propensity to oxidative stressin β-cells.The enzyme glucose-6-phosphate dehydrogenase (G6PD) is a defense mechanism against oxidative stress, and G6PD deficiency, an X-linked genetic disorder with male predominance, is frequent in West Africans. We hypothesized that mutations in the *G6PD* gene could predispose to KPD.

Design: We studied G6PD erythrocyte enzyme activity and the insulin secretory reserve (glucagon-stimulated C peptide) in a cohort of hospitalized West Africans with KPD (n = 59) or type 2 diabetes (T2DM; n = 59) and in normoglycemic controls (n = 55). We also studied the *G6PD* gene in an extended population of KPD patients (n = 100), T2DM patients (n = 59), and controls (n=85).

Results: The prevalence of G6PD deficiency was higher in KPD than in T2DM and controls (42.3%; 16.9%; 16.4%; $P = 0.01$). In KPD, but not in T2DM, insulin deficiency was proportional to the decreased G6PD activity (r = 0.33; $P = 0.04$). We found no increase in the prevalence of *G6PD* gene mutations in KPD compared with T2DM and controls.Rather,we found a 20.3% prevalence of G6PD deficiency in KPD without gene mutation.

Conclusions: This study suggests that 1) G6PD deficiency alone is not causative of KPD; and 2) alterations in genes controlling both insulin secretion and G6PD-mediated antioxidant defenses may contribute to the predisposition to KPD in West Africans. (***J Clin Endocrinol Metab*** **90: 4446–4451, 2005**)

KETOSIS-PRONE DIABETES (KPD), also referred to as idiopathic type 1 diabetes, is a phenotypically defined form of diabetes mostly observed in male subjects of West African ancestry (such as African-Americans) and is characterized by phasic or permanent insulin dependence, leading to diabetic ketoacidosis (DKA) without a patent autoimmune process (1). Like maturity-onset diabetes of the young, KPD is a genetically heterogeneous form of diabetes, and we have recently reported that functional gene variants in the β-cell transcription factor PAX4 predispose to the disease in a subset of patients (2). KPD subjects also show a propensity to hyperglycemia-induced insulin deficiency, as suggested by the close association between episodes of hyperglycemia and the phasic evolution of insulin dependence. 1) After the initial DKA, normalization of blood glucose is followed by long-term normoglycemic remissions without insulin treatment. 2) Relapses in DKA and insulin dependence are observed after a short period of hyperglycemia (1, 3). The genetic basis for this predisposition to glucose toxicity remains unknown.

In diabetes, chronic elevation of blood glucose impairs glucose-stimulated insulin secretion (4–6) and puts pancreatic islets at risk for oxidative damage (7). Pancreatic β-cells have low

antioxidant protection (8, 9), and both in vivo in rodent models of type 2 diabetes and *in vitro*, high glucose concentrations increase the level of reactive oxygen species (ROS), leading to oxidative stress within the pancreatic islets (10, 11). Thus, hyperglycemia induces chronic oxidative injury, which is initially responsible for impairment of insulin secretion and ultimately leads to β-cell apoptosis.

The intracellular enzyme glucose-6-phosphate dehydrogenase (G6PD) catalyzes the first step of the pentose phosphate pathway, producing reduced nicotinamide adenine dinucleotide (NADPH), the principal cellular reductant in all cell types (Fig. 1). Although there are other metabolic pathways that produce NADPH, G6PD is the predominant source for cellular defense against oxidative stress (12, 13). G6PD deficiency is an X-linked genetic disorder, mostly affecting males, and showing a high prevalence in West Africans (14). Thus, we hypothesized that mutations in the *G6PD* gene, leading to G6PD deficiency, may predispose to ketosis-prone diabetes.

Patients and Methods

Patient and control populations

For the clinical study, we examined 59 consecutive KPD patients (40 men and 17 women), 59 patients with type 2 diabetes (T2D; 32 men and 27 women), and 55 normoglycemic controls (30 men and 25 women). The criteria used to define ketosis-prone diabetes have been described previously (1). Briefly, KPD was defined as new-onset diabetes without precipitating illness (infection or stress), with the presence of strong ketosis (urinary ketones,>80 mg/dl) or DKA, and in the absence of autoantibodies to islet cells and to glutamic acid decarboxylase 65. T2DM was defined as diabetes treated by diet or oral hypoglycemic agents, with no episode of ketosis and in the absence of autoantibodies to islet cells and glutamic acid decarboxylase 65. The control population was composed of subjects with normal fasting blood glucose and without a known family history of diabetes. Diabetic and control populations were comparable with regard to age.

