Pathogenetic Mechanisms and Cardiovascular Risk

Differences between HbA_{1c} and oral glucose tolerance test for the diagnosis of glucose tolerance

CRISTINA BIANCHI, MD, PHD[1]
ROBERTO MICCOLI, MD, PHD[1]
RICCARDO C. BONADONNA, MD[2]
FRANCESCO GIORGINO, MD[3]
SIMONA FRONTONI, MD[4]
EMANUELA FALOIA, MD[5]
GIULIO MARCHESINI, MD[6]
MARIA A. DOLCI, MD[7]
FRANCO CAVALOT, MD[8]
GISELLA M. CAVALLO, MD[9]
FRIDA LEONETTI, MD[10]
STEFANO DEL PRATO, MD[1]
ON BEHALF OF THE GENFIEV INVESTIGATORS*

OBJECTIVE—To ascertain to which extent the use of HbA_{1c} and oral glucose tolerance test (OGTT) for diagnosis of glucose tolerance could identify individuals with different pathogenetic mechanisms and cardiovascular risk profile.

RESEARCH DESIGN AND METHODS—A total of 844 subjects (44% men; age 49.5 ± 11 years; BMI 29 ± 5 kg/m^2) participated in this study. Parameters of β-cell function were derived from deconvolution of the plasma C-peptide concentration after a 75-g OGTT and insulin sensitivity assessed by homeostasis model assessment of insulin resistance (IR). Cardiovascular risk profile was based on determination of plasma lipids and measurements of body weight, waist circumference, and blood pressure. Glucose regulation categories by OGTT and HbA_{1c} were compared with respect to insulin action, insulin secretion, and cardiovascular risk profile.

RESULTS—OGTT results showed 42% of the subjects had prediabetes and 15% had type 2 diabetes mellitus (T2DM), whereas the corresponding figures based on HbA_{1c} were 38 and 11%, with a respective concordance rate of 54 and 44%. Subjects meeting both diagnostic criteria for prediabetes presented greater IR and impairment of insulin secretion and had a worse cardiovascular risk profile than those with normal glucose tolerance at both diagnostic methods. In a logistic regression analyses adjusted for age, sex, and BMI, prediabetic subjects, and even more T2DM subjects by OGTT, had greater chance to have IR and impaired insulin secretion.

CONCLUSIONS—HbA_{1c} identifies a smaller proportion of prediabetic individuals and even a smaller proportion of T2DM individuals than OGTT, with no difference in IR, insulin secretion, and cardiovascular risk profile. Subjects fulfilling both diagnostic methods for prediabetes or T2DM are characterized by a worse metabolic profile.

Diabetes Care 35:2607–2612, 2012

From the [1]Department of Endocrinology and Metabolism, Section of Diabetes and Metabolic Diseases, University of Pisa, Pisa, Italy; the [2]Department of Biomedical and Surgical Sciences, Section of Endocrinology and Metabolic Diseases, University of Verona, Verona, Italy; the [3]Department of Emergency and Organ Transplantation, Section of Internal Medicine, Endocrinology and Metabolic Diseases, University of Bari, Bari, Italy; the [4]Diabetes Center, Department of Internal Medicine, University of Rome Tor Vergata, Rome, Italy; the [5]Division of Endocrinology, Polytechnic University of Marche, Ancona, Italy; the [6]Unit of Clinical Dietetics, Alma Mater Studiorum, University of Bologna, Bologna, Italy; the [7]Section of Diabetes and Metabolic Diseases, SS. Giacomo e Cristoforo Hospital, Massa, Italy; the [8]Diabetes Unit, Department of Clinical Biological Sciences, University of Turin, Turin, Italy; the [9]Department of Clinic and Medical Therapy, University of Rome "La Sapienza," Rome, Italy; and the [10]Department of Clinical Sciences, University of Rome "La Sapienza," Rome, Italy.
Corresponding author: Stefano Del Prato, stefano.delprato@med.unipi.it.
Received 23 December 2011 and accepted 31 May 2012.
DOI: 10.2337/dc11-2504
*A complete list of the GENFIEV Investigators can be found in the APPENDIX.

The early identification of subjects at high risk for type 2 diabetes mellitus (T2DM) or with unknown DM is crucial to implement measures that may prevent or delay progression from prediabetes to T2DM and reduce the incidence of chronic complications. Diagnostic criteria for these categories of impaired glucose tolerance (IGT) have been classically based on glucose measurements, in particular after a glucose loading during an oral glucose tolerance test (OGTT). The OGTT, however, can be cumbersome, time consuming, and expensive, so that alternative diagnostic tools have been sought. The use of HbA_{1c} has been repeatedly considered for such a purpose, but the American Diabetes Association (ADA) has only recently proposed adoption of cutoff values of 5.7–6.4% and ≥6.5% for identification of individuals with prediabetes and overt diabetes, respectively (1). The World Health Organization has advocated a similar HbA_{1c} cutoff for the diabetes diagnosis, although no high-risk category has been identified (2).

