Clinical Chemistry / HbA1c in Prediabetes Testing

Hemoglobin A1c Testing Alone Does Not Sufficiently Identify Patients With Prediabetes

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Abstract

Whether hemoglobin A1c (HbA1c) values are suitable for diagnosing diabetes has been debated. We sought to assess the prevalence of elevated HbA1c levels in a prediabetes patient population.

Oral glucose tolerance tests and HbA1c levels were analyzed for patients entering a diabetes prevention program between January 1, 2007, and September 13, 2009. We calculated the percentage of patients with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) who had HbA1c values in the 6.0% to 6.4% range or in the 5.7% to 6.4% range.

The mean age of the 242 patients was 62 years; 64.0% were women, and 88.0% were white. Isolated IFG was detected in about 56.2% of patients and combined IFG and IGT in about 37.2%. Only 28.5% of patients had HbA1c values in the 6.0% to 6.4% range, whereas 65.3% had values in the 5.7% to 6.4% range.

Our data suggest that reliance on HbA1c testing alone to identify candidates for a diabetes prevention program would miss a substantial number of eligible patients.

A hemoglobin A1c (HbA1c) level of 6.5% or more was recommended recently as a cutoff to diagnose diabetes mellitus when confirmed by repeated testing.1 Recent analyses have demonstrated, however, that HbA1c may not be suitable for diagnosing diabetes because of its low sensitivity in identifying persons with the disease.2,3 Thus, the recommendation to use HbA1c in place of glucose levels to screen for and diagnose diabetes has come under recent criticism, remains controversial, and is not universally accepted.4,5

The prediabetes state is denoted by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or combined IFG and IGT. Recently, an HbA1c value in the 5.7% to 6.4% range was added as a criterion for diagnosing prediabetes.6 Persons in any one of these categories are considered to be at greater risk for the development of type 2 diabetes; patients with HbA1c values in the narrower 6.0% to 6.4% range are considered at particularly high risk.6 It is now well established that patients with prediabetes can derive long-term benefit from intensive lifestyle interventions and can delay progression to type 2 diabetes. Referral to an ongoing support program to provide these interventions is recommended6; therefore, the identification of patients in a clinical setting who would qualify for such intervention is important.

Although the use of HbA1c testing as a laboratory method to diagnose diabetes has been extensively discussed and critiqued, it is unclear how well HbA1c testing would identify patients with prediabetes. By using a clinic population with known prediabetes, we assessed the prevalence of patients who had HbA1c levels in the range of 6.0% to 6.4% or in the broader range of 5.7% to 6.4%.
Research Design and Methods

In January 2007, we implemented a clinic-based type 2 diabetes prevention program known as Diet-Exercise-Activity-Lifestyle (DEAL). The DEAL program has been previously described. Briefly, patients are referred after a provisional diagnosis of IFG is detected during a standard fasting blood chemistry panel. A stepped-care approach to prevention is used, with intensive lifestyle changes encouraged during the first 6 months and introduction of metformin treatment if there is any evidence of worsening glycemic control. The 2-hour oral glucose tolerance test (75 g) is conducted, and HbA1c values are checked at baseline and then again at 6 and 12 months. Patients entering the DEAL program are stable ambulatory nonpregnant people without any recent acute illnesses, hospitalizations, transfusions, or evidence of hemolytic anemia (mean hemoglobin level, 14 g/dL [140 g/L]; hematocrit, 41% [0.41]; platelet count, 258 \( \times 10^3 \)–10^9/L [258 \( \times 10^3 \)–10^9/L]—all within normal limits).

HbA1c and glucose determinations are performed on a Roche Cobas 6000 chemistry analyzer (Roche Professional Diagnostics, Indianapolis, IN). Glucose values are determined by the standard hexokinase assay. The HbA1c determination is based on turbidimetric immunoinhibition using hemolyzed whole blood. This method is certified by the National Glycohemoglobin Standardization Program. In our facility, the reference range for HbA1c is 4.6% to 5.8%. Most common hemoglobin variants (HbF, HbC, HbS, and HbE) do not interfere with this method. Rare variants of hemoglobin may show interference. The known variants that fall into this category are Hb Raleigh, Niigata, Deer Lodge, Okayama, Fukuoka, Graz, Agrigente, Warwickshire, and Tyne.

