Differences in Cardiovascular Risk Profile of Diabetic Subjects Discordantly Classified by Diagnostic Criteria Based on Glycated Hemoglobin and Oral Glucose Tolerance Test

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OBJECTIVE — To characterize the cardiovascular risk profile of subjects categorized differently by A1C- and oral glucose tolerance test (OGTT)-based diagnostic criteria for diabetes according to the recommendations of the American Diabetes Association (ADA).

RESEARCH DESIGN AND METHODS — An OGTT, A1C, and several cardiovascular risk factors were assessed in 964 individuals without known diabetes participating in a cross-sectional epidemiological survey in Gran Canaria, Spain.

RESULTS — Taking the OGTT as the gold standard, the sensitivity and specificity of an A1C value ≥6.5% were 38.7 and 99.6%, respectively. Subjects who fulfilled A1C-based criterion presented greater measures of BMI and waist circumference, lower values for HDL cholesterol, and higher values for fasting plasma glucose, homeostasis model assessment of insulin resistance, and fibrinogen than subjects with diabetic OGTT but A1C <6.5%.

CONCLUSIONS — Newly diagnosed diabetic individuals who fulfill A1C-based diagnostic criterion for the disease display a more unfavorable cardiovascular risk profile than individuals who only meet the glucose-based criteria.

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Last year, an International Expert Committee advocated the use of A1C testing for the diagnosis of diabetes (1). Based on the correlation between A1C levels and risk of retinopathy in several epidemiological studies, the committee determined that an A1C value ≥6.5% should be used as the diagnostic threshold. Guided by this report, the American Diabetes Association (ADA) has approved the use of A1C as an additional criterion for diagnosing type 2 diabetes (2).

Increasing evidence, however, demonstrates a low level of agreement between a diabetes diagnosis made by A1C and one obtained using conventional criteria based on plasma glucose (3–7). As stressed by the ADA, the characterization of subjects discordantly categorized by both tests is now pending (2). The present report targeted the assessment of differences in the cardiovascular risk profiles of subjects categorized differently as having or not having diabetes with diagnostic criteria based on plasma glucose and A1C.

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RESEARCH DESIGN AND METHODS

— The Telde Study is a cross-sectional population-based survey conducted in Telde, a city located on the island of Gran Canaria, Canary Islands, Spain. The present study was carried out on the 964 participants (at least 30 years of age) without a previous diagnosis of diabetes. The design and conduct of the survey have been previously described (8).

A1C was determined using high-performance liquid chromatography with an HA-8140 analyzer (Menarini Diagnostics-Arkray, Kyoto, Japan) calibrated to the Japanese Diabetes Society and the Japanese Society for Clinical Chemistry (JDS/JSCC) system. Realignment to the U.S. National Glycohemoglobin Standardization Program (NGSP) values was done according to a national consensus document for the harmonization of A1C in Spain (9) using the following formula: NGSP (%) = 0.985 × JDS/JSCC (%) + 0.46. Participants were categorized according to the results of fasting and 2-h plasma glucose from a standard 75-g oral glucose tolerance test (OGTT) (diabetes or no diabetes) and A1C levels (<6.5 or ≥6.5%) (2). The metabolic syndrome was defined according to the joint statement recently proposed by a number of professional organizations (10). Insulin resistance and pancreatic β-cell function were estimated using the homeostasis model assessment for insulin resistance (HOMA-IR) and the HOMA for β-cell, respectively.

Statistical analyses

Age- and sex-adjusted percentages and means were obtained using logistic regression and ANCOVA, respectively. When necessary, logarithmical transformation was performed to reduce skewness, and values were expressed as geometric means. Percentages and means were compared using the likelihood ratio test and the *F* test, respectively, and ho-

Table 1—*Age- and sex-adjusted cardiovascular risk factors and measures of insulin resistance and insulin secretion according to diagnosis of diabetes based on OGTT and A1C*