The performance of these criteria have been compared with determination of fasting plasma glucose levels and/or OGTT in various populations (3–9), but few data have explored whether the two criteria identify in the same individuals the prevalent pathogenetic mechanisms (i.e., insulin secretion and insulin action) and cardiovascular (CV) risk profile. Previous studies have shown that impaired β-cell function can be recognized in people at risk for diabetes even at the time they still have normal glucose tolerance (NGT) (10–13). A recent study, however, has reported that the relationship between β-cell function and HbA_{1c} can be quite different between those with impaired fasting glucose and those with altered 2-h postload glucose concentrations (14). This raises the possibility that individuals with impaired glucose regulation, as identified by HbA_{1c} or OGTT, also may differ in their pathogenetic mechanisms and, therefore, their CV risk profile. Therefore, the aim of the current study was to assess insulin secretion, insulin action,

and CV risk profile based on different diagnostic criteria for abnormal glucose tolerance.

RESEARCH DESIGN AND METHODS

—The participants in this study included 844 subjects of the GENFIEV (GENetics, pathoPHYsiology and EVolution of type 2 diabetes) study, a multicenter, nationwide, Italian study designed to recruit individuals at risk for developing type 2 diabetes mellitus (T2DM) in the attempt to define phenotypic and genotypic features that may allow more accurate identification of high-risk subjects (http://clinicaltrials.gov/ct2/show/NCT00879801?term=GENFIEV&rank=1). Opportunistic recruitment was adopted by screening individuals referred to diabetes clinics because of their potential risk of T2DM. Nine centers across Italy participated in the study. The study protocol was approved by local institutional review boards, and all subjects gave written informed consent before entering the study.

A standardized medical history and accurate physical examination was obtained in all subjects before a basal blood specimen was obtained and a 75-g OGTT was administered. Height, weight, and waist circumference (at the umbilicus with the subject standing) were recorded, and BMI was calculated by dividing the body weight (in kilograms) by the height (in meters squared). Two blood pressure measurements were taken with a standard mercury sphygmomanometer with subjects recumbent, and the mean value was calculated. A 12-lead standard electrocardiogram was also recorded.

All OGTTs were performed after an overnight fast, with all subjects refraining from smoking for no less than 12 h before the test. An antecubital vein was cannulated for blood sampling. Plasma glucose, insulin, and C-peptide levels, lipid profile, and HbA_{1c} were determined in the fasting state. Subjects then ingested a 75-g glucose load over 5 min, and samples were drawn at 15, 30, 60, 90, and 120 min for plasma glucose and C-peptide measurement.

All biochemical parameters were determined by standard methods on a Roche-Modular Autoanalyzer (Milan, Italy). HbA_{1c} was measured by high-performance liquid chromatography with coefficients of variations <2% at low (5%) and high (10%) HbA_{1c} values. HbA_{1c} was standardized against the Diabetes Control and Complications Trial (DCCT) standard. Insulin and C-peptide were determined by immunoassay (Immulite; DPC, Los Angeles, CA). LDL cholesterol (LDL-C) levels were calculated according to the Friedewald formula. The OGTT results were used to divide subjects into four categories: NGT, impaired fasting glucose (IFG), IGT, and T2DM according to the ADA 2003 criteria (15). Glucose tolerance was also determined based on HbA_{1c} levels according to the 2010 ADA clinical practice recommendation (≥6.5%, T2DM; 5.7–6.4%, high-risk individuals; <5.7% normal glucose homeostasis) (1). Insulin sensitivity was determined by the homeostasis model assessment of insulin resistance (HOMA-IR) index [fasting insulin (mU/L) × fasting plasma glucose (mmol/L)/22.5] as described by Matthews et al. (16). The insulinogenic index was calculated as

$$(CP_{30} - CP_0)/18 * (G_{30} - G_0)$$

where CP_0 and G_0 are the baseline fasting plasma levels of plasma C-peptide and glucose, respectively, and CP_{30} and G_{30} are their levels at 30 min.

β-Cell function was also estimated by minimal model analysis of plasma glucose and C-peptide response to a 2-h 75 g OGTT (17). This analysis allows quantification of basal (prehepatic) insulin secretion rate (BSR − body surface area [BSA]), β-cell sensitivity at glucose (i.e., derivative control [*S*-DC: pmol/m^2 BSA per mmol/L/min]) and the stimulus-response curve of the insulin secretion rate at incremental glucose (i.e., proportional control [*S*-PC: pmol/m^2 BSA per mmol/L/min] at 4.0, 5.5, 8.0, and 11.0 mmol/L of glucose). The insulin secretion-to-IR ratio (disposition index) was calculated as the insulinogenic index–HOMA-IR ratio. The presence of metabolic syndrome was ascertained according to the Adult Treatment Panel III (ATPIII) criteria (18).

