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Evaluation of Hemoglobin A1c Criteria to Assess Preoperative Diabetes Risk in Cardiac Surgery Patients

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Abstract

Objective: Hemoglobin A1c (A1C) has recently been recommended for diagnosing diabetes mellitus and diabetes risk (prediabetes). Its performance compared with fasting plasma glucose (FPG) and 2-h post-glucose load (2HPG) is not well delineated. We compared the performance of A1C with that of FPG and 2HPG in preoperative cardiac surgery patients.

Methods: Data from 92 patients without a history of diabetes were analyzed. Patients were classified with diabetes or prediabetes using established cutoffs for FPG, 2HPG, and A1C. Sensitivity and specificity of the new A1C criteria were evaluated.

Results: All patients diagnosed with diabetes by A1C also had impaired fasting glucose, impaired glucose tolerance, or diabetes by other criteria. Using FPG as the reference, sensitivity and specificity of A1C for diagnosing diabetes were 50% and 96%, and using 2HPG as the reference they were 25% and 95%. Sensitivity and specificity for identifying prediabetes with FPG as the reference were 51% and 51%, respectively, and with 2HPG were 53% and 51%, respectively. One-third each of patients with prediabetes was identified using FPG, A1C, or both. When testing A1C and FPG concurrently, the sensitivity of diagnosing dysglycemia increased to 93% stipulating one or both tests are abnormal; specificity increased to 100% if both tests were required to be abnormal.

Conclusions: In patients before cardiac surgery, A1C criteria identified the largest number of patients with diabetes and prediabetes. For diagnosing prediabetes, A1C and FPG were discordant and characterized different groups of patients, therefore altering the distribution of diabetes risk. Simultaneous measurement of FGP and A1C may be a more sensitive and specific tool for identifying high-risk individuals with diabetes and prediabetes.

Introduction

Diabetes mellitus is one of the major epidemics of our era, and approximately 48.3 million people in the United States will have this diagnosis by year 2050.[1,2] Screening for diabetes should be routinely recommended in current health care management. Hemoglobin A1c (A1C) criteria have recently been recommended by International Expert Committee Report[3] and adopted by the American Diabetes Association to diagnose diabetes (A1C $\geq$6.5%) and to identify people at high risk for diabetes (A1C 5.7–6.4%).[4] Unlike current tests such as fasting plasma glucose (FPG) or 2-h post-glucose load (2HPG) during an oral glucose tolerance test (OGTT), A1C offers a practical advantage and obviates the need for an overnight fast or a glucose load. It additionally tests longer-term glycemic control and has considerable analytic stability.[5,6] We expect that the ease of obtaining an A1C will make it the most popular preoperative screening test. Also, recent data demonstrating that A1C independently predicts cardiovascular disease and death will further reinforce its use.[7] Despite the recommendation for the use of A1C, its relationship to FPG and 2HPG screening remain unclear. Recent studies that

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compared these three diagnostic tests in detecting diabetes and diabetes risk reported conflicting results.[8,9] Most of these analyses are of large databases or populations.

In this study we investigated the relationship between the three diabetes screening criteria in a clinical setting. We examined how the new A1C criteria perform in detecting glucose abnormalities in cardiothoracic surgery patients with no known history of diabetes mellitus. Patients with heart disease, especially coronary artery disease, have a high diabetes risk, and because A1C is a practical test, we suspect it will become the default preoperative test for glucose abnormalities in this population.

Research Design and Methods

We analyzed baseline data from 92 consecutive patients with no known diabetes history participating in an ongoing prospective study of acute blood glucose elevations following cardiovascular surgery. Study evaluations were obtained in all subjects during an initial ambulatory assessment preceding cardiothoracic surgery procedures including valve replacement, coronary artery bypass grafting, thoracic aortic corrections, or a combination of these procedures. Subjects with a history of diabetes or of taking any medication that interferes with glucose metabolism (glucocorticoids, immunosuppressive agents) were excluded. The study was approved by the University of Michigan Institutional Review Board.

After written informed consent was obtained, anthropometric measurements (height, weight, body mass index, and waist and hip circumference) were recorded, and plasma glucose and A1C were collected after an overnight fast. On the same study day all subjects underwent an OGTT with a 75-g oral glucose load (Glucola, NERL Diagnostics LLC, part of Thermo Scientific, East Providence, RI), and plasma was obtained for glucose measurement 2 h later.