	Group 1 (A1C ≥6.5%)	Group 2 (OGTT +/A1C <6.5%)	Group 3 (OGTT −/A1C <6.5%)	
n	28	38	898	*P*
Age (years)	54.8 (10.9)[a]	58.5 (10.9)[a]	46.4 (11.3)[b]	<0.001
Men/women (%)	67.9/32.1[a]	60.5/39.5[a]	41.5/58.5[b]	0.002
BMI (kg/m^2)	30.7 (0.9)[a]	28.2 (0.78)[b]	27.9 (0.16)[b]	0.009
Waist (cm)	105.4 (2.2)[a]	99.0 (1.9)[b]	96.2 (0.4)[b]	<0.001
Systolic blood pressure (mmHg)	127.3 (2.6)[a]	124.2 (2.3)[a]	117.2 (0.47)[b]	<0.001
Diastolic blood pressure (mmHg)	79.4 (1.9)[a]	75.2 (1.7)[a,b]	72.8 (0.3) [b]	0.001
Hypertension (%)	34.7 (10.3)	34.0 (9.0)	24.9 (2.0)	0.290
Smoking (%)	22.8 (11.7)	13.0 (13.4)	24.8 (2.0)	0.269
Glucose (mmol/l)*	8.12 (0.20)[a]	6.32 (0.16)[b]	4.98 (3.2)[c]	<0.001
2-h glucose (mmol/l)*	11.43 (0.75)[a]	10.4 (0.4)[a]	5.5 (0.08)[b]	<0.001
A1C (%)*	7.47 (0.11)[a]	5.61 (0.08)[b]	5.29 (1.5)[c]	<0.001
Cholesterol (mmol/l)	5.35 (0.18)	5.56 (0.16)	5.49 (0.03)	0.646
HDL cholesterol (mmol/l)	1.24 (0.06)[a]	1.41 (0.05)[b]	1.40 (0.01)[b]	0.018
Triglycerides (mmol/l)*	1.40 (0.13)[a]	1.40 (0.10)[a]	1.16 (0.02)[b]	0.018
LDL cholesterol (mmol/l)	3.38 (0.16)	3.48 (0.14)	3.48 (0.03)	0.840
CRP >1 mg/l (%)	20.2 (12.0)[a]	7.1 (15.7)[a,b]	3.3 (4.7)[b]	0.003†
PAI-1 (ng/ml)	40.5 (3.35)[a]	32.2 (2.9)[a,b]	27.7 (0.6)[b]	<0.001
Fibrinogen (mg/dl)	3.56 (0.12)[a]	3.21 (0.11)[b]	3.16 (0.02)[b]	0.005
Von Willebrand factor (IU/l)	126.0 (6.8)[a]	116.3 (5.9)[a,b]	106.1 (1.2)[b]	0.006
Homocysteine (μmol/l)*	10.9 (0.79)	10.7 (0.67)	10.6 (0.13)	0.916
Metabolic syndrome (%)	82.1 (13.7)[a]	60.6 (9.3)[a]	23.6 (2.2)[b]	<0.001‡
Insulin (pmol/l)*	90.38 (11.48)[a]	76.05 (7.89)[a]	48.79 (1.43)[b]	<0.001
HOMA-IR*	4.54 (0.61)[a]	2.98 (0.32)[b]	1.49 (0.06)[c]	<0.001
HOMA-β*	24.9 (3.61)	29.2 (3.12)	23.1 (0.63)	0.178

Values are expressed as percentages and arithmetic or geometric* means (SE). Values followed by the same letter do not differ statistically. †OR (95% CI) group 1 vs. group 3: 7.4 (2.7–20.4). ‡OR (95% CI) group 1 vs. group 3: 14.8 (5.0–44.0) and group 2 vs. group 3: 5.0 (2.4–10.5). CRP, C-reactive protein. PAI-1, plasminogen activator inhibitor 1.

mogeneity groups were determined when significant differences were found by using the corresponding linear contrasts. Multiple backward stepwise logistic regression analysis was used to investigate independent effects of associated factors with A1C ≥6.5%.

RESULTS — Sixty-two subjects were diagnosed with diabetes according to the OGTT results (35 with fasting glucose ≥7 mmol/l and the remaining 27 only by 2-h glucose). Twenty-eight subjects presented an A1C value ≥6.5%, 24 of whom also had diabetes using the OGTT criteria. Thus, the diagnosis of diabetes based on an A1C ≥6.5% yielded a sensitivity of 38.7% and a specificity of 99.6%. The agreement between the glucose- and A1C-based criteria for diagnosis was moderate (κ statistic = 0.51; 95% CI [0.387–0.641]). Table 1 presents the age- and sex-adjusted measures of a set of cardiovascular risk factors and indirect indicators of insulin resistance and insulin secretion according to A1C- and glucose-based diagnosis of diabetes.

