Performance Characteristics of the New Definition of Diabetes

The Insulin Resistance Atherosclerosis Study

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OBJECTIVE — A1C ≥6.5% has been recently proposed as the defining criterion for diabetes. However, performance characteristics of this definition have not been described.

RESEARCH DESIGN AND METHODS — In the Insulin Resistance Atherosclerosis Study, we compared new to previous definitions of diabetes: 1999 World Health Organization ($DM_{1999WHO}$) and 2003 American Diabetes Association based on fasting glucose alone (DM_{FPG126}).

RESULTS — Participants with A1C ≥6.5%, $DM_{1999WHO}$, and DM_{FPG126} were 44 (5.2%), 132 (15.4%), and 61 (7.1%), respectively. In individuals with $DM_{1999WHO}$, mean, median, and interquartile range of A1C were 6.3, 5.9, and 5.5–6.6%, respectively; in individuals with DM_{FPG126}, mean, median, and interquartile range of A1C were 7.0, 6.6, and 6.0–7.1%.

CONCLUSIONS — A1C ≥6.5% identifies fewer individuals than $DM_{1999WHO}$ or DM_{FPG126}. Studies are needed to determine that A1C ≥6.5% compromises neither blood pressure and lipid management in early diabetes nor the implementation of lifestyle interventions for diabetes prevention.

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An expert committee recently recommended using A1C as the preferred marker for diagnosing diabetes (≥6.5%) and detecting individuals at the highest risk for developing diabetes (6.0–6.4%) (1). Early definition attempts were based on a perceived bimodal glucose distribution in some populations (2) and later on the relationship between glucose levels and the presence of long-term complications, particularly retinopathy (3). A1C is now recommended, because A1C correlates well with retinopathy (4) and has superior technical attributes (less biological variability and more convenience by requiring no fasting or timed samples) (1). However, clinical consequences of A1C testing are not known.

In this study, we compared performance characteristics of the new definition relative to the 1999 World Health Organization (WHO) ($DM_{1999WHO}$) (5) and 2003 American Diabetes Association (ADA) (DM_{FPG126}) (6) definitions in the Insulin Resistance Atherosclerosis Study (IRAS) (5).

RESEARCH DESIGN AND METHODS

The design and methods of the IRAS have been previously described (7). The IRAS protocol was approved by local institutional review committees, and all participants provided written informed consent.

We used follow-up data (n = 855), because A1C was not measured at baseline. DM_{FPG126} was defined as fasting plasma glucose concentration ≥126 mg/dl (6) and $DM_{1999WHO}$ as fasting plasma glucose concentration ≥126 mg/dl and/or 2-h plasma glucose concentration ≥200 mg/dl (5). Individuals treated with antidiabetic medications were excluded. Indication for treatment with antihypertensive and LDL-lowering medications was examined using the Seventh Report of the Joint Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) and the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATPIII) guidelines, respectively.

Logistic regression model was used to study the diagnostic performance of A1C using receiver operating characteristic (ROC) curves (SAS statistical software, version 9.1; SAS, Cary, NC).

RESULTS

The number of participants with A1C <6.0, 6.0–6.4, and ≥6.5% was 766 (89.5%), 45 (5.3%), and 44 (5.2%), respectively. A1C 6.0–6.4% and ≥6.5% categories had comparable insulin sensitivity index (0.45 ± 0.10 vs. 0.46 ± 0.76 × 10^{-4} $min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$, P = 0.994) and metabolic syndrome prevalence (71.3% [56.0–82.9] vs. 80.5% [66.1–89.7], P = 0.519) (see supplementary Table 1 in the online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc09-1357/DC1). However, acute insulin response was higher in the A1C 6.0–6.4% category (51.4 ± 6.3 vs. 27.2 ± 3.4 μU/ml, P < 0.001).

There were 132 (15.4%) individuals with $DM_{1999WHO}$ and 61 (7.1%) with DM_{FPG126}. In individuals with $DM_{1999WHO}$, mean, median, and interquartile range of A1C levels were 6.3, 5.9, and 5.5–6.6%, respectively; in individuals with DM_{FPG126}, mean, median, and interquartile range of A1C levels were 7.0, 6.6, and 6.0–7.1%. The area under the ROC curve of A1C for identifying participants with $DM_{1999WHO}$ and DM_{FPG126} was 0.843 and 0.931, respectively (Fig. 1). Because of the low sensitivity and high specificity, A1C ≥6.5% was a strong indicator of the presence of $DM_{1999WHO}$ and DM_{FPG126}; however, absence of A1C ≥6.5% could exclude neither. To a certain degree, results were similar for the 6.0% A1C threshold.

