The Significance of Impaired Fasting Glucose Versus Impaired Glucose Tolerance

Importance of insulin secretion and resistance

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OBJECTIVE — The American Diabetes Association recommended substituting 2hBS (glycemia at the second hour of an oral glucose tolerance test [OGTT]) for fasting blood glucose (FBS) in screening for glucose intolerance. It is debated whether these tests measure the same abnormality and relate to defective insulin secretion or resistance. This study examines the diagnostic effectiveness of FBS versus 2hBS and their relationship with insulin secretion and resistance.

RESEARCH DESIGN AND METHODS — Based on history or physical findings suggesting glucose intolerance, we enrolled 398 unselected subjects admitted to a general Internal Medicine ward. After 5 days of a weight-maintaining diet, FBS, 2hBS, and insulin were measured during OGTT. The homeostatic model assessment was used to assess β-cell function and insulin resistance.

RESULTS — Excluding 19 patients with diabetes (5%), we identified 284 subjects with normal glucose tolerance (NGT), 22 with isolated impaired fasting glucose (IFG), 59 with isolated impaired glucose tolerance (IGT), and 14 with associated IFG/IGT. The sensitivity of FBS in predicting 2hBS was 19%, specificity 93%. Positive and negative predictive values were 39% and 83%, respectively. Insulin resistance was absent in NGT and IFG and markedly elevated in IGT and IFG/IGT, whereas defective insulin release was significant only in isolated IFG.

CONCLUSIONS — In unselected patients, elevated FBS depends primarily on defective insulin secretion, and impaired 2hBS on insulin resistance. Because these tests measure different alterations, they are useful in combination.

Diabetes Care **26**:1333–1337, 2003

T he American Diabetes Association (ADA) (1) and the World Health Organization (WHO) (2) have revised the diagnostic criteria of diabetes and glucose intolerance. A new category of impaired fasting glucose (IFG) when fasting blood glucose (FBS) is 6.1–6.9 mmol/l replaced impaired glucose tolerance (IGT). However, studies in different ethnic groups disclosed a poor concordance between IGT, a known risk factor for diabetes and cardiovascular disease (3), and IFG, the predictive value of which is undetermined. When only FBS is measured, IGT remains undetected in many subjects (4,5). Insulin resistance and impaired secretion concur toward diabetes and glucose intolerance, but it is unclear which defect arises first (6,7) and which relates to either IFG or IGT, which reflect different alterations in glucose homeostasis (8). Whereas some reports show that subjects with IFG have hyperinsulinemia and/or worsening of insulin resistance, those with IGT have defective secretion in response to glucose loading (9–11). Other reports demonstrate a pronounced defect in early insulin secretion in IFG and marked insulin resistance in IGT (12–14). Thus, the characteristic metabolic abnormalities of IFG, compared with IGT, remain to be elucidated.

The major goal of our study was to evaluate the diagnostic power of FBS with respect to 2hBS (second-hour glycemia after oral load), assuming that the latter can be considered a reference indicator of metabolic disease. Therefore, the diagnostic process could be effectively simplified in the general unselected population by resorting to one measurement only, as was demonstrated in epidemiological studies that established ADA and WHO criteria (1,2). This study also offered the opportunity for analyzing the relationship of FBS and 2hBS with insulin resistance and secretion in isolated IFG, isolated IGT, and combined IFG and IGT.

RESEARCH DESIGN AND METHODS — The study was performed in a general Internal Medicine ward with outpatient facilities, affiliated with a Medical School. Those enrolled were consecutive unselected patients admitted between 1997 and 2002 whose medical history and physical examination prompted further studies to screen for metabolic abnormalities. We excluded patients with known type 2 diabetes or other abnormalities defined by ADA (1)

Table 1—Clinical characteristics of the four groups of subjects

	NGT (1)	Isolated IFG (2)	Isolated IGT (3)	IFG/IGT (4)	Significance
Age (years)	43.5 ± 12.7	47.9 ± 10.2	47.7 ± 10.3	52.3 ± 10.6	NS
M/F	146/138	12/10	14/45	8/6	$\chi^2 = 16.1$, df = 3, $P < 0.002$
BMI (kg/m^2)	27.4 ± 5.2	29.8 ± 5.6	30.6 ± 5.8	31.5 ± 6.9	1 vs. 4 $P < 0.006$
					1 vs. 3 $P < 0.001$
WHR	0.89 ± 0.09	0.93 ± 0.09	0.90 ± 0.08	0.94 ± 0.06	NS
NBP/HBP	123/161	6/16	7/52	4/10	$\chi^2 = 22.2$, df = 3, $P < 0.0001$