Data are expressed as mean ± SD. The nonparametric statistic was used to compare categoric variables among groups, and ANOVA was used to test mean differences among groups. Logistic regression analyses were applied to study the association of OGTT categories or HbA_{1c} with insulin sensitivity or β-cell function. Odds ratios and 95% CIs were presented for adjusted models. StatView software (SAS Institute; Cary, NC) on Power Mac G5 (Apple Corp., Cupertino, CA) was used for statistical analysis. The discriminative effectiveness of HbA_{1c} to identify diabetes was evaluated by the area under receiver operating characteristic (AUROC) curves using SPSS 16.0 software (SPSS, Chicago, IL). *P* values <0.05 were considered statistically significant for all calculations.

RESULTS

—The 844 participants (44% men, 56% women) in the GENFIEV study were an average age of 49.5 ± 11 years (range 22–79) and had a BMI of 29 ± 5 kg/m^2 (range 16.5–51). According to the 2003 ADA criteria, 43% of the study population had NGT, 42% had impaired glucose regulation (IGR: IFG and/or IGT), and 15% had newly diagnosed T2DM. When HBA_{1c} was used to stratify the study population, 38% were at risk for T2DM (HbA_{1c} 5.7–6.4%) and only 11% met the criterion for T2DM (HbA_{1c} ≥ 6.5%), with a concordance rate of 54% and 44%, respectively. HbA_{1c} specificity was 74% for IGR and 95% for T2DM. ROC curve analyses were used to determine whether screening categorization by HbA_{1c} versus OGTT was independent of cutoff values. The AUROC curve was lowest for prediabetes and higher for diabetes. The AUROC curve was 0.80 (95% CI 0.725–0.849) for diabetes and 0.726 (0.688–0.764) for prediabetes.

Among subjects with HbA_{1c} in the normal range (<5.7%), 33% showed IGR and 5% were T2DM. Compared with NGT subjects, IGR and T2DM subjects both presented a higher HOMA-IR (1.37 ± 0.84 and 1.59 ± 0.25 vs. 1.13 ± 0.71, $P < 0.01$), and a lower insulinogenic index (0.059 ± 0.043 and 0.007 ± 0.095 vs. 0.082 ± 0.159, $P < 0.05$). Moreover, basal prehepatic insulin secretion, β-cell glucose sensitivity of derivative control, and insulin secretion rate at 4.0, 5.5, 8.0, and 11.0 mmol/L glucose were significantly impaired in the same groups of subjects. Among CV risk factors, only HDL-C and triglycerides were significantly worse (data not shown).

To explore whether the OGTT and HbA_{1c} captured subjects with different pathogenetic mechanisms (i.e., insulin resistance vs. insulin secretion) and/or different CV risk profiles, the population was subdivided by those concordant for both diagnostic (HbA_{1c}^{+}/$OGTT^{+}$) or nondiagnostic (HbA_{1c}^{-}/$OGTT^{-}$) criteria, as well as those who were discordant for one (HbA_{1c}^{+}/$OGTT^{-}$) or the other diagnostic ($HbA1c^{-}$/$OGTT^{+}$) criterion. Subjects fulfilling one or more diagnostic criteria for IGR had higher IR and worse insulin secretion than subjects with NGT (Table 1; Fig. 1*B* and *C*), as well increased basal prehepatic insulin secretion (Fig. 1*A*). No significant differences in these parameters were observed between subjects with prediabetes based on HbA_{1c} or OGTT. Similarly, no significant difference

Table 1—*Insulin secretion and action and CV profile in subjects meeting both HbA_{1c} and OGTT criteria ($HbA_{1c}^+/OGTT^+$) for prediabetes and individuals meeting only HbA_{1c} ($HbA_{1c}^+/OGTT^-$) or OGTT ($HbA_{1c}^-/OGTT^+$) criteria, compared with NGT subjects meeting both criteria ($HbA_{1c}^-/OGTT^-$)*