Among the 92 individuals with $DM_{1999WHO}$ and A1C <6.5, 75.8, and 82.6% met the criteria for antihyperten-

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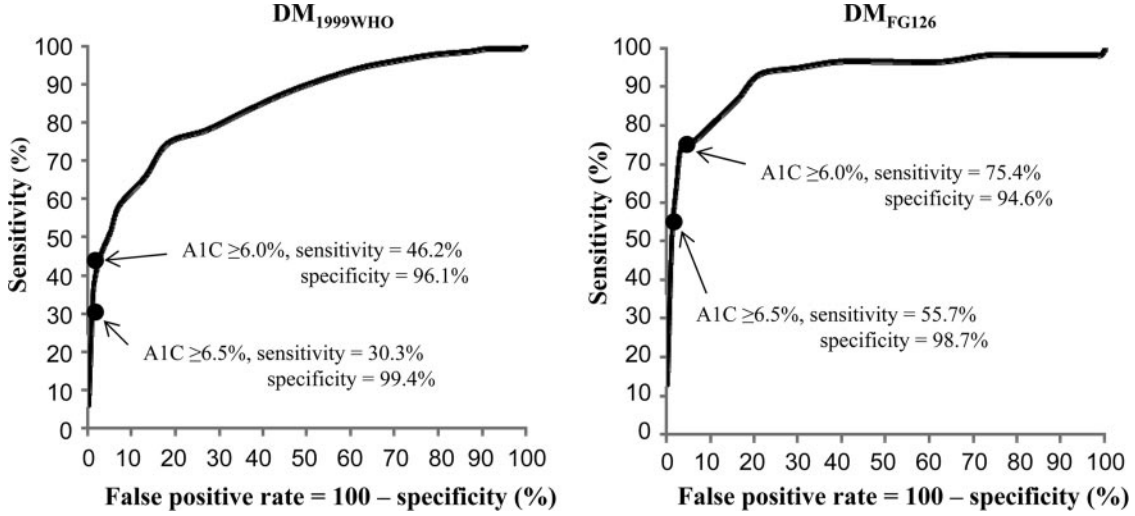

Figure 1—*ROC curves for detecting subjects with $DM_{1999WHO}$ or DM_{FPG126} for A1C. In subjects with A1C ≥6.5%, 40 had $DM_{1999WHO}$ and 4 did not; in subjects with A1C <6.5%, 92 had $DM_{1999WHO}$ and 719 did not. DM_{FPG126} was present and absent in 34 and 10 individuals with A1C ≥6.5%, respectively; corresponding numbers of individuals in the A1C <6.5% category were 27 and 784, respectively. $DM_{1999WHO}$ and DM_{FPG126} indicate type 2 diabetes by 1999 WHO and 2003 ADA criteria, respectively.*

sive (≥130/80 mmHg) and LDL-lowering treatment (LDL cholesterol ≥100 mg/dl), respectively. Because these individuals were considered nondiabetic by the new definition, only 56.0 and 59.1% fulfilled the requirements for treatment by JNC-7 (≥140/90 mmHg) and NCEP-ATPIII (based on global risk score) guidelines, respectively; consequently, 19.8 and 23.5% could potentially miss treatment.

CONCLUSIONS — The number of individuals identified by A1C ≥6.5% is one-third the number of individuals identified with the 1999 WHO criteria and 70% the number of individuals identified with the 2003 ADA criteria. Individuals with A1C 6.0–6.4% differ little from those with A1C ≥6.5% in terms of insulin resistance and metabolic syndrome, but have less β-cell dysfunction.

The question whether the new definition of diabetes (A1C ≥6.5%) improves previous attempts falls outside the scope of this study. Outcome data are needed. A1C correlates well with retinopathy (4), but 2-h glucose concentration better predicts mortality and/or cardiovascular disease than A1C and fasting glucose concentration in most studies (8–11) but not all (12). Our results indicate that A1C ≥6.5% is insensitive; therefore, this threshold could jeopardize treatment benefits of blood pressure and lipids in early diabetes.

Insulin resistance is, for the most part, fully developed, and β-cell function is largely compromised in individuals with impaired glucose tolerance (13). Because more than half of the individuals with $DM_{1999WHO}$ have A1C levels <6.0%, this A1C threshold has the potential of deemphasizing the implementation of lifestyle interventions with proven efficacy for preventing diabetes (14).

A significant limitation of our study is the use of single determinations of plasma glucose levels to diagnose diabetes. Concordance for obtaining fasting glucose concentration ≥126 mg/dl (or 2-h glucose concentration ≥140 mg/dl) in two different days is 70% (15). However, imprecision in measurement cannot explain much of the disparity between the new and 1999 WHO definitions.

In summary, the new definition identifies fewer individuals than the 1999 WHO definition. Studies are needed to demonstrate that the 6.5 and 6.0% A1C cut-points compromise neither the management of blood pressure and lipids in early diabetes nor the implementation of lifestyle interventions to delay the disease process. New and old definitions should be tested in studies with outcome data.

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