Data are means ± SD or *n*. HBP, high blood pressure; NBP, normal blood pressure; WHR, waist-to-hip ratio.

and WHO (2) diagnostic criteria. We enrolled 398 subjects, 183 male and 215 female (83 postmenopausal). None was taking medications affecting glucose or insulin metabolism and, based on physical examination and routine laboratory exams, all were healthy. We pre-established the use of ADA and WHO criteria (1,2) to classify patients into groups, based on glycemic values expressed in mmol/l: *1*) normal glucose tolerance (NGT) with FBS <6.1 and 2hBS <7.8; *2*) isolated IFG (FBS 6.1–6.9 and 2hBS <7.8); *3*) isolated IGT (FBS <6.1 and 2hBS 7.8–11.1); *4*) combined IFG/IGT (FBS 6.1–6.9 and 2hBS 7.8–11.1); and *5*) type 2 diabetes with FBS >7 and/or 2hBS >11.1. The 19 patients belonging to this fifth group are not further described here.

After at least 5 days of a weight-maintaining diet (55% of calories from carbohydrates, 25% from fats, 20% from proteins) and avoidance of strenuous exercise, the fasting subjects underwent a 75-g oral glucose tolerance test (OGTT). Two venous blood samples were drawn at baseline and a third 120 min later for determination of 2-h insulin and 2hBS. The fasting values were the average of the two baseline samples. Plasma glucose concentrations were determined by glucose oxidase, and serum insulin concentrations with an immunometric "sandwich" assay (Immulite 2000). On the morning of OGTT, we measured BMI (kg/m^2) and waist-to-hip ratio (WHR) as an index of body fat distribution. We calculated pancreatic β-cell function and insulin resistance (IR) from fasting glucose and insulin concentrations using homeostatic model assessment (HOMA β-cell and HOMA IR, respectively) (15). HOMA β-cell was calculated from fasting glycemia and insulin levels, as follows: [20 × fasting insulin (μU/ml)]/[fasting glucose (mmol/l) − 3.5]. The numbers were divided by 100. FBS values <3.5 mmol/l

were excluded to avoid negative results. The HOMA β-cell, which correlates for 57% only with the modified euglycemic clamp (16), more reliably estimates fasting insulin secretion. The HOMA IR instead is directly related to insulin resistance and calculated as follows: fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5. Insulin resistance inversely relates to the insulin sensitivity index (ISI) for glycemia (ISI$_{gly}$, calculated as: 2/[(insulin$_p$ × glycemia$_p$) + 1]) (17). Insulin$_p$ and glycemia$_p$ are obtained by dividing the sum of the measurements of insulin (μU/ml) and glycemia (mmol/l), measured at 0 and 2 h after OGTT, by the sum of their respective normal values. Our normal reference values were obtained on 50 of the study subjects (20 male and 30 female, aged 17 to 58 years) with normal BMI and WHR, according to the criteria published by the Italian Consensus Conference (18). HOMA and ISI$_{gly}$ have been validated with euglycemic and hyperglycemic clamp techniques (17,19) and used in epidemiologic studies (19,20). The ISI$_{gly}$, calculated from OGTT data, seems to be more specific and useful than HOMA IR, more closely reflecting physiologic insulin actions. It represents a simple tool suitable for clinical or epidemiologic studies (17,20,21). We selected the 2hBS as indicative of glucose intolerance because of its simplicity, which matches that of FBS, and its high discriminating power (2,3). We could not estimate beforehand the number of observations necessary to reach statistical significance, because the relative prevalence of the different metabolic abnormalities is unknown, the only previous report (8) being based on cut-off values different from those of the ADA used here. We computed means and SDs from the means for each measurement. Statistical comparisons were performed using χ^2 and Bonferroni's tests.

RESULTS — The patients were aged 17 to 66 years; 84 smoked <10 cigarettes/day; 242 had asymptomatic essential hypertension, diagnosed by blood pressure >140/90 and/or history of continuous antihypertensive treatment. Of the 379 nondiabetic subjects, 284 (75%) were classified as NGT, 22 (6%) as isolated IFG, 59 (16%) as isolated IGT, and 14 (4%) as IFG/IGT. Compared with NGT, BMI was significantly higher in IFG/IGT and IGT groups (Table 1). Whereas WHR and smoking were similar in the four groups, hypertension, as expected, was more prevalent in the glucose intolerance groups.

