Utility of A1C for Diabetes Screening in the 1999–2004 NHANES Population

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Thirty percent of people with diabetes are undiagnosed (1), and up to 25% already have microvascular complications at diagnosis (2). The American Diabetes Association recommends screening adults ≥45 years of age, especially those with a BMI ≥25 kg/m^2, at 3-year intervals with a fasting plasma glucose (FPG) measurement (3). However, physicians infrequently use an FPG for screening. For example, in a large health maintenance organization within the University of Michigan health system, 184 physicians at 22 separate locations screened 5,752 (69%) of 8,286 people without diabetes over a 3-year period. Ninety-five percent of the screening tests were random glucose measurements, 3% were FPGs, and 2% were A1Cs (4). Random glucose levels depend on the length of time after the previous meal and the carbohydrate content of that meal. There is no agreement on what random glucose values should lead to further investigations.

Because A1C levels reflect average glycemia during the preceding 3–4 months, meal issues are not a factor. To determine what A1C level should lead to further tests to diagnose diabetes, we examined the 1999–2004 National Health and Nutrition Examination Survey (NHANES) population of those not known to have diabetes to determine the sensitivity and specificity with which various A1C levels identified people with diabetes.

RESEARCH DESIGN AND METHODS

— NHANES oversampled African-American and Hispanic individuals to obtain enough data for analysis in this minority subset. Accordingly, results were weighted to reflect the U.S. population. SUDAAN statistical software was used to obtain weighted estimates that account for the complex survey design of NHANES (5). Of the 8,881 subjects with a 6-year weighting variable identified, 6,036 were 20 years of age or older and 6,012 had fasting blood samples drawn. Glycated hemoglobin levels were measured by a boronate affinity high-performance liquid chromatography (HPLC) system and converted to A1C levels (6). The normal range was 4.0–6.0% (personal communication, Randie Little, PhD, University of Missouri School of Medicine, Columbia, MO). Subjects were queried by questionnaire, and 532 were excluded because of a previous diagnosis of diabetes. An additional 535 subjects were excluded due to missing questionnaire data and 10 for missing laboratory data. The final dataset included 4,935 individuals. Those whose FPG concentrations were ≥126 mg/dl were diagnosed with diabetes. The results were analyzed by a receiver operating characteristic (ROC) curve.

RESULTS

— Of the final cohort of 4,935 subjects, 3,280 were normal (FPG <100 mg/dl), 1,485 had impaired fasting glucose (FPG 100–125 mg/dl), and 170 had previously undiagnosed diabetes (FPG ≥126 mg/dl). The relationship between A1C level and diagnosis of diabetes is shown in Fig. 1. An A1C level of 5.8% yielded the highest combination of sensitivity (86%) and specificity (92%) in the total population. Analyses of subsets of these NHANES subjects revealed sensitivities of 84, 90, 84, 93, and 95% in 2,334 men, 2,601 women, 2,631 non-Hispanic whites, 874 African Americans, and 1,295 Hispanics, respectively. Specificities were 92, 92, 93, 86, and 91%, respectively. The 135 subjects who listed their race as "other" were not analyzed separately because of their small number.

CONCLUSIONS

— The American Diabetes Association recommends confirmation of an FPG level to diagnose diabetes (3). Requiring confirmation (not available in NHANES data) would decrease sensitivity and increase specificity. However, an A1C level of 5.8% is consistent with the results of a previous ROC analysis on the 1988–1994 NHANES III population utilizing an ion exchange HPLC A1C assay (normal 5.17 ± 0.45% [SD]) with diabetes also diagnosed by an FPG ≥126 mg/dl. They concluded that the best screening value lay between 1 and 2 SDs above the mean (7). The two NHANES studies relate A1C levels to the prevalence of diabetes. Two studies have related A1C levels to the incidence of diabetes. In 1,253 veterans aged 45–64 years, the 3-year incidence of diabetes (by self-report, FPG ≥126 mg/dl or A1C ≥7.0%) at baseline A1C levels of ≤5.5, 5.6–6.0, and 6.1–6.9% was 0.8, 2.5, and 7.8 per 100 person-years, respectively (8). In 2,820 French people aged 30–65 years whose baseline A1C levels were split into deciles, the 6-year incidence of diabetes (diabetes drugs or FPG ≥126 mg/dl) was ~2.5, 5.0, and 10% in the upper three A1C deciles of 5.7, 5.8, and 5.8–7.1%, respectively (9).

Based on the results of these studies relating A1C levels to both prevalent and incident diabetes, an A1C value in a DCCT (Diabetes Control and Complications Trial)-standardized assay (10) of ≥5.8% could effectively serve to identify individuals in whom further investiga-

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Abbreviations: FPG, fasting plasma glucose; HPLC, high-performance liquid chromatography; NHANES, National Health and Nutrition Examination Survey; ROC, receiver operating characteristic.

