Diagnosis of Hyperglycemia in a Cohort of Brazilian Subjects

Fasting plasma glucose– and oral glucose tolerance test–based glycemic status are associated with different profiles of insulin sensitivity and insulin secretion

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Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) represent intermediate states between normal fasting glucose (NFG) or normal glucose tolerance (NGT), respectively, and diabetes (1). The regulation of fasting and glucose concentrations after an oral glucose load is dependent on different physiological mechanisms (2), and current evidence suggests that IFG and IGT have different pathophysiologies (3,4). Measurement of fasting plasma glucose (FPG) is the most frequently used screening test for diabetes. However, the oral glucose tolerance test (OGTT) might be a preferable test because FPG underestimates the severity of glucose intolerance (5,6) and because IFG and IGT define two distinct populations with only partial overlap (5,7,8). The present study was undertaken to compare insulin sensitivity and insulin secretion profiles associated with different stages of hyperglycemia as assessed by FPG only or by FPG and 2-h plasma glucose during an OGTT.

RESEARCH DESIGN AND METHODS — We analyzed data from 900 subjects without previously known diabetes who underwent an OGTT for diagnostic purposes at Fleury Institute, São Paulo, Brazil. A double-glycemic status was determined for each subject. A first set was based on FPG only as follows: NFG (FPG <5.6 mmol/l), IFG (5.6 mmol/l ≤ FPG <7.0 mmol/l), and diabetes (FPG ≥7.0 mmol/l). Subjects with IFG were further stratified into two groups according to the severity of FPG: IFG new criteria (IFG_{nc}) (5.6 mmol/l ≤ FPG <6.1 mmol/l) and IFG old criteria (IFG_{oc}) (6.1 mmol/l ≤ FPG <7.0 mmol/l) (1). A second set of glycemic status values was based on both FPG and 2-h plasma glucose as follows: NFG/NGT (FPG <5.6 mmol/l and 2-h plasma glucose <7.8 mmol/l), isolated IFG (5.6 mmol/l ≤ FPG <7.0 mmol/l and 2-h plasma glucose <7.8 mmol/l), isolated IGT (FPG <5.6 mmol/l and 7.8 ≤ 2-h plasma glucose <11.1 mmol/l), combined IFG/IGT (5.6 mmol/l ≤ FPG <7.0 mmol/l and 7.8 ≤ 2-h plasma glucose <11.1 mmol/l), and diabetes (FPG ≥7.0 mmol/l or 2-h plasma glucose ≥11.1 mmol/l). β-Cell function was estimated as the ratio of $\Delta insulin_{30-0\ min}$ to $glucose_{30\ min}$ (9). Insulin sensitivity was estimated by Matsuda's composite index (10) and by homeostasis model assessment of insulin sensitivity (HOMA%S) (11). Differences between groups were assessed by ANOVA with log-transformed data. Comparisons between pairs were made using the Tukey-Kramer honestly significant difference (HSD) test. Insulin secretion was compared between groups with adjustment for insulin sensitivity levels (HOMA%S) during regression analyses.

RESULTS — Subjects with IFG_{nc}, IFG_{oc}, or diabetes as defined by FPG had lower insulin sensitivity than subjects with NFG, but there were no differences in insulin sensitivity among the hyperglycemic groups (Table 1). Insulin secretion decreased with the severity of hyperglycemia and was significantly different in all intergroup comparisons.

When OGTT-based glycemic status was considered, subjects with isolated IFG or with isolated IGT had decreased insulin sensitivity that was intermediate between that of subjects with NFG/NGT and that of subjects with both IFG/IGT and diabetes (Table 1). The $\Delta insulin_{30-0\ min}$-to-$glucose_{30\ min}$ ratio was decreased in all groups with hyperglycemia compared with values in subjects with NFG/NGT. Similar values were observed in subjects with isolated IFG or with isolated IGT that were intermediate between those in subjects with NFG/NGT and those in subjects with combined IFG/IGT or with diabetes.

We have looked at the correlation between hyperglycemic status determined by FPG only and by FPG and 2-h plasma glucose. FPG-based stratification underestimated the severity of hyperglycemia and glucose intolerance, as 19% of subjects with NFG had IGT and 3% had diabetes when we considered the OGTT-based stratification. Moreover, 44% of subjects with IFG in the FPG-based stratification also had IGT and 24% had diabetes according to the OGTT-based criteria.

CONCLUSIONS — We have observed that the increase in the severity of hyper-

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Received for publication 30 January 2007 and accepted in revised form 25 April 2007.

Published ahead of print at http://care.diabetesjournals.org on 1 May 2007. DOI: 10.2337/dc07-0188.

