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The Relationship Between β-Cell Function and Glycated Hemoglobin

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OBJECTIVE—The study objective was to assess the relationship between β-cell function and HbA_{1c}.

RESEARCH DESIGN AND METHODS—A total of 522 Mexican American subjects participated in this study. Each subject received a 75-g oral glucose tolerance test (OGTT) after a 10–12-h overnight fast. Insulin sensitivity was assessed with the Matsuda index. Insulin secretory rate was quantitated from deconvolution of the plasma C-peptide concentration. β-Cell function was assessed with the insulin secretion/insulin resistance (IS/IR) (disposition) index and was related to the level of HbA_{1c}.

RESULTS—At HbA_{1c} levels <5.5%, both the Matsuda index of insulin sensitivity and IS/IR index were constant. However, as the HbA_{1c} increased >5.5%, there was a precipitous decrease in both the Matsuda index and the IS/IR index. Subjects with HbA_{1c} = 6.0–6.4% had a 44 and 74% decrease in the Matsuda index and the IS/IR index, respectively, compared with subjects with HbA_{1c} <5.5% ($P < 0.01$ for both indices). Subjects with normal glucose tolerance and HbA_{1c} <5.7% had β-cell function comparable to that of subjects with normal glucose tolerance with HbA_{1c} = 5.7–6.4%. However, subjects with impaired fasting glucose or impaired glucose tolerance had a marked decrease in β-cell function independent of their HbA_{1c} level.

CONCLUSIONS—The results of the current study demonstrate that in Mexican Americans, as HbA_{1c} increases >6.0%, both insulin sensitivity and β-cell function decrease markedly. Performing an OGTT is pivotal for accurate identification of subjects with impaired β-cell function.

In 1997, the American Diabetes Association (ADA) revised its criteria for the diagnosis of type 2 diabetes and determined that subjects with fasting plasma glucose (FPG) >126 mg/dL and 2-h plasma glucose ≥200 mg/dL are considered to have type 2 diabetes (1). These cut points were chosen on the basis of the increased incidence of diabetic retinopathy rather than on the presence of metabolic abnormalities (i.e., insulin resistance and β-cell dysfunction) that are responsible for type 2 diabetes (1).

Impaired β-cell function is the principal factor responsible for the development and progression of type 2 diabetes (2). In addition to β-cell dysfunction, subjects with type 2 diabetes manifest severe insulin resistance in skeletal muscle, liver, and adipocytes (3–6). Insulin resistance is the earliest metabolic abnormality detected in subjects destined to develop type 2 diabetes. In response to insulin resistance, the β-cell appropriately increases insulin secretion and normal glucose tolerance (NGT) is maintained. However, when β-cell failure ensues, glucose intolerance develops. Initially, this is manifest as impaired glucose tolerance (IGT) and subsequently as overt diabetes (1). Thus, impaired β-cell function is an essential condition in (1).

Although normal β-cell function is pivotal to the maintenance of NGT, β-cell failure develops long before hyperglycemia becomes evident. Recent studies have demonstrated that the decrease in β-cell function begins in the range considered to be well within NGT according to the 1997 ADA criteria (7–10). Studies that have related β-cell function to FPG (7,8) and 2-h plasma glucose (9,10) concentrations reported that β-cell function progressively declined with the increase in both FPG and 2-h plasma glucose from the low normal range to the high normal range, to the impaired glucose tolerant and diabetic ranges. These results indicate that the decrease in β-cell function, which is the primary factor responsible for the deterioration of glucose tolerance, is a continuum with no threshold above which develops.

The ADA recently changed the diagnostic criteria for to include individuals with HbA_{1c} ≥6.5%; high-risk individuals are defined as having an HbA_{1c} = 5.7–6.4% (11,12). No data are available relating the HbA_{1c} to β-cell function. Therefore, the aim of the current study was to examine the relationship between β-cell function and HbA_{1c}.