Outcome measures

Glucose tolerance classifications recommended by the American Diabetes Association were used: FPG < 100 mg/dL was defined as normal, 100–125 mg/dL as impaired fasting glucose (IFG), and ≥ 126 mg/dL as diabetes. A 2HPG during a 75-g OGTT of < 140 mg/dL was classified as normal, that between 140 and 199 mg/dL as impaired glucose tolerance (IGT), and ≥ 200 mg/dL as diabetes. A1C of ≥ 6.5% was defined as diabetes, and a level of 5.7–6.4% was defined as prediabetes.[4]

Assays

Glucose assays were performed by the glucose oxidase method on a Cobas Mira chemistry analyzer (Roche Diagnostics Corp., Indianapolis, IN). A1C was measured by National Glycohemoglobin Standardization Program–certified immunoassay using whole blood (Pointe Scientific, Inc., Canton, MI), standardized to the Diabetes Control and Complications Trial assay. Hemoglobin variants HbA2, HbC, and HbS do not interfere with this method.

Statistical analysis

Variables of interest were expressed as mean ± SE values, median (25^{th}, 75^{th} percentile), or percentages as appropriate. Participants were categorized according to FPG, 2HPG-, and A1C-based cutpoints for diabetes and prediabetes as described above.[4] Venn diagrams were constructed to illustrate the concordance and discordance among FPG, 2HPG-, and A1C-based classifications. A1C was also analyzed relative to IFG alone, IGT alone, and combined IFG, IGT, and diabetes. All analyses were performed using SAS (version 9.1) (SAS Institute, Cary, NC) or SPSS (version 17) (SPSS, Inc., Chicago, IL) statistical software.

The sensitivity and specificity of the A1C criteria to detect diabetes and prediabetes were calculated relative to FPG and 2HPG. Sensitivity is the probability of having an abnormal A1C in the presence of diabetes or prediabetes. Specificity is the probability of having a normal A1C in the absence of diabetes or prediabetes. A similar analysis was performed to determine the sensitivity and specificity of concurrent testing of A1C and FPG as a diagnostic tool. The reference used for determining diabetes or diabetes risk for this analysis was

Table 1. Demographic Data

	Normal	*Prediabetes*			*Diabetes*		
	By all criteria	*By FPG only (100–125 mg/dL)*	*2HPG only (140–199 mg/dL)*	*By A1C only (5.7–6.4%)*	*By FPG only (≥126 mg/dL)*	*By 2HPG only (≥200 mg/dL)*	*By A1C only (≥6.5%)*
n (%)	25 (27)	18 (19.5)	8 (8.6)	24 (26)	1 (1)	3 (3.2)	4 (4.3)
Age (years)	56 ± 11.4	62 ± 12.5	64 ± 16.7	62 ± 13.9	66.0	76 ± 3.0	72 ± 7.7
Sex (% male)	52	50	50	63	100	100	50
Race (% white)	96	100	100	92	100	100	100
Family history of diabetes (%)	45.8	39	75	42	100	33	75
BMI (kg/m^2)	29.1 ± 6.4	29.9 ± 6.0	31.1 ± 5.0	30.5 ± 6.6	31.0	21.9 ± 0.3	30.6 ± 4.8
Waist circumference (cm)	103 ± 19.1	101 ± 24.7	108 ± 15	105 ± 19.8	121.0	77 ± 1.3	105 ± 20.7
A1C (%) mean	5.23 ± 0.3	5.7 ± 0.7	5.9 ± 0.9	5.9 ± 0.2	5.8	5.6 ± 0.4	6.9 ± 0.3
FPG (mg/dL) mean	87.4 ± 7.2	106 ± 7.0	114 ± 27.5	93.2 ± 10.3	135	104 ± 4.4	112 ± 8.9
2HPG (mg/dL) mean	94 ± 25.13	134.5 ± 45.2	172 ± 13.9	108.4 ± 37	89	210 ± 6.2	166 ± 50

Data are mean ± SD values or percentages as indicated.
A1C, hemoglobin A1c; BMI, body mass index; FPG, fasting plasma glucose; 2HPG, 2-h post-glucose load.

FPG or 2HPG, and risk was calculated relative to A1C alone, FPG alone, and A1C and FPG together. We tested sensitivity and specificity for either FPG or A1C being positive (screening) and for both FPG and A1C being positive (diagnosis).