Table 2 reports the results of OGTTs. The comparisons between glycemic values are meaningless, because the groups were built according to pre-established values. The fasting serum insulin concentrations in IFG/IGT and IGT were significantly higher than in NGT and IFG groups. These differences were also present for 2-h insulin values.

The results of the HOMA analysis and ISI$_{gly}$ are shown in Table 3. The means ± SD of our own normal values for HOMA IR, HOMA β-cell, and ISI$_{gly}$, not shown in the table, were 1.42 ± 0.72, 1.89 ± 2.72, and 1.08 ± 0.31, respectively. Compared with that of NGT, the HOMA IR was significantly higher in IFG/IGT and isolated IGT groups. The HOMA IR in IFG/IGT subjects was significantly higher than that in IGT and IFG groups. With respect to NGT, the ISI$_{gly}$ was significantly lower in IFG/IGT and IGT groups, and that of IFG/IGT was significantly lower than that of the IFG group. The ISI$_{gly}$ was significantly lower compared with IFG in the IGT group, whereas the HOMA β-cell shows the opposite difference, which is also statistically significant. Subjects with normal 2hBS had significantly higher insulin sensitivity, measured by the ISI method, than those with high 2hBS.

Table 2—*Results of OGTT in the four groups of subjects*

	NGT (1)	Isolated IFG (2)	Isolated IGT (3)	IFG/IGT (4)	Significance
FBS (mmol/l)	4.83 ± 0.57	6.43 ± 0.24	5.07 ± 0.62	6.61 ± 0.32	1 vs. 2 $P < 0.001$
					1 vs. 3 $P < 0.02$
					1 vs. 4 $P < 0.001$
					2 vs. 3 $P < 0.001$
					3 vs. 4 $P < 0.001$
2hBS (mmol/l)	5.71 ± 1.04	6.3 ± 0.96	8.98 ± 1.01	9.19 ± 1.12	1 vs. 3 $P < 0.001$
					1 vs. 4 $P < 0.001$
					2 vs. 3 $P < 0.001$
					2 vs. 4 $P < 0.001$
Fasting insulin (μU/ml)	10.7 ± 5.6	12.7 ± 6.3	17.3 ± 9.5	19.8 ± 10.4	1 vs. 3 $P < 0.001$
					1 vs. 4 $P < 0.001$
					2 vs. 3 $P < 0.04$
					2 vs. 4 $P < 0.02$
2h insulin (μU/ml)	54.3 ± 37.9	44.8 ± 21.6	130.1 ± 68.1	118.9 ± 95.4	1 vs. 3 $P < 0.001$
					1 vs. 4 $P < 0.001$
					2 vs. 3 $P < 0.001$
					2 vs. 4 $P < 0.001$

Data are means ± SD.

The analysis of the diagnostic power of FBS as a screening test for metabolic disease is shown in Table 4, which reports the data as if FBS were the screening test and 2hBS were equivalent to disease. The symptom FBS has low sensitivity (19%) owing to the very high false-negative rate, and good specificity (93%), owing to a very low false-positive rate. However, the diagnostic yield, expressed by the positive predictive value, is poor (39%), whereas the power of the test in excluding impaired glucose tolerance, expressed by the negative predictive value, is more acceptable (83%).

CONCLUSIONS — After the ADA diagnostic criteria of 1997 (1), impaired glucose homeostasis can be defined not only by 2hBS of 7.8–11.1 mmol/l but also by FBS of 6.1–6.9 mmol/l. If both WHO and ADA criteria are applied, impaired glucose homeostasis can be divided into three different subgroups, implying a close linkage between the WHO category of IGT and the new category of IFG, considered intermediate steps between normal and diabetic glucose homeostasis (1,2). On the contrary, our results, consistent with recent reports in different ethnic groups (5,9,12), clearly demonstrate that IFG and IGT subjects belong to different populations with altered glucose metabolism. Our data show that if FBS alone had been used, 81% of subjects with isolated abnormalities in 2hBS (isolated IGT) would have been diagnosed as having normal glucose tolerance, while 17% of subjects considered normal would in fact be undiagnosed glucose intolerant. Only when performing an additional OGTT test was the association between IGT and IFG detected in ~39% of the subjects with IFG. Missing this association could be harmful, since subjects with IGT are at increased risk of developing diabetes and cardiovascular disease (3). The ADA criteria, which ignore this condition, could thus delay disease prevention.