	$HbA_{1c}^-/OGTT^-$ (n = 287)	$HbA_{1c}^+/OGTT^-$ (n = 128)	$HbA_{1c}^-/OGTT^+$ (n = 162)	$HbA_{1c}^+/OGTT^+$ (n = 189)	1 vs. 4 (P)
BMI (kg/m^2)	28.4 ± 5.4	28.8 ± 5.3	29.0 ± 4.9	29.6 ± 5.1	<0.02
Waist (cm)	99 ± 13	101 ± 16	100 ± 12	104 ± 13	<0.002
Blood pressure (mmHg)					
Systolic	124 ± 14	129 ± 17	133 ± 15	133 ± 16	<0.0001
Diastolic	78 ± 11	81 ± 12	83 ± 11	83 ± 12	<0.0001
Fasting plasma glucose (mmol/L)	4.74 ± 0.42	5.57 ± 0.84	5.65 ± 0.63	5.73 ± 0.59	<0.0001
Fasting plasma insulin (μU/mL)	10.6 ± 6.69	12.97 ± 8.77	12.25 ± 7.78	13.2 ± 7.26	<0.001
Total cholesterol (mmol/L)	5.28 ± 1.04	5.46 ± 0.96	5.44 ± 0.91	5.44 ± 1.06	NS
LDL-C (mmol/L)	3.26 ± 0.96	3.55 ± 0.93	3.44 ± 0.88	3.55 ± 1.04	<0.01
HDL-C (mmol/L)	1.45 ± 0.41	1.30 ± 0.36	1.32 ± 0.34	1.32 ± 0.41	<0.0001
Triglycerides (mmol/L)	1.32 ± 1.03	1.80 ± 1.33	1.72 ± 1.03	1.80 ± 1.20	<0.0001
HOMA-IR	1.16 ± 0.71	1.48 ± 0.98	1.40 ± 0.87	1.51 ± 0.81	<0.0001
Insulinogenic index	0.08 ± 0.17	0.05 ± 0.04	0.05 ± 0.03	0.05 ± 0.05	<0.01

was detected between subjects meeting only one or both diagnostic criteria.

The same analysis was performed in T2DM subjects concordant as well as discordant for the HbA_{1c} and OGTT criteria. The former had greater IR and a more severe impairment of insulin secretion than those who fulfilled only one diagnostic criterion (data not shown).

Individuals classified as NGT by both diagnostic criteria had the most favorable CV profile. In contrast, those who met the HbA_{1c} or the OGTT criterion for prediabetes had greater BMIs and waist circumferences, lower values of HDL-C, and higher values of LDL-C, triglyceride, and systolic and diastolic blood pressure (Table 1). No significant difference in CV risk profile was observed between subjects with prediabetes based on HbA_{1c} or OGTT criteria, with the exception of systolic blood pressure ($P < 0.05$). Similarly, no significant difference was detected between subjects meeting one or both diagnostic criteria for IGR, with the exception of waist measurement ($P < 0.01$).

No major difference was found in pathogenetic mechanisms and CV risk profile among individuals identified with the OGTT or by HbA_{1c}. However, a logistic regression analysis adjusted for age, sex, and BMI, showed that individuals with prediabetes, and even more those with T2DM by OGTT, had a greater chance to have IR and impaired insulin secretion and only a marginally increased chance to be associated with the metabolic syndrome than those with prediabetes and T2DM when diagnosed on the basis of HbA_{1c} (Fig. 2).

CONCLUSIONS—In a high-risk Italian population, HbA_{1c} and OGTT criteria for prediabetes both identify subjects with higher IR and worse insulin secretion compared with NGT subjects. Similarly, T2DM patients, irrespective of diagnostic criteria, manifest the highest degree of IR and β-cell dysfunction. Finally, there was no difference in insulin action and secretion according to the diagnostic criterion, although by multiple logistic analysis, subjects with T2DM by OGTT were at greater risk of more severe IR and impaired insulin secretion.

Though HbA_{1c} may represent an attractive test for T2DM screening and diagnosis, data from several studies (3–9) highlight how its use results in an NGT excess, with fewer high-risk and T2DM diagnoses. Our findings are in agreement with those observed in other Caucasian populations (4–7) and confirm that HbA_{1c} is a specific but insensitive method for diagnosis of T2DM or prediabetes. In our hands, the concordance rate was <54%, confirming data obtained in another Italian cohort (19). Moreover, ROC curve analyses confirm that screening categorization by HbA_{1c} versus OGTT was independent of cutoff values (20). The low concordance may be due to measurement variability or to the different physiologic processes probed by HbA_{1c} and OGTT. IFG is mainly associated with hepatic IR, whereas muscle IR characterizes IGT (11). Impaired β-cell function is common to both conditions, but this is mainly due to loss of first-phase insulin secretion in IFG, whereas the second-phase is altered in IGT (11). In contrast, HbA_{1c} reflects long-term exposure to basal and postprandial hyperglycemia and results from the combination of these alterations (21). Despite this, we did not detect any difference in insulin action, insulin secretion, or in other metabolic parameters between individuals meeting HbA_{1c} or OGTT criteria for prediabetes.