The extended KPD and control populations used for the genetic study have been described and consisted of 100 KPD patients (71 men and 29 women) and 85 normoglycemic control subjects (41 men and 44 women) (2). All patients and controls originated from West Africa. The local ethical committee approved the study.

Measurement of erythrocyte G6PD enzyme activity

We measured the erythrocyte G6PD enzyme activity 48 h after normalization of blood glucose using the spectrophotometric method (15). Erythrocyte homogenate was saturated with G6PD and NADPH, followed by spectrophotometric detection of NADPH appearance at the absorbance of 340 nm in the kinetic mode. The results are calculated by evaluating the increase in OD per minute (slope) for unknowns against the slope for a standard with a known G6PD activity. Total erythrocyte enzyme activity was determined (units per gram of hemoglobin) and residual erythrocyte enzyme activity (REA) was calculated by dividing the observed value for each patient by the value of standard with known normal G6PD activity. G6PD deficiency was defined as an REA less than 40% of the normal value (16). The

presence of G6PD deficiency was confirmed by a second measurement after at least 3 months of metabolic stabilization.

Insulin secretion

Pancreatic insulin secretory reserve was assessed 48 h after resolution of ketosis and normalization of blood glucose by measuring the C peptide level before and 8 min after the iv injection of 1 mg glucagon as previously described (1). The test was performed 12 h after an overnight fast and before the morning insulin injection in a subset of patients who agreed to participate and whose baseline characteristics were representative of the rest of the group. C Peptide was measured by RIA (IRMA-C-PEP, CIS Bio International, Gif-sur-Yvette, France).

G6PD gene screening

Genomic DNA was extracted from peripheral leukocytes in 100 unrelated KPD patients. The coding region of the human *G6PD* gene was amplified in five different reactions: exon 1: primers G6PD1F2 (CACAAGGAGTGATTTGGGCA) and G6PD-1R (GCACTTCCTGGCTTTTAAGA); exons 2 and 3: primers G6PDAF (CAGCCACTTCTAACCACACACCT) and G6PDAR (CCGAAGTTGGCCATGCTGGG); exon 4: primers G6PD-4F (CGGACTCAAAGAGAGGGGCT) and G6PD-4R (GCACTGCCTGGGCCAGCCT); exons 5–7: primers G6PD5F (GCAGCTGTGATCCTCACTCC) and G6PD7R (CTGCGACAGGGCATGCTCCT); exons 8–10: primers G6PD8F (GCACCCCAACTCAACACCCA) and G6PD-9R (CGCCCACCCTCCACACTGCT); exons 11 and 12: primers G6PD11F (GAG AAG GAG CAG TGT GGA GG) and G6PD12R (GAG GAG AGG CAT GAG GTA GC); and exon 13: primers G6PD13F (ATG GCA GGT GAG GAA AGG GTG) and G6PD13R (GAC CCA GTG GCC AAT AAG CTC). Sequencing reactions were performed with the BigDye terminator kit (Applied Biosystems, Foster City, CA). Sequencing was performed on an ABI PRISM 3700 automated DNA sequencer (Applied Biosystems). Sequences were analyzed using Sequence Navigator (Applied Biosystems).

Single nucleotide polymorphism (SNP) genotyping

G6PD gene variants were genotyped in T2DM and controls using a TaqMan allelic discrimination assay system after designing flanking primers and fluorogenic probes, both of which were specific to target alleles, as previously described (2).

Statistical analysis

Results are expressed as the frequency or as the mean ± sd unless otherwise stated. Group comparison was performed by x^2 tests, a test for proportions was performed with continuity correction when necessary, and ANOVA and Mann-Whitney U test for means were conducted. The relation between insulin secretion and residual enzyme activity was analyzed by Spearman's rank-order correlation. The haplotypes for the females in each of the three groups were constructed for SNPs A202G, A376G, A542T, and T968C using the SNPHAP program (http://www.gene.cimr.cam.ac.uk/clayton/software/snphap.txt). The haplotypes for the males were constructed based upon the observed of their hemizygous genotypes. The

Fisher-Freeman-Halton exact test was used to test for differences in haplotype frequencies among the three groups (controls, T2DM, and KPD), because some of the expected values in the contingency table were less than 2.