Abbreviations: FPG, fasting plasma glucose; HOMA%S, homeostasis model of insulin sensitivity; IFG, impaired fasting glucose; IFG_{nc}, IFG new criteria; IFG_{oc}, IFG old criteria; IGT, impaired glucose tolerance; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of subjects according to FPG- or OGTT-based glycemic status*

	FPG-based glycemic status						OGTT-based glycemic status					
	NFG	All IFG	IFG_{nc}	IFG_{oc}	Diabetes	*P* value*	NFG/NGT	IFG	IGT	IFG/IGT	Diabetes	*P* value
n	638	235	154	81	27		500	74	119	104	103	
Male sex (%)	26	52	51	54	56	<0.0001	25	45	33	50	57	<0.0001
Age (years)	41 ± 14[a]	51 ± 11	50 ± 11[a,b]	53 ± 12[b]	60 ± 10[b]	<0.0001	39 ± 13[d]	48 ± 10[d,e]	48 ± 15[d,e]	51 ± 11[d,e]	57 ± 12[e]	<0.0001
BMI (kg/m^2)†	26.8 ± 6.5[a]	29.5 ± 5.0	28.9 ± 4.1[a,b]	30.6 ± 6.3[b]	32.8 ± 7.9[b]	<0.0001	26.1 ± 5.4[d]	28.3 ± 5.2[d]	29.2 ± 4.7[e]	29.9 ± 4.5[e]	30.9 ± 6.3[e]	<0.0001
FPG (mmol/l)	4.8 ± 0.4[c]	6.0 ± 0.4	5.8 ± 0.2[c]	6.4 ± 0.3[c]	7.7 ± 0.7[c]	<0.0001	4.7 ± 0.4[f]	5.9 ± 0.2[d,e]	5.0 ± 0.3[d,e]	5.9 ± 0.4[f]	6.5 ± 1.0[f]	<0.0001
2-h plasma glucose (mmol/l)	—	—	—	—	—	—	5.7 ± 1.1[f]	6.5 ± 0.8[f]	9.0 ± 0.9[d,e]	9.1 ± 0.9[de]	13.7 ± 2.4[f]	<0.0001
ISI_{comp} (AU)	5.4 ± 3.5[c]	2.7 ± 1.7	2.9 ± 1.7[b]	2.4 ± 1.7[b]	2.4 ± 1.9[b]	<0.0001	6.0 ± 3.6[f]	3.2 ± 2.1[d,e]	3.6 ± 2.4[d,e]	2.6 ± 1.4[e]	2.7 ± 1.9[e]	<0.0001
HOMA%S	129 ± 70[c]	83 ± 52	84 ± 49[b]	83 ± 58[b]	81 ± 55[b]	<0.0001	137 ± 70[f]	99 ± 57[d,e]	100 ± 57[d,e]	76 ± 44[e]	85 ± 62[e]	<0.0001
$\Delta I_{30-0}/G_{30}$ (pmol insulin/mmol glucose)	47 ± 30[c]	37 ± 30	40 ± 28[c]	30 ± 33[c]	15 ± 12[c]	<0.0001	49 ± 30[d]	49 ± 42[d]	42 ± 28[d]	37 ± 22[de]	22 ± 17[e]	<0.0001
Adjusted $\Delta I_{30-0}/G_{30}$‡	50 ± 27[c]	30 ± 28	34 ± 28[c]	21 ± 29[c]	5 ± 31[c]	<0.0001	54 ± 27[f]	44 ± 27[d,e]	40 ± 26[d,e]	29 ± 28[f]	13 ± 27[f]	<0.0001

Data are means ± SD. Statistic analyses were χ^2 test (sex) and ANOVA with log-transformed data. For FPG-based glycemic status, *P values refer to comparisons of four groups: NFG, IFG_{nc}, IFG_{oc}, and diabetes. Tukey-Kramer homestly significant difference (HSD) test following ANOVA: [a]different from diabetes; [b]different from NFG; [c]different from all other groups. For OGTT-based glycemic status, Tukey-Kramer HSD test following ANOVA: [d]different from diabetes; [e]different from NFG/NGT; [f]different from all other groups. †BMI comparison adjusted by age and sex. ‡Adjusted by logHOMA%S. AU, arbitrary units; $\Delta I_{30-0}/G_{30}$, ratio of $\Delta insulin_{30-0\ min}$ to $glucose_{30\ min}$.

glycemia assessed by FPG only or by the OGTT is associated with different profiles of insulin sensitivity and insulin secretion. When glycemic status was assessed by FPG only, differences in IFG and diabetes were best explained by the degree of β-cell defects, as both dysglycemic states were associated with similar degrees of insulin resistance. The new FPG cutoff for defining IFG (≤5.6 mmol/l) identifies subjects with decreased insulin sensitivity and decreased β-cell function compared with subjects with NFG/NGT but with a lesser degree of insulin secretion deficit than subjects defined by the older FPG cutoff (≤6.1 mmol/l). When we take into account both FPG and 2-h plasma glucose, the severity of hyperglycemia and glucose intolerance was associated with progressive decreases in insulin sensitivity and in insulin secretion.

These differences in insulin sensitivity and insulin secretion profiles when hyperglycemia was diagnosed by FPG only or by the OGTT are due to the underestimation by FPG of the severity of glucose intolerance. Our results are in agreement with other studies suggesting that FPG remains a poor discriminator of IGT and of diabetes (5,6). Our analysis illustrates the effects of using FPG as the single test of glycemic status. Even with the new cutoff for IFG (FPG ≥5.6 mmol/l), ~25% of subjects with IGT or diabetes would be misclassified as normal.

In summary, our data demonstrate that different patterns of insulin sensitivity and insulin secretion are associated with the increase in the severity of hyperglycemia assessed by FPG only or by FPG and the 2-h plasma glucose during an OGTT.

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