RESEARCH DESIGN AND METHODS

Subjects

The participants in this study included 522 subjects of Mexican American descent who were part of the San Antonio Veterans Administration Genetic Epidemiology Study (5). In the Veterans Administration Genetic Epidemiology Study, Mexican American families with one diabetic and one nondiabetic parent and two siblings with were recruited through advertising within the medical center and in local newspapers. Subjects responding to the advertisement were screened with a 75-g oral glucose tolerance test (OGTT). All family members who responded to the advertisement and fulfilled the inclusion criteria agreed to participate in the study. This study reports on 521 subjects who were free of diabetes and received a 75-g OGTT and had NGT, IGT, impaired fasting glucose (IFG), or based on the 2003 glucose criteria established by the ADA (13). None of the subjects with knew that he/she had diabetes, and was diagnosed for the first time with the OGTT. Thus, no subject with in the study had used antidiabetic medications.

All subjects had normal liver, cardiopulmonary, and kidney function as

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determined by medical history, physical examination, screening blood tests, electrocardiogram, and urinalysis. No subject with NGT, IFG, IGT, or was taking any medication known to affect glucose tolerance. Body weight was stable (±2 kg) for at least 3 months before the study in all subjects. No subject participated in an excessively heavy exercise program. The study protocol was approved by the institutional review board of the University of Texas Health Science Center, San Antonio, and informed written consent was obtained from all subjects before their participation. All studies were performed at the General Clinical Research Center of the University of Texas Health Science Center at 0800 h after a 10–12-h overnight fast.

OGTT

Before the start of the OGTT, a small polyethylene catheter was placed into an antecubital vein and blood samples were collected at −30, −15, 0, 15, 30, 45, 60, 75, 90, 105, and 120 min for the measurement of plasma glucose, C-peptide, and insulin concentrations. On the day of the OGTT, height, weight, and waist circumference were determined at the narrowest part of the torso, and a blood sample was obtained for HbA_{1c} measurement.

Analytic techniques

Plasma glucose concentration was measured by the glucose oxidase reaction (Glucose Oxidase Analyzer, Beckman, Fullerton, CA). Plasma insulin and C-peptide concentrations were measured by radioimmunoassay (Linco Research, St. Louis, MO). HbA_{1c} was measured with high-performance liquid chromatography.

Calculations

Insulin secretory rate (ISR) during the OGTT was calculated from deconvolution of the plasma C-peptide concentration as previously described (8), and the incremental area under the ISR curve was related to the incremental area under the plasma glucose curve ($\Delta ISR[AUC]_{0–120}/\Delta G[AUC]_{0–120}$). The insulin secretion/insulin resistance (IS/IR) (disposition) index was determined by dividing ΔISR/ΔG by the severity of insulin resistance [$\Delta ISR(AUC)_{0–120}/\Delta G(AUC)_{0–120} \div IR$], as measured by the inverse of the Matsuda index (14). The Matsuda index incorporates both hepatic and muscle components of insulin resistance, correlates well with the measurement of insulin sensitivity from the euglycemic insulin clamp, and was calculated as follows:

$$\text{Mastuda index} = 10,000 / \sqrt{(FPG \times FPI \times (mean PG \times mean PI)} \quad (1)$$

The incremental area under the ISR curve [$\Delta ISR(AUC)_{0–120}$] and the incremental area under the plasma glucose concentration curve [$\Delta G(AUC)_{0–120}$] were calculated according to the trapezoid rule.

Statistical analysis

Subjects were divided into deciles based on the HbA_{1c}, and the mean HbA_{1c} in each decile was related to the mean IS/IR index in the same decile. Data are presented as the mean ± SD. For comparison between two groups, Student *t* test was used. To compare the mean of more than two groups, ANOVA was used. Significant differences were confirmed by the Bonferroni test. Statistical significance was considered at $P < 0.05$.

Table 1—*Characteristics of study participants: Diagnosis of glucose tolerance status is based on the 2003 ADA criteria*

Age (years)	47 ± 1
Sex (M/F)	178/344
BMI (kg/m^2)	33.0 ± 0.3
Waist circumference (cm)	100.9 ± 0.8
FPG (mg/dL)	120 ± 2
HbA_{1c} (%)	6.2 + 0.07
NGT (%)	21.5
IFG or IGT (%)	35.9
(%)	42.6

RESULTS—Table 1 presents the characteristics of the study participants. Some 21.5% of subjects had NGT, 35.9% had IFG or IGT, and 42.6% had according to the 2003 ADA criteria (13). However, if subjects were classified on the basis of the HbA_{1c} level according to the ADA clinical practice recommendation (12), only 29.5% had ($HbA_{1c} \geq 6.5\%$) and 21.4% were characterized as high-risk individuals (HbA_{1c} = 5.7–6.4%), whereas 49.1% had NGT ($HbA_{1c} < 5.7\%$) (Table 2).