The diversity between IFG and IGT groups involves both insulin secretion and resistance. There is general agreement that subjects with type 2 diabetes have both β-cell dysfunction and insulin resistance (6,7). However, the stage of progression of glucose intolerance during which these metabolic abnormalities develop is still a matter of debate. Defective insulin action is the major identifiable defect in subjects at risk for type 2 diabetes (6,11), whereas β-cell dysfunction seems to become abnormal only when FBS is elevated (7,22). Nevertheless, defective insulin secretion may be present before the onset of overt diabetes (9,23).

Before the introduction of the ADA criteria, the IGT category included all nondiabetic subjects with impaired glucose homeostasis. Considerable controversy regarded the relative contributions of insulin resistance and abnormal insulin secretion in the pathogenesis of IGT (11,24), and this is now accounted for by

Table 3—*HOMA IR, ISI(gly) and HOMA β-cell in the four groups of subjects*

	NGT (1)	Isolated IFG (2)	Isolated IGT (3)	IFG/IGT (4)	Significance
HOMA IR	2.3 ± 1.4	3.6 ± 1.8	3.9 ± 2.2	5.8 ± 2.8	1 vs. 2 $P < 0.003$
					1 vs. 3 $P < 0.001$
					1 vs. 4 $P < 0.001$
					2 vs. 4 $P < 0.002$
					3 vs. 4 $P < 0.002$
ISI_{gly}	0.83 ± 0.32	0.75 ± 0.21	0.36 ± 0.14	0.41 ± 0.23	1 vs. 3 $P < 0.001$
					1 vs. 4 $P < 0.001$
	0.82 ± 0.31		0.38 ± 0.16		2 vs. 3 $P < 0.001$
		$P < 0.001$			2 vs. 4 $P < 0.003$
HOMA β-cell	2.1 ± 2.9	0.9 ± 0.4	3.1 ± 4.6	1.3 ± 0.7	2 vs. 3 $P < 0.03$

Data are means ± SD.

Table 4—*Diagnostic power of FBS*

		2hBS (mmol/l)	
		<7.8	>7.8 <11.1
FBS (mmol/l)	≤6.1	NGT, $n = 284$	Isolated IGT, $n = 59$
	>6.1 to <6.9	Isolated IFG, $n = 22$	Combined IFG/IGT, $n = 14$

The relationships between "the symptom" (FBS) and "the disease" (2hBS). Specificity = 284/306 = 93%; sensitivity = 14/73 = 19%; positive predictive value = 14/36 = 39%; and negative predictive value = 284/343 = 83%.

the new category of IFG. Considering the information yielded by the HOMA β-cell analysis together with ISI$_{gly}$, we can argue that insulin secretion is defective in IFG compared with IGT subjects, whereas, in the isolated IGT group, impaired insulin sensitivity is more apparent. These results agree with those reported by some (12–14), but not all (9–11), authors.

In a longitudinal study (11), a marked deficit of insulin secretion after intravenous glucose load was observed in Pima Indians with IGT who later manifested overt diabetes. It was subsequently demonstrated that defective insulin secretion is more pronounced in Pima Indians with isolated IFG than in other subjects with isolated IGT (12). Several studies on insulin secretion and resistance in IGT subjects attempted to determine which of these two defects predominates during the early stage of the disease and which constitutes the primary abnormality (7,24). Although the results of most cross-sectional studies of IGT subjects indicate that insulin resistance represents a major feature (in agreement with the present study), extended follow-up shows that reduced insulin secretion is strongly predictive of progression to overt diabetes (11,25).

Defects in insulin resistance or secretion have different effects on fasting and postprandial glucose metabolism. This has been demonstrated in studies conducted on identical twins of parents with type 2 diabetes (22), hemipancreatectomized normal subjects (26), and insulin-resistant Asian subjects (27), data which collectively show that the onset of fasting metabolic abnormalities occurs in response to a primary impairment of insulin secretion, whereas primary insulin resistance preferentially affects postprandial glucose metabolism. FBS, which depends essentially on hepatic glucose production, is strongly influenced by the feedback between liver and β-cells (7). In our

study, in fact, subjects with IFG had significantly higher FBS and significantly lower fasting insulin levels than IGT patients. Moreover, they exhibited a lower HOMA β-cell, the insulin secretion index based on baseline findings. Therefore, they would need to secrete more insulin to control their fasting glycemia.