With respect to pathogenesis, our results are at variance with those obtained in other populations. In the Insulin Resistance Atherosclerosis Study (6), including three different ethnic groups, HbA_{1c} had a weaker correlation with IR and insulin secretion than single determinations of fasting and 2-h plasma glucose. Moreover, in Mexican Americans, diagnosis based on the OGTT provided a better tool than HbA_{1c} to identify subjects with β-cell impairment (14), implying that the glucose load allows more accurate identification of subtle impairment in β-cell functions compared with fasting plasma glucose or HbA_{1c}. As a partial reconciliation with these data and besides the potential influence of ethnicity, we found that individuals with prediabetes and T2DM identified by OGTT had a greater chance to have impaired insulin action (odds ratio 8.02 vs. 3.95) and insulin secretion (14.24 vs. 8.56) compared with those diagnosed by HbA_{1c} (Fig. 2).

In a recent analysis of another Italian cohort, Marini et al. (19) reported that subjects diagnosed by HbA_{1c} had higher BMIs and lower insulin sensitivity. However, recruitment in that study was based one or more cardiometabolic factors, whereas we used an opportunistic approach that might

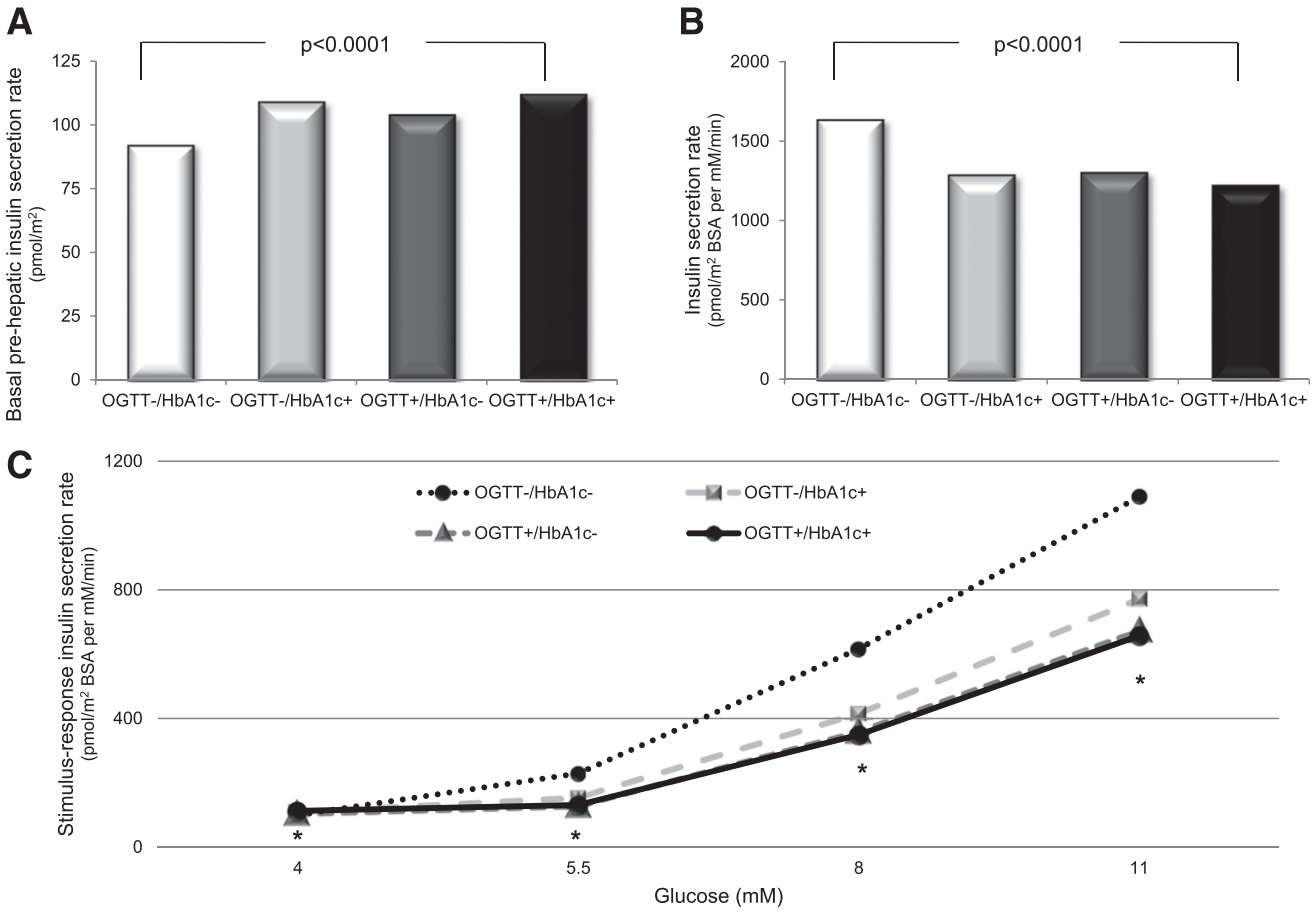

Figure 1—*Insulin secretion by minimal model in NGT subjects by HbA$_{1c}$ and OGTT criteria (HbA$_{1c}^{-}$/OGTT^{-}) compared with subjects meeting both criteria (HbA$_{1c}^{+}$/OGTT^{+}) for prediabetes and individuals meeting only HbA$_{1c}$ (HbA$_{1c}^{+}$/OGTT^{-}) or OGTT (HbA$_{1c}^{-}$/OGTT^{+}) criteria. All measures are age-adjusted.* A: *Basal, prehepatic insulin secretion.* B: *β-Cell glucose sensitivity of derivative control (cognate of first-phase insulin secretion).* C: *Insulin secretion rate at 4.0, 5.5, 8.0, and 11.0 mmol/L glucose, by the stimulus-response curve, which defines glucose sensitivity of proportional control, cognate of second-phase insulin secretion.* *P $<$ *0.001 OGTT^{+}/HbA$_{1c}^{+}$ vs. OGTT^{-}/HbA$_{1c}^{-}$.*

have resulted in the selection of people at greater risk for diabetes.

The effect of different methods used for measurement of insulin secretion and action in these studies should be considered as well. In our study, only C-peptide was measured during OGTT, allowing state-of-the-art assessment of β-cell function by mathematic modeling (17) but limiting assessment of insulin action to the HOMA model (16). Therefore, additional studies using the gold standard measurement of insulin action (i.e., euglycemic insulin clamp) are desirable to provide further insights.