We divided subjects with $HbA_{1c} < 5.7\%$ (columns A and B in Table 3) and high-risk individuals with HbA_{1c} = 5.7–6.4% (columns D and E in Table 3) into two groups based on plasma glucose values during the OGTT: *i*) NGT (FPG <100 mg/dL and 2-h plasma glucose <140 mg/dL, columns A and D) and *ii*) IFG or IGT (FPG = 100–125 mg/dL or 2 h plasma glucose = 140–199 mg/dL, columns B and E), and compared the metabolic characteristics of the various groups. Table 3 demonstrates that, in subjects with NGT with HbA_{1c} = 5.7–6.4% (column D), the Matsuda index of insulin sensitivity was decreased by 35% compared with NGT subjects with $HbA_{1c} < 5.7\%$ (column A) (3.1 ± 0.5 and 4.5 ± 0.4, respectively, $P = 0.03$). However, the IS/IR (disposition) index was comparable between the two groups (Table 3). Likewise, in subjects with IFG or IGT and an HbA_{1c} = 5.7–6.4% (column E), the Matsuda index of insulin sensitivity was significantly reduced compared with subjects with $HbA_{1c} < 5.7\%$ (column B) (3.1 ± 0.5 and 2.2 ± 0.2, respectively, $P < 0.001$). However, the IS/IR index in subjects with IFG or IGT was similarly reduced in both groups (Table 3). Changing the HbA_{1c} cut points to <5.5%, 5.5–6%, 6.0–6.49%, and 6.5–7.0% (Table 3) demonstrated that NGT groups with $HbA_{1c} < 5.5\%$ (column G) and HbA_{1c} = 5.5–6.0% (column H) were more insulin sensitive and had a greater insulin secretion/insulin resistance (disposition) index compared with subjects with IFG or IGT with $HbA_{1c} < 5.5\%$ (column H) and HbA_{1c} = 5.5–6% (column K). However, subjects with HbA_{1c} = 6–6.5% (column M) and 6.5–7% (column N) had a marked decrease in the insulin secretion/insulin resistance index (0.1 ± 0.01 and

Table 2—*Relationship between HbA_{1c} and diagnostic category (NGT, IFG or IGT,) based on glucose criteria during the OGTT according to the ADA 2003 criteria*

	NGT	IFG or IGT		Total
$HbA_{1c} < 5.7\%$	97	128	31	256
HbA_{1c} = 5.7–6.4%	15	56	40	111
$HbA_{1c} \geq 6.5\%$	0	3	151	154
$HbA_{1c} < 5.5\%$	90	103	28	221
HbA_{1c} = 5.5–6.0%	18	62	21	101
$HbA_{1c} > 6.0$	5	22	172	199

0.07 ± 0.02, respectively) compared with subjects with HbA_{1c} <6.0%.

When all subjects were pooled into one group and the Matsuda index of insulin sensitivity and IS/IR index were related to the HbA_{1c} as a continuous variable, the relationship between the two was highly nonlinear. Whole-body insulin sensitivity, measured with the Matsuda index, remained unchanged up to an HbA_{1c} = 5.5%. However, as the HbA_{1c} increased >5.5%, there was a steep decrease in the Matsuda index (Fig. 1). Subjects with HbA_{1c} = 6.0–6.4% had a 44% decrease in insulin sensitivity compared with subjects with HbA_{1c} <5.5% ($P < 0.01$).

The postload plasma glucose concentration, measured as the incremental area under the plasma glucose curve ($\Delta G_{0–120}$), remained unchanged with the increase in HbA_{1c} up to a value = 5.5%, and, as observed when the HbA_{1c} exceeded 5.5%, $\Delta G_{0–120}$ progressively increased with the increase in HbA_{1c}. Likewise, insulin secretion, measured as the incremental area under the ISR ($\Delta ISR_{0–120}/\Delta G_{0–120}$) curve, remained unchanged up to an HbA_{1c} = 5.5%, and, as observed when the HbA_{1c} increased >5.5%, $\Delta ISR_{0–120}/\Delta G_{0–120}$ progressively decreased with further increases in the HbA_{1c}. β-Cell function, measured with the IS/IR (disposition) index, did not change significantly up to an HbA_{1c} = 5.7%. However, as the HbA_{1c} increased >5.7%, there was a marked decrease in β-cell function. Subjects with HbA_{1c} = 6.0% had a 62% decrease in the IS/IR index compared with subjects with HbA_{1c} <5.7%.