Normal insulin action is important in clearing an oral glucose load (28). In our study, subjects with IGT showed significantly higher 2hBS and 2-h insulin levels than those with IFG. They also had significantly higher insulin resistance, as demonstrated by their lower ISI$_{gly}$. In other words, the excessive insulin secretion of these patients is not sufficient to control their 2hBS. This demonstrates the presence of marked insulin resistance.

Consequently, our findings suggest that IFG and IGT subjects represent two distinct populations with altered glucose metabolism. Thus, both FBS and 2hBS are useful diagnostic tools, since their combined use allows the stratification of subjects with impaired glucose homeostasis into three specific subgroups with different metabolic abnormalities: isolated IFG, isolated IGT, and combined IFG/IGT. This distinction may help clinicians in choosing strategies to prevent cardiovascular disease and diabetes.

In the absence of euglycemic clamp values, it is difficult to precisely assess the relative importance of insulin secretion and resistance. However, the tests we used to measure insulin resistance were concordant and gave clear-cut results, whereas the test to estimate secretion was significantly different between patients with IFG and IGT. The lack of significance with respect to the IFG/IGT group might be due to the conflicting influence on the HOMA β-cell value of defective secretion with respect to altered peripheral glucose disposal in IFG/IGT patients, although a rather limited sample size could account for it. This latter explana-

tion is supported by the comparison, not reported in Table 3, between NGT + IGT (all 337 subjects with normal FBS) and IFG + IFG/IGT (all 36 patients with high FBS), which is significant at the 0.03 level because of the larger sample size. We did not perform the euglycemic clamp because the aim of our study was to evaluate the diagnostic power of a very simple test, FBS, that can be performed in practically all clinical settings, in the doctor's office, and even by the patients. Although we cannot establish which is the primary, initial abnormality in glucose intolerance, defective secretion or resistance, we have important data to assess the diagnostic power of the simple measurement of fasting glucose in diagnosing glucose intolerance. It is meaningful then to compute the diagnostic power of FBS, the test recommended by the ADA as a simplified estimate of impaired glucose tolerance. As shown in Table 4, the positive predictive value is insufficient to support the use of FBS alone to screen the unselected general population for metabolic abnormalities.

Probably, the discrepancy between our results and those expected by following the ADA recommendations is more apparent than real. In fact, we collected our data from a general medical ward and clinics. In this unselected population, diabetes has such a low prevalence (4.7%) as to reduce, according to Bayes formula (29), the diagnostic yield of FBS when used as a single test. The ADA criteria may be more applicable to referral centers for diabetes, where the higher disease prevalence improves the diagnostic power of FBS. In a general medical ward or in a general practitioner's office, however, the information yielded by FBS and 2hBS is complementary and provides a more complete picture of the patient's metabolic state, useful in identifying the appropriate treatment. Reliable diagnostic conclusions and clinical decisions cannot be reached if the information is limited to FBS.

References

1. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
2. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications: 1. Diagnosis

and classification of diabetes mellitus: provisional report of a WHO consultation. *Diabet Med* 15:539–553, 1998

3. Hanefeld M, Koehler C, Henkel E, Fuecker K, Schaper F, Temelkova-Kurktschiev T: Post-challenge hyperglycemia relates more strongly than fasting hyperglycemia with carotid intima-media thickness: the RIAD Study. Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes. *Diabet Med* 17:835–840, 2000

4. Larsson H, Berglund G, Lindgarde F, Ahren B: Comparison of ADA and WHO criteria for diagnosis of diabetes and glucose intolerance. *Diabetologia* 41:1124–1125, 1998

5. De Vegt F, Dekker JM, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: The 1997 American Diabetes Association criteria versus the 1985 World Health Organization criteria for the diagnosis of abnormal glucose tolerance: poor agreement in the Hoorn Study. Diabetes Care 21:1686–1690, 1998

6. Osei K, Cottrell DA, Orabella MM: Insulin sensitivity, glucose effectiveness, and body fat distribution pattern in nondiabetic offspring of patients with NIDDM. *Diabetes Care* 14:890–896, 1991

7. De Fronzo RA, Ferrannini E, Simonsen DC: Fasting hyperglycemia in non insulin-dependent diabetes mellitus: contributions of excessive hepatic glucose production and impaired tissue glucose uptake. *Metabolism* 38:387–395, 1989