Recent data demonstrated that increased CV risk in nondiabetic subjects was associated not only with fasting and postload glucose but also with HbA$_{1c}$ (22). Subjects in our study who met HbA$_{1c}$ and OGTT criteria for the diagnosis of prediabetes had a worse CV risk profile than NGT individuals. No significant difference was found between prediabetes diagnosed by HbA$_{1c}$ or OGTT criteria, with the exception of systolic blood pressure ($P < 0.05$). Subjects with diabetes, irrespective of diagnostic criteria, had greater prevalence of the metabolic syndrome, with a marginal increase in the odds ratio (4.31 vs. 3.36) for those diagnosed by OGTT. In contrast, in the Danish Inter99 study (23), HbA$_{1c}$ was a better, although not statistically significant, tool at discriminating individuals at low- versus high-risk for ischemic heart disease. Again, differences in study populations may account for the discrepancy, because the Danish Inter99 study is a population-based primary CV prevention study (24).

Other discrepancies are present in the literature. In the Telde Study (25), among individuals with discordant T2DM status by HbA$_{1c}$ and OGTT, those who met the HbA$_{1c}$ criterion had greater measures of BMI and waist circumference and lower values for HDL-C than those with diabetic OGTT but HbA$_{1c}$ <6.5%. On the contrary, subjects in the Rancho Bernardo cohort (26) who met the OGTT criteria had the least favorable CV risk profile compared with those who met only the HbA$_{1c}$ criterion. In the only published prospective population-based study (27), HbA$_{1c}$ at a range of 5.7 to 6.4% was not predictive of CV disease. Therefore, further prospective population-based studies using common methodologic approaches are needed to evaluate the effect of the proposed HbA$_{1c}$ diagnostic criterion on CV morbidity and mortality.

Our study has several limitations. First, each test (HbA$_{1c}$ and OGTT) was performed only once, but such an approach reflects clinical practice, in particular with respect to the OGTT. Second, our study population was not assessed for factors that can affect HbA$_{1c}$ levels such as anemia or hemoglobinopathies