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

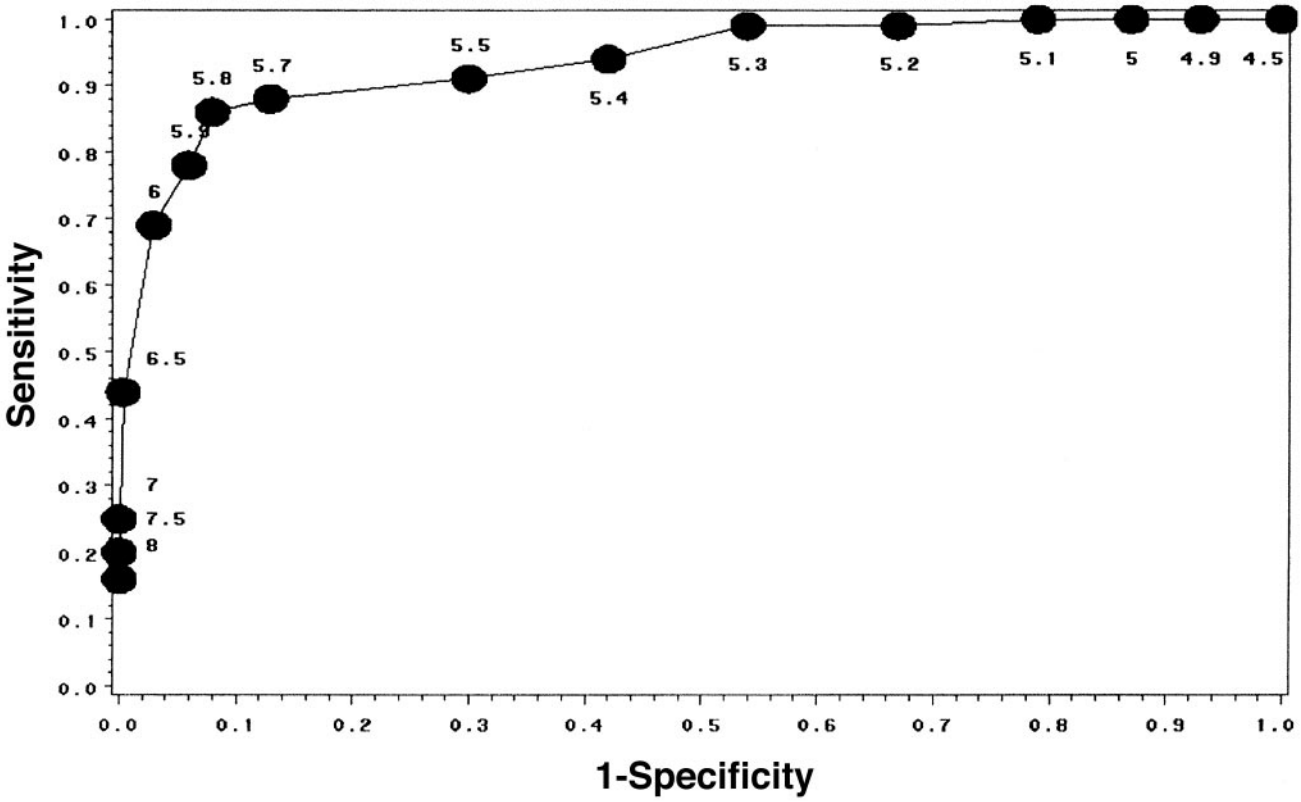

Figure 1—*ROC curve for A1C levels to screen for diabetes (defined as an FPG ≥126 mg/dl).*

tions might be fruitful. Since fasting is not necessary for A1C measurements, this approach would markedly reduce the number of people required to return for a fasting test. Given the A1C result, both physicians and their patients might be more motivated to further explore the potential diagnosis of diabetes.

Alternatively, an argument can be made to utilize only A1C levels for the diagnosis of pre-diabetes/diabetes. The levels of glycemia that are associated with the microvascular complications of diabetes are generally agreed upon as appropriate diagnostic criteria (11). In both type 1 (12–14) and type 2 (15,16) diabetic patients, these complications did not develop or progress for 6–9 years when the average A1C level was kept at <7.0%. Supporting this relationship, when A1C levels in three large diabetic populations were divided into deciles, the mean value in the first decile, in which retinopathy increased, ranged from 6.7 to 7.5% (17). Regarding A1C levels and pre-diabetes, people in the DPP (Diabetes Prevention Program) (18) with values of 6.1–6.9% were twice as likely to progress to diabetes as those with lower values (19).

Thus, we propose that individuals with A1C levels measured in a DCCT-standardized assay of ≤6.0% are normal, 6.1–6.9% have pre-diabetes, and ≥7.0% have diabetes. Since metformin is recommended for those with type 2 diabetes (20) and in younger obese people with pre-diabetes (19), A1C levels should be confirmed in these patients. Alternatively, an A1C level of ≥5.8% could lead to a glucose measurement (an FPG or even an oral glucose tolerance test). In either approach, diabetes will be diagnosed in those at clear risk for microvascular complications. Those with pre-diabetes will be identified so that appropriate measures can be adopted to reduce their chances of developing diabetes.

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