Results

Prevalence of G6PD deficiency is increased in KPD

We assessed the G6PD REA in a cohort of KPD subjects, T2D subjects, and normoglycemic controls. Although T2D subjects and controls had similar REAs, the REA was 30% lower in KPD subjects (Fig. 1A). The prevalence of G6PD deficiency (REA, 40% of the normal value) was similar in T2D patients and controls, but was 2-fold higher in KPD subjects (Fig. 1B).

G6PD deficiency is associated with the severity of pancreatic β-cell failure

We examined the hypothesized relationship between G6PD deficiency and insulin secretory reserve during an iv glucagon stimulation test in all diabetic subjects. The C peptide response to glucagon in each group is presented in Fig. 1C. In T2D patients, there was no significant correlation between G6PD deficiency and insulin deficiency (r = 0.27; $P = 0.3$). Conversely, KPD patients presenting with G6PD deficiency had lower insulin secretory reserve compared with those with G6PD REA greater than 40% (increase in C peptide between 0 and 8 min, 0.90 ± 0.60 *vs.* 1.33 ± 0.53 μg/liter; $P = 0.03$). Moreover, in KPD patients, the degree of decreased G6PD activity was correlated to the severity of insulin deficiency (Fig. 1D). This correlation was stronger in insulin-dependent KPD patients (r = 0.62; $P = 0.03$).

Analysis of coding variants of the G6PD gene in KPD

G6PD deficiency could result from 1) *G6PD* gene mutations, or 2) alterations in factors controlling G6PD expression/activity (17). *G6PD* gene variations are common in West Africans, and the most common mutations associated with biochemical G6PD deficiency through enzyme instability consist of the amino acid change $Asn^{126}Asp$ (A376G) associated with either amino acid change $Met^{68}Val$ (G202A) or, less frequently, $Asp^{181}Val$ (A542T) or $Leu^{323}Pro$ (T968C). The last three mutations are not found alone; they are always associated with $Asn^{126}Asp$, the double mutation creating enzyme instability and G6PD deficiency (G6PD A^-). $Asn^{126}Asp$ is frequently found alone, but does not cause G6PD deficiency (G6PD A^+). The wild-type gene without mutation is the form G6PD B (14, 18).

We screened the coding region of the *G6PD* gene in 100 unrelated KPD subjects, and we genotyped the observed variants in a common type 2 diabetic and normoglycemic control population (Table 1). All the mutations described above were detected in KPD subjects at a frequency not different from those in the T2D and control populations (Table 1). Furthermore, we analyzed the haplotypes for the SNP A202G, A376G, A542T, and T968C in KPD, T2D, and control subjects. There was no statistical difference in haplotype frequencies among the three groups ($P = 0.76$).

Prevalence of G6PD mutations in subjects with G6PD deficiency

The *G6PD* gene mutations described in Table 1 explained half of the G6PD deficiencies observed in KPD (G6PD A^-). The frequency of A^- functional gene mutations associated with G6PD deficiency was not significantly increased in the KPD patients (22%) compared with T2DM (16.9%; $P = 0.5$) and control subjects (14.5%; $P = 0.3$; Table 2). This may be related to our small sample size. However, in the remaining KPD patients with G6PD deficiency, no other functional mutation was found (G6PD B). Rather, we observed a 20.3% prevalence of G6PD deficiency with no mutation, which was not observed in the T2DM subjects and controls. In these G6PD-deficient subjects, we did not find variants in intronic regulatory sequences (data not shown; Table 2).

Discussion

We assessed whether deficiency in the antioxidant enzyme G6PD could be implicated in KPD, a form of diabetes with phasic or permanent insulin dependence, mostly observed in male subjects of West African ancestry. G6PD deficiency has a high prevalence in West African populations, which confers a selective advantage against malaria (19).