Results

Of 116 patients screened for the study, 12 were excluded because of rescheduled surgeries, 10 declined to participate, one withdrew consent, and one did not meet eligibility criteria, so 92 were included. Demographic and clinical characteristics of these participants are shown in Table 1. Subjects with normal glucose tolerance were younger than those with prediabetes, and subjects with diabetes were the oldest. There were no statistically significant differences in the other demographic characteristics.

Twenty-five patients (27%) had normal glucose tolerance by all three criteria. Diabetes was identified in two (2.2%)

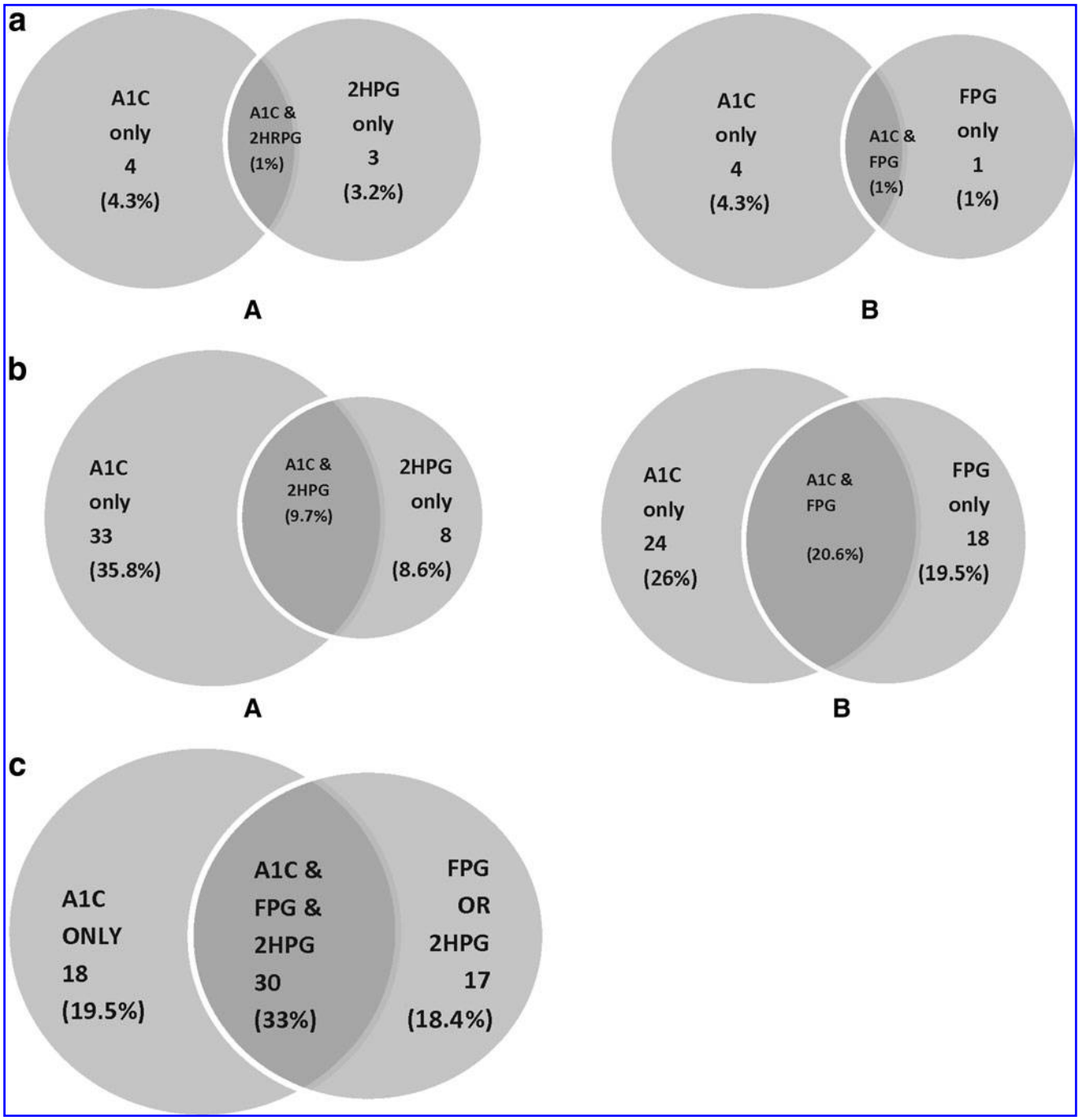

FIG. 1. (**a**) Venn diagrams for diabetes: individuals meeting criteria for diabetes as (**A**) hemoglobin A1c (A1C) ≥6.5%, 2-h post-glucose load (2HPG) ≥200 mg/dL and (**B**) as A1C ≥6.5%, fasting plasma glucose (FPG) ≥126 mg/dL. (**b**) Venn diagrams for prediabetes: individuals meeting criteria for prediabetes as (**A**) A1C 5.7–6.5%, 2HPG 140–200 mg/dL and (**B**) as A1C 5.7–6.5%, FPG 100–125 mg/dL. (**c**) Venn diagram indicating abnormality (diabetes or prediabetes) by A1C, FPG, or 2HPG.

Table 2. Sensitivity Analysis for Hemoglobin A1C

	With reference standard	
	FPG	*2HPG*
Diabetes		
Sensitivity	50%	25%
Specificity	96%	95%
Prediabetes		
Sensitivity	51%	53%
Specificity	51%	51%

FPG, fasting plasma glucose; 2HPG, 2-h post-glucose load.

patients by FPG, in four (4.3%) patients by 2HPG, and in five (5.4%) patients by A1C. Prediabetes was identified in 38 (42.3%) by FPG, in 17 (19.3%) by 2HPG, and in 43 (49.4%) by A1C. Classification of patients as having diabetes or prediabetes by the different criteria is shown in Figure 1, as is overlap between FPG, 2HPG, and A1C. The sensitivity and specificity of A1C for diagnosing diabetes were 50% and 96%, respectively, using FPG as the gold standard and 25% and 95%, respectively, using 2HPG (Table 2).