As expected, individuals classified as nondiabetic by both diagnostic methods showed the most favorable cardiovascular risk profile. By contrast, the group meeting A1C diabetes criteria presented greater measures of BMI and waist circumference, lower values of HDL cholesterol, and higher values of fasting plasma glucose, fibrinogen, and HOMA-IR than the group fulfilling only the glucose-based criteria. Multivariate logistic regression analysis demonstrated that abdominal obesity (dichotomized with the cutoff for diagnosis of the metabolic syndrome) and 2-h plasma glucose were the only variables independently associated with an A1C value ≥6.5%.

CONCLUSIONS — Several recent studies have compared A1C and OGTT for the detection of undiagnosed diabetes among the participants in different epidemiological surveys. While notable divergences have been found across ethnic groups (6), our findings are in agreement with those observed in other Caucasian-majority populations (3–6) and confirm that, considered in isolation, A1C is a very specific but too insensitive method of diagnosing diabetes.

On the other hand, although differences were not observed for other cardiovascular risk factors, such as hypertension, metabolic syndrome, or elevation of C-reactive protein, the present data show that individuals who met the A1C criterion for diabetes were characterized by greater measures of BMI and waist circumference; higher values of fasting glucose, HOMA-IR, and fibrinogen; and lower values of HDL cholesterol than individuals fulfilling only the OGTT diagnostic criteria. These results in subjects with newly diagnosed diabetes expand previous data that have related the A1C measurement to the metabolic syndrome and several markers of systemic inflammation and disturbed hemostasis among the nondiabetic population (11–13). In fact, abdominal obesity was one of the only two variables that were independently associated with an A1C value ≥6.5% in our multivariate regression model. The sec-

ond variable was 2-h plasma glucose, which displaced fasting plasma glucose from the model. This finding indicates that the presence of A1C levels ≥6.5% in this subset of individuals without a previous diagnosis of diabetes depends more on postprandial plasma glucose than on basal glucose. A greater contribution of postprandial versus fasting glucose to A1C levels has been similarly observed among subjects with established diabetes and moderately increased levels of A1C (14). The particular influence of postprandial glucose, a well established cardiovascular risk factor (15), on A1C levels could reinforce the role of A1C as a potential marker of cardiovascular risk.

Accepting the limitations inherent to this small cross-sectional study, these findings could suggest the following: are individuals in the early stages of diagnosis who meet the A1C criteria for diabetes more insulin resistant and display a more unfavorable cardiovascular risk profile than those who fulfill only the OGTT-based criteria? Prospective studies focusing on this question will be needed to examine this possibility.

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References

1. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–1334
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33:S62–S69
3. 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
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. Lorenzo C, Haffner SM. Performance characteristics of the new definition of diabetes: the Insulin Resistance Atherosclerosis Study. Diabetes Care 2010;33:335–337
6. Christensen DL, Witte DR, Kaduka L, Jørgensen ME, Borch-Johnsen K, Mohan V, Shaw JE, Tabák AG, Vistisen D. Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. Diabetes Care 2010; 33:580–582
7. Kramer CK, Araneta MR, Barrett-Connor E. A1C and diabetes diagnosis: the Rancho Bernardo Study. Diabetes Care 2010; 33:101–103
8. Boronat M, Varillas VF, Saavedra P, Suárez V, Bosch E, Carrillo A, Nóvoa FJ. Diabetes mellitus and impaired glucose regulation in the Canary Islands (Spain): prevalence and associated factors in the adult population of Telde, Gran Canaria. Diabet Med 2006;23: 148–155
9. Goberna R, Aguilar-Diosdado M, Santos-Rey K, Mateo J. Consensus document for the harmonization of HbA1c results in Spain. Av Diabetol 2009;25:35–37
10. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WPT, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity Circulation 2009; 120:1640–1645
11. Muntner P, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. Diabetes Care 2005;28: 1981–1987
12. Sung KC, Rhee EJ. Glycated haemoglobin as a predictor for metabolic syndrome in non-diabetic Korean adults. Diabet Med 2007;24:848–854
13. Nguyen QM, Srinivasan SR, Xu JH, Chen W, Berenson GS. Distribution and cardiovascular risk correlates of hemoglobin A(1c) in nondiabetic younger adults: the Bogalusa Heart Study. Metabolism 2008; 57:1487–1492
14. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). Diabetes Care 2003;26:881–885
15. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001; 161:397–405