CONCLUSIONS—Although the HbA_{1c} represents the mean plasma glucose level (fasting and postprandial) throughout the day, the results of the current study demonstrate that, in Mexican Americans, the relationship between β-cell function and HbA_{1c} differs significantly from the relationship between β-cell function and the fasting and 2-h plasma glucose concentrations (7–10). Similarly, the relationship between insulin sensitivity and HbA_{1c} differs from that obtained using the fasting and 2-h plasma glucose concentrations (3). Although both insulin sensitivity (measured with the euglycemic insulin clamp) (3) and β-cell function (measured with the IS/IR index) progressively decreased with the increase in both fasting (8) and 2-h (9) plasma glucose concentrations, they remained unchanged with the increase in HbA_{1c} up to a value = 5.5%; thereafter, both insulin sensitivity

Table 3—*Relationship between HbA_{1c} and measures of glucose tolerance, insulin sensitivity, and β-cell function*

	HbA_{1c} <5.7%			HbA_{1c} = 5.7–6.5%			HbA_{1c} <5.5%			HbA_{1c} = 5–5.9%					
	NGT	IFG or IGT	*P* value	NGT	IFG or IGT	*P* value	NGT	IGT or IFG	*P* value	NGT	IGT or IFG	*P* value	HbA_{1c} = 6.0–6.49%	HbA_{1c} = 6.5–7.0%	*P* value
Column No.	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
n	122	105		25	46		90	103		18	61		46	29	
HbA_{1c} (%)	4.9 ± 0.1	5.1 ± 0.05	<0.05	5.8 ± 0.04	6.0 ± 0.05	NS	4.8 ± 0.07	4.9 ± 0.05	NS	5.6 ± 0.03	5.7 ± 0.02	NS	6.2 ± 0.02	6.8 ± 0.03	<0.001
FPG (mg/dL)	90 ± 1	99 ± 1	<0.0001	90 ± 2	109 ± 2	<0.0001	89 ± 1	99 ± 1	<0.0001	90 ± 1	100 ± 1	<0.0001	110 ± 2	135 ± 4	<0.001
2-h PG (mg/dL)	116 ± 2	163 ± 3	<0.0001	121 ± 4	192 ± 5	<0.0001	116 ± 2	151 ± 2	<0.0001	118 ± 4	157 ± 3	<0.0001	197 ± 8	261 ± 9	<0.001
$\Delta G_{0–120}$ (mg/dL)	75 ± 3	124 ± 3	<0.0001	88 ± 7	150 ± 5	<0.0001	75 ± 3	112 ± 3	<0.0001	85 ± 8	112 ± 5	<0.0001	162 ± 7	174 ± 8	NS
$\Delta ISR_{0–120}$	11.5 ± 0.7	10.6 ± 0.7	NS	13.9 ± 1.9	8.0 ± 0.7	NS	11.2 ± 0.7	10.8 ± 0.9	NS	14.3 ± 1.7	11.4 ± 1.0	NS	7.5 ± 0.9	4.7 ± 1	<0.05
$\Delta ISR/\Delta G_{0–120}$	0.17 ± 0.01	0.1 ± 0.01	<0.0001	0.16 ± 0.02	0.07 ± 0.01	<0.0001	0.17 ± 0.01	0.11 ± 0.01	<0.0001	0.2 ± 0.04	0.11 ± 0.01	<0.0001	0.05 ± 0.01	0.03 ± 0.01	<0.05
Matsuda index	4.5 ± 0.4	3.1 ± 0.2	<0.001	3.1 ± 0.5	2.2 ± 0.2	<0.001	4.6 ± 0.4	3.0 ± 0.2	<0.0001	3.7 ± 0.4	2.7 ± 0.2	<0.01	2.2 ± 0.2	2.3 ± 0.2	NS
$\Delta ISR/\Delta G_{0–120}$ X Matsuda	0.56 ± 0.09	0.25 ± 0.02	<0.0001	0.46 ± 0.07	0.15 ± 0.03	<0.0001	0.56 ± 0.03	0.27 ± 0.03	<0.0001	0.64 ± 0.08	0.3 ± 0.04	<0.0001	0.1 ± 0.01	0.07 ± 0.02	NS

PG, plasma glucose; NS, not significant.