The main finding of this study is the high prevalence of G6PD deficiency without *G6PD* gene mutation in KPD, a unique and phenotypically defined form of diabetes (1, 2), which is not observed in T2D, a more heterogeneous group. Several studies have reported different levels of associations between diabetes and G6PD deficiency in various populations (20–25). The strongest association was observed in Saudi patients in which the prevalence G6PD deficiency was 12.4% compared with 2.0% in a healthy control population (25). In these studies, the contribution of the *G6PD* gene has not been ascertained. We found no significant increase in *G6PD* mutations in the KPD population, suggesting that G6PD deficiency alone does not predispose to KPD. Rather, we found a high prevalence (20%) of KPD subjects with G6PD deficiency without *G6PD* coding or intronic mutations. Gene promoter mutations are extremely rare; they have never been described in the G6PD gene, and it is unlikely that they explain such a high frequency of G6PD deficiency.

The second finding of this study is that in KPD, but not in T2DM, the severity of deficit in G6PD activity is correlated to the severity of insulin deficiency. This suggests that G6PD activity normally protects β-cell function. This is supported by the study by Monte Alegre *et al.* (26) in which a blunted acute insulin response to glucose was observed in nondiabetic G6PD-deficient subjects of West African descent. G6PD helps keep glutathione in its reduced form, which acts, in concert with glutathione peroxidase, as a scavenger for ROS (14). In rats, hyperglycemia is followed by a major increase in glutathione peroxidase in islets, which contributes to their ability to survive under conditions of oxidative stress (27). In addition, inhibition of glutathione synthesis in islets decreases the insulin gene expression (11). Finally, inhibition of G6PD enhances apoptosis induced by ROS in β-cells (13). Thus, in KPD patients, by decreasing glutathione peroxidase-mediated antioxidant defenses, G6PD deficiency could exacerbate oxidative injury in β-cells. This may predispose to β-cell dysfunction.

An alternate explanation for the observed correlation between G6PD and insulin deficiency could be that severe insulin deficiency and metabolic decompensation in KPD can itself alter G6PD activity. We believe that this is unlikely in our study for the following reasons. 1) We studied a small group of autoimmune type 1 diabetic patients with absolute insulin deficiency (1), and we found a similar prevalence of G6PD deficiency as in the controls and T2DM subjects (data not shown). 2) To avoid the effect of metabolic decompensation on G6PD activity, patients were studied while normoglycemic, and we performed a second measurement after a long period of metabolic stabilization. Finally, in a heterogeneous population of 250 diabetic patients followed in our department, we did not find a correlation between G6PD activity and chronic hyperglycemia (data not shown).

The absence of a clearly defined association between G6PD mutations and KPD may seem contradictory with the role of G6PD deficiency in β-cell failure. We believe that because or our sample size, we cannot exclude this association.

How can we integrate these findings into the pathogenesis of KPD? Genetic alterations in transcription factors controlling the normal development/function of pancreatic β-cells have been implicated in maturity-onset diabetes of the young, and we have recently shown that a gene variant in the transcription factor PAX4 (R133W), specific to West Africans, predisposes to KPD (2). We found no association between the R133W variant and G6PD deficiency (data not shown).

We therefore hypothesize that genetic alterations in one or multiple genes involved in both regulation of insulin secretion and *G6PD* expression by β-cells could predispose a subset of subjects to KPD. Such mutations would 1) lead to insulin deficiency and decreased G6PD-mediated antioxidant defense, thereby contributing to the specific phenotype of phasic β-cell dysfunction; and 2) confer a selective advantage against malaria and explain the high prevalence of G6PD deficiency without *G6PD* mutations in KPD (Fig. 2).

In summary, we found a high prevalence of G6PD deficiency without *G6PD* mutations in West African KPD subjects with severe insulin deficiency. Our data suggest that G6PD deficiency alone is not causative of KPD. Rather, alterations in genetic regulators of both β-cell function and *G6PD* expression may contribute to KPD. This finding may help focus research efforts on the genetic predisposition to this disease.