Eighteen (19.5%) patients with abnormal FPG had normal A1C values. Twenty-four (26%) patients with normal FPG met the A1C criteria for prediabetes. Eight (8.6%) patients with abnormal 2HPG had normal A1C values, and 33 (35.8%) with normal 2HPG had prediabetes by A1C (Fig. 1b). The sensitivity and specificity of A1C for diagnosing prediabetes were both 51% using FPG as the gold standard and 53% and 51%, respectively, using 2HPG (Table 2). By combining FPG with A1C, the sensitivity for detecting diabetes or prediabetes was 93% when either test was positive, and specificity was 100% when both tests were positive (Table 3).

Discussion

In this study, we analyzed the sensitivity and specificity of the new A1C criteria[4] to detect diabetes and prediabetes compared with FPG and 2HPG in 92 preoperative cardiac surgery patients with no history of diabetes. Only five (5.4%) patients were found to have an A1C value in the diabetes range. In comparison, FPG and 2-h OGTT identified two and four patients with diabetes, respectively. One patient each met criteria for diabetes by both A1C and FPG or both A1C and 2HPG (Fig. 1a). Therefore, A1C identified the largest number of patients with diabetes. All patients with A1C $\geq$6.5% had another glucose abnormality (IFG, IGT, or diabetes) and would be identified as dysglycemic by conventional criteria. These data suggest that abnormalities in glucose tolerance detected by A1C differ from those detected by FPG or OGTT. Being an integrated measure of mean glucose excursions, A1C has the distinct advantage over the other tests of assessing average glycemic trends over 2–3 months. In contrast, plasma glucose (both fasting and 2 h) assesses only one time point in glucose metabolism.

Several recent reports have compared A1C and glucose. A good concordance was found between A1C and FPG for the diagnosis of diabetes mellitus in a population of more than 6,000 adults.[9] In a large cohort of 12,485 participants, Selvin et al.[10] found that A1C strongly predicted the development of diabetes. The usefulness of A1C as a diagnostic tool varied according to the criteria used to diagnose diabetes and improved if two FPG values were considered.[10] In another recent report, A1C identified a smaller population of patients with undiagnosed diabetes than FPG and 2HPG, underscoring the varying abnormalities assessed by different diagnostic tests in different populations.[11]