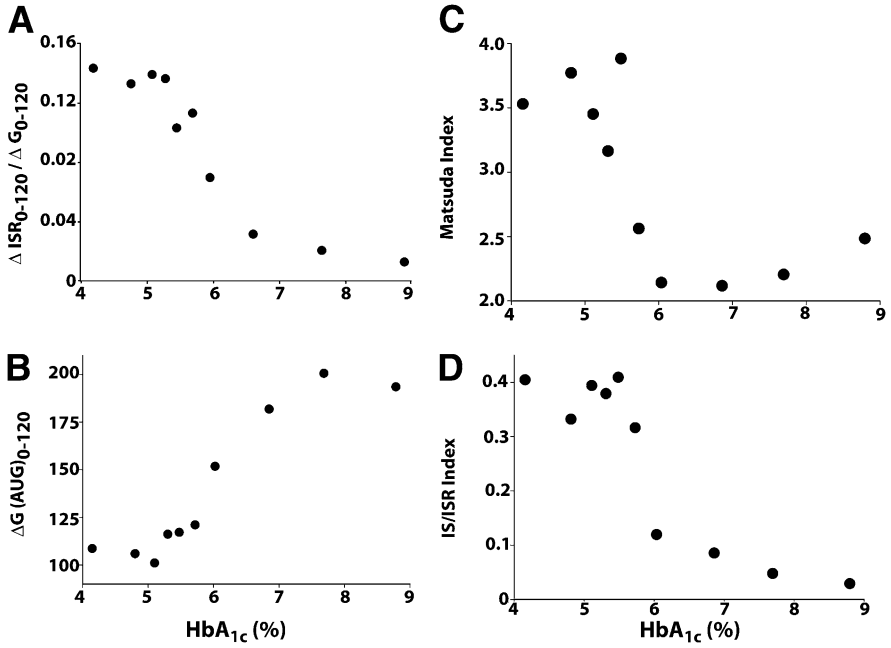

Figure 1—*Relationship between HbA_{1c} and $\Delta ISR_{0–120}/\Delta G_{0–120}$* (A)*, $\Delta G(AUC)_{0–120}$* (B)*, Matsuda index of insulin sensitivity* (C)*, and IS/IR index* (D) *in all 521 subjects.*

and β-cell function precipitously decreased with increasing HbA_{1c} levels >5.5%.

The ADA and the International Diabetes Federation recently revised their criteria for the diagnosis of and high-risk individuals (11,12). With both criteria, subjects with an HbA_{1c} >6.5% are diagnosed with . The ADA criteria state that subjects with HbA_{1c} = 5.7–6.5% are at high risk to develop diabetes, whereas the international expert committee suggested that subjects with HbA_{1c} = 6.0–6.5% represent high-risk individuals. The results of the current study demonstrate that, in Mexican Americans, subjects with HbA_{1c} = 6.0% already manifest severe forms of both core defects that are characteristic of, i.e., insulin resistance (44% decrease in insulin sensitivity) and β-cell dysfunction (62% decrease in IS/IR index). In subjects with HbA_{1c} = 6.0–6.4%, insulin sensitivity, measured with the Matsuda index, did not differ from that in subjects with HbA_{1c} ≥6.5%, and the IS/IR index was decreased by 74% compared with subjects with HbA_{1c} <5.5%. Furthermore, the majority of studies that have evaluated the relationship between the incidence of diabetic retinopathy and HbA_{1c} have reported a significant increase in the incidence of diabetic retinopathy as the HbA_{1c} increased >6.0% (15–20). For example, the threshold for the increase in retinopathy was 5.5% in the 2005–2006 National Health and Nutrition Examination Survey (15) and the Hisayama study (16), 6.0% in the National Health and Nutrition Examination Survey III (17), 6.2% in the Pima Indian study (18), and 6.3% in the Egyptian study (19). Moreover, when the risk for heart attack and stroke was related to HbA_{1c} in nondiabetic subjects in the Atherosclerosis Risk in the Community Study (21), subjects with HbA_{1c} = 6–6.4% had a 78% increase in the risk for heart attack and stroke compared with subjects with HbA_{1c} <5.5%. Taken together, these results indicate that subjects with HbA_{1c} = 6.0–6.4% manifest maximal insulin resistance with ~75% decrease in β-cell function and increased risk of diabetic retinopathy and cardiovascular disease. On the basis of these pathophysiologic and anatomic abnormalities, these subjects should be considered to have, and an HbA_{1c} cut point of 6.0% seems more appropriate for the diagnosis of than the HbA_{1c} cut point of ≥6.5% established by both the ADA and the international expert committee. Moreover, consistent with other studies (22–25), an HbA_{1c} cut point of 6.5% underdiagnoses many subjects with. The prevalence of in this cohort was only 29.5% (HbA_{1c} ≥6.5%) compared with 42.6% with the 2003 ADA criteria based on fasting and 2-h plasma glucose levels (Table 2). Conversely, if an HbA_{1c} cut point of 6.0% is used to diagnose, the prevalence of in this cohort would be 38%, which is comparable to that with the ADA glucose criteria. Thus, an HbA_{1c} cut point of 6.5% for the diagnosis of would leave ~30% of subjects with undiagnosed. Moreover, in subjects with HbA_{1c} = 6.0–6.5%, only ~5% were nondiabetic and ~95% had based on the results of the OGTT (Table 2). Thus, decreasing the HbA_{1c} cut point for from 6.5 to 6.0% would result in only a small number of false-positives.