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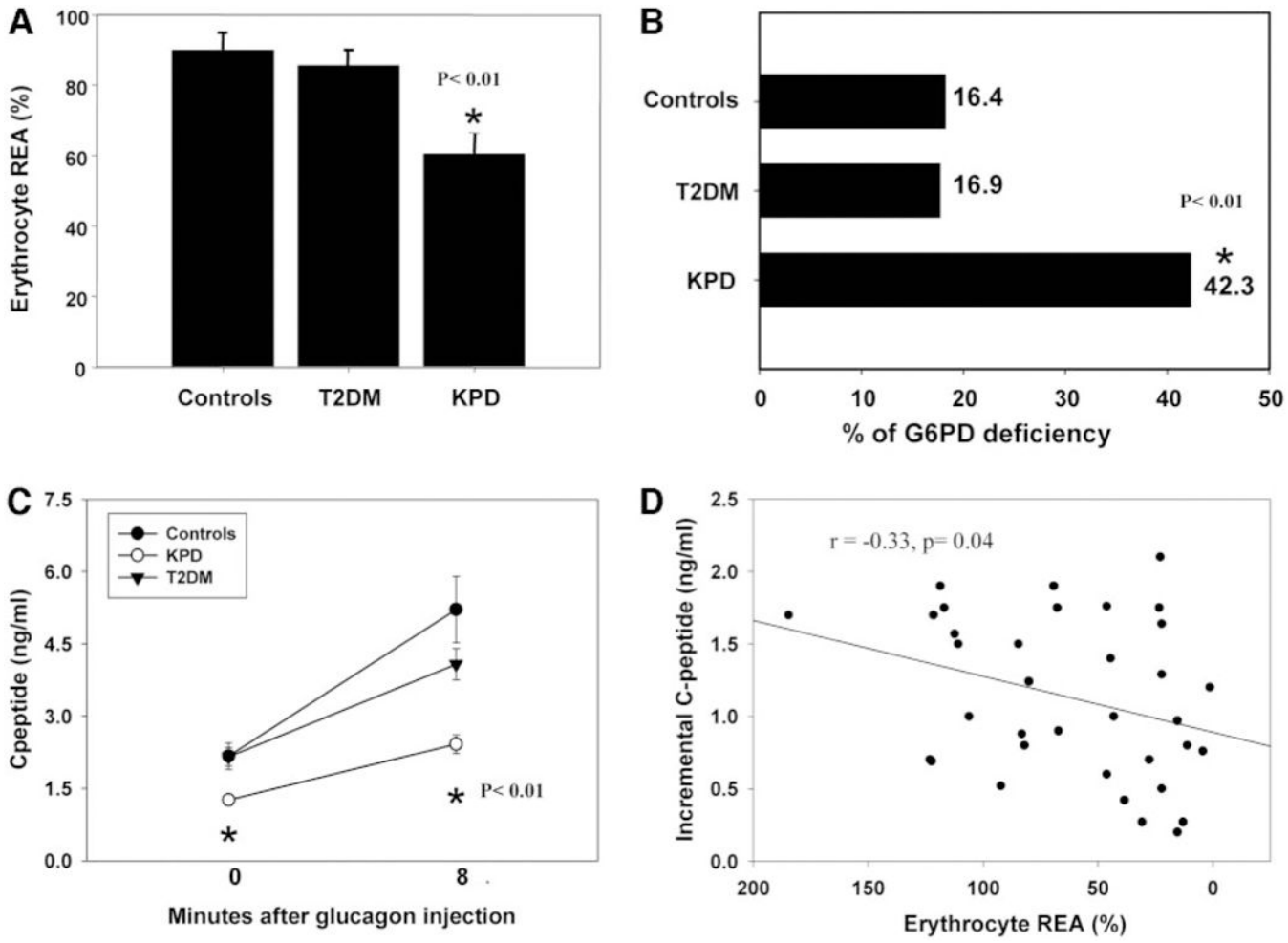

FIG. 1.

Prevalence of G6PD deficiency in KPD. A, REA in controls, T2DM, and KPD subjects. Results are expressed as the mean ± SE (percentage). *, By ANOVA: F = 7.80; $P = 0.001$. B, Prevalence of erythrocyte G6PD deficiency in controls, T2DM, and KPD subjects (percentage of the population). *, $P = 0.005$, KPD *vs.* T2DM; $P = 0.006$, KPD *vs.* controls. Relation between G6PD deficiency and insulin secretion in KPD. C, β-Cell insulin secretory reserve was assessed in a cohort of normoglycemic controls (n = 7), KPD patients (n = 34), and T2DM patients (n = 36) by measuring basal C peptide (0 min) and C peptide response after an iv glucagon injection (8 min). Data represent the mean ± SE. *, $P < 0.01$. D, Correlation between residual erythrocyte G6PD activity (percentage) and glucagon-stimulated incremental C peptide (nanograms per milliliter) in 34 patients with KPD. Spearman rank-order correlation coefficient: $r_s = -0.33$; $P = 0.04$.