8. Vaccaro O, Ruffa G, Imperatore G, Iovino V, Rivellese AA, Riccardi G: Risk of diabetes in the new diagnostic category of impaired fasting glucose: a prospective analysis. *Diabetes Care* 22:1490–1493, 1999

9. Tripathy D, Carlsson M, Almgren P, Isomaa B, Taskinen MR, Tuomi T, Groop LC: Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. *Diabetes* 49:975–980, 2000

10. Guerrero-Romero F, Rodriguez-Moran M: Impaired glucose tolerance is a more advanced stage of alteration in the glucose metabolism than impaired fasting glucose. *J Diabetes Complications* 15:34–37, 2001

11. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory disfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999

12. Weyer C, Bogardus C, Pratley RE: Metabolic characteristics of individuals with impaired fasting glucose and/or impaired glucose tolerance. *Diabetes* 48:2197–2203, 1999

13. Davies MJ, Raymond NT, Day JL, Hales CN, Burden AC: Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. *Diabet Med* 17:433–440, 2000

14. Conget I, Fernandez Real JM, Costa A, Casamitjana R, Ricart W: Insulin secretion and insulin sensitivity in relation to glucose tolerance in a group of subjects at a high risk for type 2 diabetes mellitus. *Med Clin* 116:491–492, 2001

15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985

16. Stumvoll M, Mitrakou A, Pimenta W, Jenssen T, Yki-Järvinen H, Van Haeften T, Renn W, Gerich J: Use of the oral glucose tolerance test to assess insulin release and insulin sensitivity. *Diabetes Care* 23:295–301, 2000

17. Belfiore F, Iannello S, Volpicelli G: Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. *Mol Genet Metab* 63:134–141, 1998

18. Crepaldi G, Belfiore F, Bosello O, Caviezel F, Contaldo F, Enzi G, Melchionda N: Italian Consensus Conference: overweight, obesity and health (ICC S.O.S. 1991). *Recenti Prog Med* 82:417–434, 1991

19. Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H: A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care* 19:1138–1141, 1996

20. Gutt M, Davis CL, Spitzer SB, Llabre M, Kumar M, Czarnecki EM, Scheiderman N, Skyler JS, Marks JB: Validation of the insulin sensitivity index [ISI (0,120)]: comparison with other measures. *Diabetes Res Clin Pract* 47:177–184, 2000

21. Belfiore F, Iannello S, Camuto M, Fagone S, Cavaleri A: Insulin sensitivity of blood glucose versus insulin sensitivity of blood free fatty acids in normal, obese, and obese-diabetic subjects. *Metabolism* 50:573–582, 2001

22. O'Rahilly S, Hattersley A, Vaag A, Gray H: Insulin resistance as the major cause of impaired glucose tolerance: a self-fulfilling prophesy? *Lancet* 344:585–589, 1994

23. Pimenta W, Korytkowski M, Mitrakou A, Yki-Järvinen, Evron W, Gerich J: Pancreatic β-cell dysfunction as the primary genetic lesion in NIDDM: evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. *JAMA* 273:1855–1861, 1995

24. Haffner SM, Miettinen H, Gaskill SP, Stern MP: Decreased insulin action and insulin secretion predict the development of impaired glucose tolerance. *Diabetologia* 39:1201–1207, 1996

25. Lundgren H, Bengtsson C, Blohme G, Lapidus L, Waldenstrom J: Fasting serum insulin concentration and early insulin response as risk determinants for developing diabetes. *Diabet Med* 7:407–413, 1990

26. Kendall DM, Sutherland DE, Najarian JS, Goetz FC, Robertson RP: Effects of emipancreatectomy on insulin secretion and glucose tolerance in healthy humans. *N Engl J Med* 322:898–903, 1990

27. McKeigue PM, Miller GJ, Marmot MG: Coronary heart disease in South Asians: a review. *J Clin Epidemiol* 42:597–609, 1989

28. Ferrannini E, Bjorkman O, Reichard GA Jr, Pilo A, Olsson M, Wahren J, DeFronzo RA: The disposal of an oral glucose load in healthy subjects: a quantitative study. *Diabetes* 34:580–588, 1985

29. Sox HC: Probability theory in the use of diagnostic tests: an introduction to critical study of the literature. *Ann Intern Med* 104:60–66, 1986