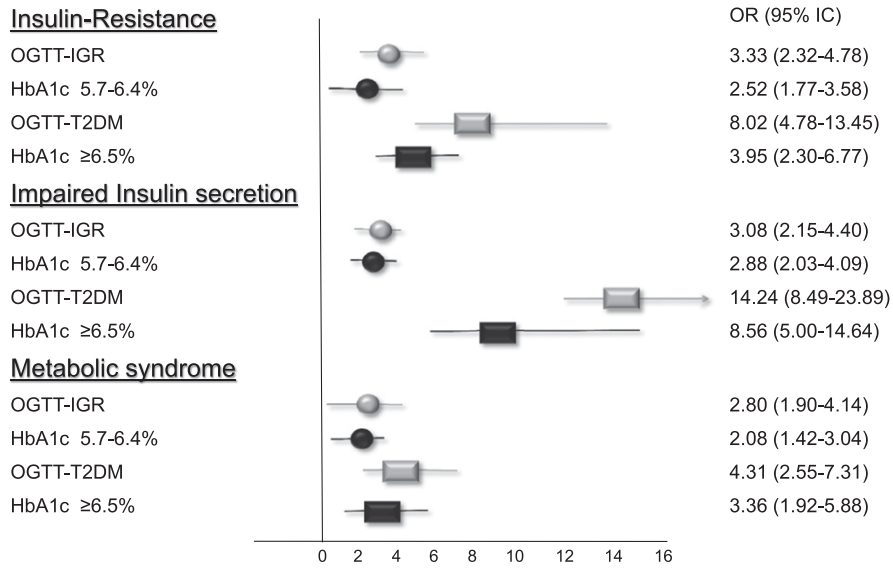

Figure 2—*Association of HbA_{1c} and OGTT categories with impaired insulin secretion (insulinogenic index <1st quartile of NGT subjects), IR (HOMA-IR >4th quartile of NGT subjects), and the metabolic syndrome. Odds ratio (OR) and 95% CI, adjusted for age, sex, and BMI.*

(28). Third, our cohort is not representative of the general population because participants were deemed at risk for T2DM to be recruited.

In conclusion, HbA_{1c} identifies a smaller proportion of individuals with prediabetes and an even smaller proportion with T2DM than OGTT; however, no significant difference in IR, insulin secretion, and CV risk profile was detected in subjects identified as prediabetic with HbA_{1c} or OGTT criteria. Subjects who fulfill both diagnostic methods for prediabetes or T2DM are characterized by a worse metabolic profile.

Acknowledgments—This study was supported by FoRiSID (Foundation for the Research of the Società Italiana di Diabetologia), Rome, Italy, and by an unconditional grant from Eli Lilly, Italy. S.D.P. has served on the scientific board and received honoraria for consulting fees from Novartis Pharmaceuticals, Merck Sharp & Dohme, Roche Pharmaceuticals, Eli Lilly and Co., Boehringer Ingelheim, Bristol-Myers Squibb, AstraZeneca, GlaxoSmithKline, sanofi-aventis, Takeda Pharmaceuticals, Novo Nordisk, and Intarcia. S.D.P. also received research support from Merck Sharp & Dohme, Takeda Pharmaceuticals, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

C.B. and R.M. designed the study, analyzed data, and wrote the manuscript. R.C.B. designed the study, recruited subjects, and contributed to data analysis. F.G. recruited study subjects and contributed to study design and data analysis. S.F., E.F., M.A.D., F.C., G.C., and F.L. recruited study subjects. G.M. recruited study subjects and contributed to study design. S.D.P. designed the study, analyzed data, and wrote the manuscript. S.D.P. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank Francesca Venditti, for secretarial coordination, and Dr. Francesco Caricato and Dr. Giovanna Giovannitti, for laboratory determinations, from the Department of Endocrinology and Metabolism, Section of Diabetes and Metabolic Diseases, University of Pisa, Pisa, Italy.

Parts of this study were presented in abstract form at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

APPENDIX—The GENFIEV investigators: Angelo Cignarelli, University of Bari, Department of Emergency and Organ Transplantation–Section on Internal Medicine, Endocrinology and Metabolic Diseases, Bari, Italy; Fernanda Cerrelli, Simona Moscatiello, Unit of Clinical Dietetics, Alma Mater Studiorum, University of Bologna, Bologna, Italy; Agostino Gnasso, Concetta Irace, University of Catanzaro, Department of Clinical and Experimental Medicine, Catanzaro, Italy; Agostino Consoli, Merilda Taraborelli, Gloria Formoso, University of Chieti, Department of Medicine and Aging Sciences, Chieti, Italy; Meri Mori, Giovanna Gregori, SS. Giacomo e Cristoforo Hospital, Section of Diabetes and Metabolic Diseases, Massa, Italy; Mariella Trovati, Katia Bonomo, University of Turin, Diabetes Unit, Department of Clinical Biological Sciences, Turin, Italy; Giuseppe Penno, Annalisa Agostini, University of Pisa, Department of Endocrinology and Metabolism–Section of Diabetes and Metabolic Diseases, Pisa, Italy; Roberto Anichini, Alessandra De Bellis, Hospital of Pistoia, Section of Diabetes and Metabolic Diseases, Pistoia, Italy; Daniela Bracaglia, Michela Perna, University of Rome Tor Vergata, Diabetes Center, Department of Internal Medicine, Rome, Italy; Marilena Calabria, Alessandra Zappaterreno, University of Rome "La Sapienza," Department of Clinical Sciences, Rome, Italy; Ilaria Barchetta, Giovanna Taverni, University of Rome "La Sapienza," Department of Clinic and Medical Therapy, Rome, Italy; Andrea Giaccari, Alessia Antonelli, Catholic University of Rome, Institute of Endocrinology, Rome, Italy; Maddalena Trombetta, Anna Calì, University of Verona, Department of Biomedical and Surgical Sciences–Section of Endocrinology and Metabolic Diseases, Verona, Italy.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33(Suppl. 1):S62–S69
2. WHO. *Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus*. WHO Press, World Health Organization, Geneva, Switzerland, 2011
3. Kramer CK, Araneta MR, Barrett-Connor E. A1C and diabetes diagnosis: the Rancho Bernardo Study. Diabetes Care 2010; 33:101–103
4. Carson AP, Reynolds K, Fonseca VA, Muntner P. Comparison of A1C and fasting glucose criteria to diagnose diabetes among U.S. adults. Diabetes Care 2010;33:95–97
5. Christensen DL, Witte DR, Kaduka L, et al. Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. Diabetes Care 2010;33:580–582
6. van 't Riet E, Alssema M, Rijkelijkhuizen JM, Kostense PJ, Nijpels G, Dekker JM. Relationship between A1C and glucose levels in the general Dutch population: the new Hoorn study. Diabetes Care 2010;33: 61–66
7. Lorenzo C, Haffner SM. Performance characteristics of the new definition of diabetes: the insulin resistance atherosclerosis study. Diabetes Care 2010;33:335–337
8. Mohan V, Vijayachandrika V, Gokulakrishnan K, et al. A1C cut points to define various