In this study of preoperative cardiac surgery patients, the prevalence of diabetes and prediabetes differed by the diagnostic criteria used. A1C identified a larger group of patients with prediabetes or diabetes than FPG or 2HPG alone. Unfortunately, only a portion of the groups overlapped (Fig. 1b), and different subsets of patients were identified with prediabetes by FPG, by 2HPG, and by A1C. Two-thirds of the cardiac surgery patients had prediabetes by either the A1C or FPG criterion. Thirty percent of this group would have been missed using A1C alone and 40% with FPG alone. Studying an older population, Lipska et al.[8] found "considerable discordance" between FPG and A1C-based diagnosis criteria for both diabetes and prediabetes. A1C classified a similar-sized (36%) but discrete group of patients with diabetes or prediabetes compared with FPG (27.5% with diabetes and 33.6% with prediabetes), and only a subset (36.3% and 29.7%, respectively) overlapped. The public health implications of these differences were highlighted by an analysis of the 1999–2006 National Health and Nutrition Examination Survey database.[12] A1C classified 8.9 million people with normal FPG ($<$100 mg/dL) as having prediabetes, and 37.6 million with IFG had normal A1C values. A1C identified a large cohort of patients who would have been considered normal by FPG or OGTT criteria.

Studies have shown that A1C values are higher in women, blacks and other ethnic minority populations, and the elderly.[8,13–15] Varying dysglycemic mechanisms such as different rates of hemoglobin glycation and racial presence of hemoglobinopathies have been suggested causes.[16] Other factors that limit the reliability of A1C include subclinical variation in red blood cell survival, anemia, and medications.[5,17]

The strengths of this study are that it is one of the first to evaluate the use of both FPG and A1C criteria for diagnosing dysglycemia in a preoperative population and also to assess performance of A1C relative to both established FPG and

Table 3. Sensitivity Analysis: Detecting Diabetes or Prediabetes Using Both Fasting Plasma Glucose or 2-h Post-Glucose Load as Reference

	A1C only	*FPG*	*Either A1C or FPG is abnormal (screening)*	*Both A1C and FPG are abnormal (diagnosis)*
Sensitivity	63%	85%	93%	53%
Specificity	59%	100%	58%	100%

A1C, hemoglobin A1c; FPG, fasting plasma glucose.

2HPG criteria, used separately or together. It studied a group of patients with high diabetes risk using standardized screening techniques obtained during one preoperative visit day in all patients.

Limitations of this study include the relatively small sample size and lack of diversity in the population. Only one set of FPG and A1C values was available. A small group of this population had diabetes or prediabetes diagnosed by 2HPG and would have been missed if only A1C and/or FPG were tested. Because OGTT is not widely used for screening, this small population may have less clinical relevance.

It is well known that elevated levels of A1C and FPG confer risks for future type 2 diabetes and cardiovascular events and that these risks are curvilinear.[18] Patients need to be informed of these results to make appropriate lifestyle and medical interventions, especially in this high-risk cardiothoracic surgery population. A1C will identify a different group of patients than identified by FPG alone. Physicians using either test alone need to be aware of this discordance. Although other testing mechanisms have been suggested,[19] the practicality of checking an A1C may increase its routine use in diabetes screening and overcome its shortcomings. Longer-term trials are needed to determine if conversion to diabetes or development of complications differ among patients identified by each criterion.

Our data on concurrent FPG and A1C show that sensitivity and specificity were both impacted depending on the strategy used for screening and diagnosis. Similar trends for sensitivity and specificity were reported in an earlier study validating cutoff points for combined testing before the new A1C criteria were established.[20] An additional study reported a higher diabetes risk in individuals with elevated A1C and FPG levels, suggesting a role for both FPG and A1C in predicting diabetes.[10] Supporting previous data, the sensitivity and specificity for diagnosing diabetes in this presurgical cohort are improved by simultaneous testing of FPG and A1C, and this could be a practical solution for the interim (Table 3).

Conclusions

In preoperative cardiothoracic surgery patients at high risk for dysglycemia, A1C performs well for the diagnosis of prediabetes and diabetes. Although A1C identifies a different group of patients than FPG, its convenience and standardization[21] may overshadow its limitations. Using a simultaneous A1C and FPG measurement is a better screening tool to identify diabetes or preoperative diabetes risk in this population.

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Author Disclosure Statement

R.Y.G. designed the project, contributed to the discussion, and wrote the manuscript. R.P.-B. contributed to the discussion and reviewed/edited the manuscript. S.S. wrote the study protocol, enrolled patients, and edited the manuscript. C.A.Z., C.D.P., S.C.K.-C., K.G.G., and E.C.D. researched data. L.J. and T.W.B. researched data and reviewed/edited manuscript. P.V.P. did statistical analysis and contributed to the discussion. All authors approved the final version of the manuscript. The authors report no conflict of interest related to this study.

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