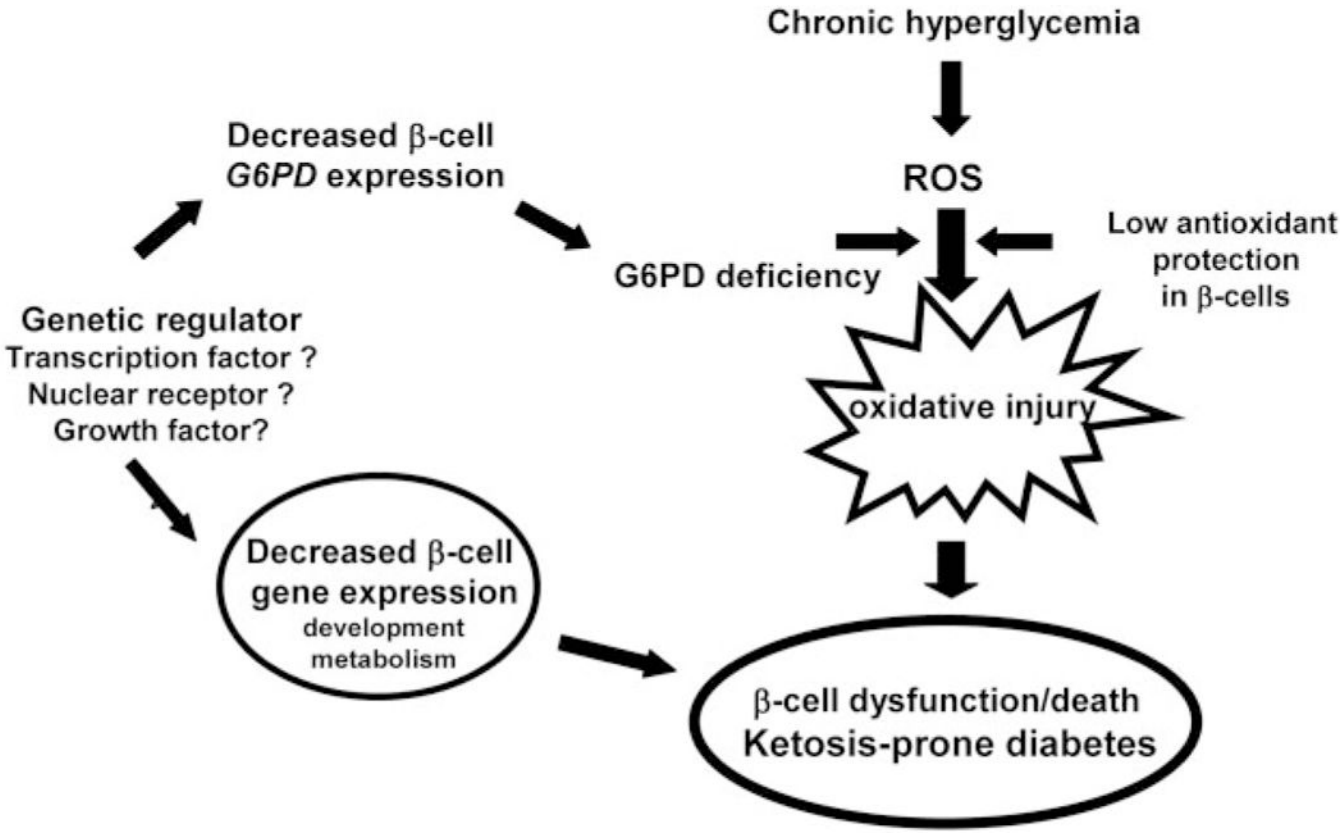

FIG. 2.
Proposed mechanism for the predisposition to KPD.

TABLE 1.