For the 242 patients who entered the DEAL program between January 1, 2007, and September 13, 2009, we analyzed baseline oral glucose tolerance test and HbA1c results. Patients were classified as having IFG, IGT, or combined IFG and IGT on the basis of oral glucose tolerance test results. We calculated the percentage of patients with IFG and IGT who had HbA1c values in the ranges of 5.7% to 6.4% and 6.0% to 6.4%. Data analysis was conducted using SAS (version 9.1, SAS Institute, Cary, NC). Differences in distributions of dichotomous variables were analyzed using the \( \chi^2 \) test.

Results

Data from the 242 patients were analyzed and reported as mean (SD). The mean age of the patients was 62 (SD, 11) years; 64.0% (155/242) were women, and 88.0% (213/242) were white. The mean fasting glucose level was 110 mg/dL (6.1 mmol/L; SD, 8 mg/dL [0.4 mmol/L]), the 2-hour glucose level was 137 mg/dL (7.6 mmol/L; SD, 35 mg/dL [1.9 mmol/L]), and HbA1c was 5.8% (SD, 0.36%). IFG alone was detected in 136 (56.2%) of the 242 patients, and combined IFG and IGT was found in 90 (37.2%). Because of the small number of patients in the IGT-only group (n = 8), their data were included with those for the combined IFG and IGT group for further analysis.

Only 28.5% (69/242) of patients had HbA1c values in the range of 6.0% to 6.4% Table I, with a significantly higher prevalence in women than in men (P = .02); no differences were found by age. Among patients with isolated IFG, 29.4% (40/136) had HbA1c values in the 6.0% to 6.4% range, with a trend toward a higher prevalence among women than among men (P = .08) and no difference by age. Finally, the percentage of patients with HbA1c values in the 6.0% to 6.4% range in the combined IFG and IGT group was also low overall (27.8% [25/90]), with no significant difference between sex or age groups.

We next examined the proportion of patients who had HbA1c values within the broader 5.7% to 6.4% range. With the lower boundary, about two thirds or fewer of patients typically had HbA1c values in this range. Compared with women, men overall (P = .03) and men with isolated IFG (P = .02) had a significantly lower percentage of HbA1c levels in the 5.7% to 6.4% range.

Discussion and Conclusion

There is no test with 100% sensitivity that can identify persons at highest risk for diabetes\(^8\); persons with glucose levels and HbA1c values even in the normal range still face a risk of diabetes. Nevertheless, practitioners need some guidance about how to screen for patients who may have prediabetes so that referrals can be made for appropriate prevention strategies.

Epidemiological studies have recently suggested that using HbA1c is not an optimal screening strategy for the diagnosis of diabetes.\(^2\)-\(^3\) From a clinical chemistry standpoint, many factors can lead to individual variability in HbA1c, making it a less than optimal test to assess glycemia. For example, ethnic variability in HbA1c levels has been documented in persons with prediabetes.\(^9\) In addition, “high glycators” and “low glycators,” possibly owing to differences in erythrocyte 2,3-diphosphoglycerate levels, have been described.\(^10\)-\(^11\)

A recent study in a general Dutch population suggested that HbA1c values correlated poorly with fasting and 2-hour glucose levels in patients with mild hyperglycemia.\(^3\) Our analysis looked specifically at how HbA1c testing might have identified patients if it had been used as the screening test to identify persons who would benefit from a diabetes prevention program. Our data suggest, at least in this clinic...
population, that HbA1c may not be the optimal screening test to identify persons with prediabetes. Fewer than one third of the persons in our study had an HbA1c value actually within the range currently defined as high risk for development of type 2 diabetes (ie, 6.0%-6.4%). Although decreasing the lower boundary of the range increased the number of persons with prediabetes who would have been identified, about one third of the patients would still have been missed. Moreover, the lower limit of the broader range (ie, 5.7%) overlaps with the upper limit of our normal HbA1c assay range; advocating this as a cutoff to select candidates for diabetes prevention likely would cause confusion among practitioners.

There are several limitations to our analysis. The DEAL program is underrepresented by members of racial and ethnic groups who are at highest risk for type 2 diabetes. In addition, the population typically is older, and the sample of persons with isolated IGT was small. Moreover, all patients in this study were preselected on the basis of already having IFG. Sensitivities and specificities cannot be calculated, and generalizations to the general population cannot be made. Nevertheless, our data suggest that reliance on HbA1c alone as a screening tool to identify persons who would benefit from a diabetes prevention program would miss a substantial number of eligible patients. It therefore seems reasonable to continue using fasting glucose levels, at least for our diabetes prevention program, as the initial screening method for determining eligibility for participation.

### References