glucose intolerance groups in Asian Indians. Diabetes Care 2010;33:515–519
9. Zhou X, Pang Z, Gao W, et al. Performance of an A1C and fasting capillary blood glucose test for screening newly diagnosed diabetes and pre-diabetes defined by an oral glucose tolerance test in Qingdao, China. Diabetes Care 2010;33:545–550
10. Godsland IF, Jeffs JA, Johnston DG. Loss of beta cell function as fasting glucose increases in the non-diabetic range. Diabetologia 2004;47:1157–1166
11. Abdul-Ghani MA, Matsuda M, Jani R, et al. The relationship between fasting hyperglycemia and insulin secretion in subjects with normal or impaired glucose tolerance. Am J Physiol Endocrinol Metab 2008;295:E401–E406
12. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA; San Antonio metabolism study. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabetologia 2004;47:31–39
13. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. J Clin Endocrinol Metab 2005;90:493–500
14. Kanat M, Winnier D, Norton L, et al. The relationship between β-cell function and glycated hemoglobin: results from the veterans administration genetic epidemiology study. Diabetes Care 2011;34:1006–1010
15. Genuth S, Alberti KG, Bennett P, et al.; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
17. Cretti A, Lehtovirta M, Bonora E, et al. Assessment of beta-cell function during the oral glucose tolerance test by a minimal model of insulin secretion. Eur J Clin Invest 2001;31:405–416
18. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497
19. Marini MA, Succurro E, Arturi F, et al. Comparison of A1C, fasting and 2-h postload plasma glucose criteria to diagnose diabetes in Italian Caucasians. Nutr Metab Cardiovasc Dis 2012;22:561–566
20. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, Phillips LS. Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. Diabetes Care 2010;33:2184–2189
21. Goldstein DE, Little RR, Lorenz RA, et al. Tests of glycemia in diabetes. Diabetes Care 2004;27:1761–1773
22. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811
23. Borg R, Vistisen D, Witte DR, Borch-Johnsen K. Comparing risk profiles of individuals diagnosed with diabetes by OGTT and HbA1c The Danish Inter99 study. Diabet Med 2010;27:906–910
24. Jørgensen T, Borch-Johnsen K, Thomsen TF, Ibsen H, Glümer C, Pisinger C. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. Eur J Cardiovasc Prev Rehabil 2003;10:377–386
25. Boronat M, Saavedra P, López-Ríos L, Riaño M, Wägner AM, Nóvoa FJ. Differences in cardiovascular risk profile of diabetic subjects discordantly classified by diagnostic criteria based on glycated hemoglobin and oral glucose tolerance test. Diabetes Care 2010;33:2671–2673
26. Kramer CK, Araneta MR. Comment on: Boronat et al. Differences in cardiovascular risk profile of diabetic subjects discordantly classified by diagnostic criteria based on glycated hemoglobin and oral glucose tolerance test. Diabetes Care 2010;33:2671–2673. Diabetes Care 2011;34:e59; author reply e60
27. Cederberg H, Saukkonen T, Laakso M, et al. Postchallenge glucose, A1C, and fasting glucose as predictors of type 2 diabetes and cardiovascular disease: a 10-year prospective cohort study. Diabetes Care 2010;33:2077–2083
28. Coban E, Ozdogan M, Timuragaoglu A. Effect of iron deficiency anemia on the levels of hemoglobin A1c in nondiabetic patients. Acta Haematol 2004;112:126–128