Variants of the *G6PD* gene in KPD

Nucleotide change	Position	Amino acid change	Genotype frequency			*P* value[a]
			KPD subjects (n = 100)	T2D subjects (n = 59)	Controls (n = 85)	
G202A	Exon 3	$Met^{68}Val$	A/A: 12 (12.0%)	8 (13.6%)	9 (10.5%)	0.93
			C/A: 9 (9.0%)	5 (8.5%)	8 (9.5%)	
			C/C: 79 (79.0%)	46 (78.0%)	68 (80.0%)	
A376G	Exon 4	$Asn^{126}Asp$	G/G: 25 (25.0%)	14 (23.7%)	24 (28.2%)	0.81
			A/G: 13 (13.0%)	7 (11.9%)	9 (10.6%)	
			A/A: 62 (62.0%)	38 (64.4%)	52 (61.2%)	
A542T	Exon 5	$Asp^{181}Val$	T/T: 1 (1.0%)	1 (1.7%)	1 (1.2%)	
			A/T: 0 (0%)	0 (0%)	0 (0%)	
			A/A: 99 (99.0%)	58 (98.3%)	84 (98.8%)	
T968C	Exon 8	$Leu^{323}Pro$	T/T: 3 (3.0%)	1 (1.7%)	2 (2.3%)	0.78
			C/T: 0 (0%)	0 (0%)	0 (0%)	
			C/C: 97 (97.0%)	58 (98.3%)	83 (97.7%)	
G1048C	Exon 8	$Asp^{353}His$	G/G: 0 (0%)	1 (1.7%)	0 (0%)	0.63
			G/C: 2 (2.0%)	0 (0%)	1 (1.2%)	
			C/C: 98 (98.0%)	58 (98.3%)	84 (98.8%)	
G1116A	Exon 9	Silent	A/A: 12 (12.0%)	N/D	N/D	
			G/A: 3 (3.0%)			
			G/G: 85 (85.0%)			
C1311T	Exon 11	Silent	T/T: 11 (11%)	N/D	N/D	
			C/T: 10 (10%)			
			C/C: 79 (79%)			
C1311T	Exon 12	Silent	T/T: 4 (4%)	N/D	N/D	
			C/T: 3 (3%)			
			C/C: 93 (93%)			
A1477G	Exon 13	Silent	G/G: 1 (1%)	N/D	N/D	
			A/G: 0 (0%)			
			A/A: 99 (99%)			

N/D, Not determined.

[a]Differences in genotype frequencies between ketosis-prone diabetic subjects and controls were tested using the X^2 test.

TABLE 2.

G6PD mutations and G6PD deficiency in West Africans

Genotype	Population					
	KPD subjects (n = 59)		T2D subjects (n = 59)		Controls (n = 55)	
	n (%)	G6PD REA (U/mg Hb)	n (%)	G6PD REA (U/mg Hb)	n (%)	G6PD REA (U/mg Hb)
G6PD A^-						
Hemizygous males	11 (18.6)	13.1 ± 1.5	8 (13.5)	13.5 ± 2.1	6 (10.9)	18.7 ± 2.6
Homozygous females	2 (3.4)	19.0 ± 4.5	2 (3.4)	18.8 ± 3.4	2 (3.6)	18.8 ± 3.4
Heterozygous females	6 (10.1)	54.5 ± 3.4	6 (10.1)	55.2 ± 2.5	2 (3.6)	57.9 ± 13.2
G6PD A^+						
Hemizygous males	6 (10.1)	75.2 ± 9.5	2 (3.4)	86.6 ± 21	8 (14.5)	87.9 ± 7.6
Homozygous females	1 (1.7)	77.1	2 (3.4)	78.6 ± 12.8	2 (3.6)	101.1 ± 27.0
Heterozygous females	1 (1.7)	67.2	2 (3.4)	72.4 ± 10.9	0 (0)	
G6PD B						
Males with deficiency	8 (13.5)	20.1 ± 4.6	0 (0)		1 (1.8)	34.7
Females with deficiency	4 (6.8)	17.9 ± 7.0	0 (0)		0 (0)	
Males without deficiency	18 (30.5)	96.1 ± 4.0	19 (32.2)	104.1 ± 4.3	14 (25.4)	113.1 ± 5.7
Females without deficiency	2 (3.4)	76.3 ± 13.0	18 (30.5)	111.9 ± 9.2	20 (36.4)	104.6 ± 3.6

G6PD A^-, $G6PD^{A376G/G202A}$ + $G6PD^{A376G/A542T}$ + $G6PD^{A376G/T968C}$; G6PD A^+, $G6PD^{A376G}$; G6PD B, wild-type G6PD. Values for G6PD REA represent the mean ± SE.