Although both insulin sensitivity and β-cell function remained unchanged in individuals with HbA_{1c} <5.7%, approximately half of the subjects in this group had IFG or IGT and therefore are at increased risk of future and could benefit from an intervention program aimed to reduce their future risk, e.g., weight loss and exercise. However, according to the new ADA criteria (HbA_{1c} <5.7%), this large group of individuals would be considered to have NGT and would remain unidentified as having glucose intolerance. Conversely, when subjects were stratified on the basis of the results of the OGTT, those with IFG or IGT (despite having HbA_{1c} <5.7%) had a marked decrease in β-cell function compared with subjects with NGT (55% decrease in IS/IR index, Table 3). Likewise, subjects with NGT with HbA_{1c} = 5.7–6.4% had comparable β-cell function compared with subjects with NGT with HbA_{1c} <5.7%. Subjects with IFG or IGT with HbA_{1c} = 5.7–6.4% had a further decrease in β-cell function. These results demonstrate that the OGTT provides a better tool to identify subjects with β-cell failure compared with the HbA_{1c}. It is likely that challenging the β-cell with a glucose load provides a "stress test" to the β-cell and exposes more subtle decreases in β-cell function compared with measurements taken during the fasting state, e.g., HbA_{1c}. Because β-cell function is the principal factor responsible for the development of, these results underscore the importance of performing an OGTT for the assessment of β-cell health and identification of subjects at increased future risk for.

A limitation to this study is that both insulin sensitivity and β-cell function were measured with OGTT-derived indices. Although these indices were validated with the insulin clamp, additional studies with the gold standard measurements (euglycemic insulin clamp and hyperglycemic clamp) are desirable to

provide definitive evidence. Because of increased rate of obesity in Mexican Americans (mean BMI = 33), β-cell dysfunction could become evident at an earlier stage of glucose intolerance compared with other ethnic groups. Therefore, validation of the present findings in other ethnic groups is warranted.

In summary, the results of the current study demonstrate that Mexican American subjects with HbA_{1c} >6% manifest both core defects of in severe form (44 and 74% decrease in insulin sensitivity and β-cell function, respectively). In addition, a cut point of HbA_{1c} = 6.0% is comparable to the OGTT in identifying subjects with. These observations, together with the increase in diabetic microvascular complications in subjects with HbA_{1c} >6.0%, favor using a cut point of HbA_{1c} = 6.0% for the diagnosis of. Further, the results of this study demonstrate that the OGTT represents a better tool for the identification of subjects with β-cell dysfunction who are at increased future risk for.

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C.J., D.W., L.N., and N.A. contributed to data generation. M.K. and M.A.-G. performed the data analysis. M.A.-G. wrote the article. R.A.D. reviewed the manuscript.

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