A1C: Recommendations, Debates, and Questions

ZACHARY T. BLOOMGARDEN, MD

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A series of elegant investigations some 4 decades ago led to the realization that elevated levels of certain hemoglobin components are found in individuals with diabetes (1). The useful measurement of A1C became standard in assessment of glycemia (2). A1C, rather than direct measures of glycemia, is now used as the "goal" for diabetes treatment (3,4).

Should A1C be used for diabetes diagnosis?

At the 69th Scientific Sessions of the American Diabetes Association (ADA), David Nathan (Boston, MA) discussed the role of A1C in the diagnosis of diabetes in nonpregnant subjects and explained the position advocated by an expert committee of ADA and the European Association for the Study of Diabetes (EASD) that the diagnosis of diabetes may be conveniently based on A1C ≥6.5%, without the need to measure a plasma glucose concentration (5). All methods previously used for the diagnosis of diabetes, he noted, have relied on measuring blood glucose, whether in the fasting state or after a stress, as in the oral glucose tolerance test. He asserted that early attempts to establish the diagnosis of diabetes were hampered by absence of standardization, for example, with different times for blood determination or with different oral glucose loads. Type 1 diabetes usually has characteristic presentation and thus is easily diagnosed, but Nathan observed that type 2 diabetes can be subtle in its onset; analyses of fasting and 2-h postload glucose levels in Korea, Nauru, Egypt, and Taiwan showed unimodal glucose distributions (6), although this may be an artifact of the relative infrequency of diabetes in the population, as studies in populations such as the Pima Indians with very high prevalence of diabetes do show evidence of bimodal glucose distributions (7).

A 1979 working group suggested that the level of glycemia used for definition of diabetes be based on risk for progression to symptomatic diabetes, but this approach was supplanted in by a 1997 expert committee report (8) and a 1999 World Health Organization consultation (9), which recommended that diagnostic criteria be based on the associations of fasting and 2-h glucose with retinopathy, with such an association noted for A1C as well in the 1997 report. Fasting blood glucose ≥110 mg/dl (6.1 mmol/l) was considered to represent impaired fasting glucose (IFG), and levels ≥126 mg/dl (7 mmol/l) were considered to represent diabetes. In a 2003 panel recommendation, the diagnostic level of fasting was lowered from 110 to 100 mg/dl (6.1 to 5.6 mmol/l) for IFG and use of A1C was not recommended for diagnosis. "What has changed," Nathan stated, is "continued and further standardization of the [A1C] assay." Analyses of the College of American Pathologists (CAP) surveys from 1993 to 2007 show much improvement in results, he said, predicting that this will be better still with plans for lowering of acceptable limits for error to ±6% over the next 2 years. Furthermore, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has prepared new A1C standards to improve standardization (10). Nathan suggested several advantages of A1C over glucose measurements. Without inhibition of erythrocyte glycolysis or rapid serum/plasma separation, there is a drop in glucose levels from the time a sample is obtained to the time of processing, leading to inaccuracy. Furthermore, weekly determination of fasting glucose shows that this measure has higher variability than does A1C (11). The biological variability of A1C within an individual is somewhat smaller than that of fasting glucose (coefficient of variation [CV] 3.6 vs. 5.7%) and considerably less than that of 2-h glucose (CV 16.6%) (12), suggesting that repeated measurements would be more consistent using A1C. Fasting glucose varies with the time of day, with acute stress and with many other factors; according to Nathan, "A1C being an integrated measurement of average glucose is relatively resilient."

Nathan reviewed further data on the relationship between different measures of glycemia and long-term complications, proposing that A1C, like glucose, gives information about risk of retinopathy (Data from an Epidemiological Study on the Insulin Resistance Syndrome [DESIR]), with A1C having a stronger association (13). He stated that the Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) analysis of databases from 13 studies of 48,416 subjects aged 20–79 years having fundus photography showed increase in prevalence of retinal abnormalities around an A1C level of 6.5% and fasting glucose level of 126 mg/dl.

Nathan concluded that A1C is a better index of glycemic exposure than blood glucose, is at least as good at predicting risk of long-term complications, has similar if not better standardization, is better in its lack of variability, and is useful in chronic management. "There are clearly limitations," he acknowledged. A1C is not readily available around the world, interfering factors such as hemoglobinopathy make the interpretation of the assay more difficult, and conditions that affect erythrocyte turnover may cause spurious results, so that clinicians using A1C in diagnosing diabetes would need to be aware of these limitations. "We do not mean to supplant glucose," Nathan said. He did offer the option that glucose testing be used when A1C measurement is not readily available.

Nathan reviewed the potential use of A1C in diagnosis of pre-diabetic states and noted that the risk of diabetes based on fasting and 2-h glucose appears to increase in a continuous fashion with in-

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Division of Endocrinology, Mount Sinai School of Medicine, New York, New York.
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creasing levels (14). Risk of diabetes similarly gradually increases at increasing levels of A1C (15,16). Nathan made the interesting comment that "as glucose testing is supplanted by A1C testing, IFG and impaired glucose tolerance (IGT) will no longer be diagnosable" and should be replaced by the notion of a continuum of risk with increasing A1C levels. The A1C level at which intervention is begun should, he said, be individualized by country or area. The question was raised regarding what levels of A1C might be considered indicative of high risk of diabetes. Nathan responded that data from the Centers for Disease Control and Prevention suggest that A1C levels of 5–5.9% correspond to IFG and IGT; he suggested that a policy decision might therefore be made to "pay particular attention" to subjects with A1C >5.5%, although he considered that levels of 6–6.5% would be "clearly . . . [the] highest risk."

In a panel discussion after Nathan's presentation, Harold Lebovitz (Staten Island, NY) asked whether this approach would negatively impact patients' understanding of their condition when there were discrepancies between A1C and glucose levels. I have raised this issue in recommending that the relationship between A1C and mean glycemia is insufficiently precise to allow the use of A1C in defining estimated average glucose (eAG) (17). The argument that A1C correlates with the complications of diabetes on a population basis does not strongly favor its use in diagnosis because any measure linked to glycemia will show such a relationship. A1C represents glycation of hemoglobin, localized to a specific biologic compartment, the erythrocyte cytoplasm, which is potentially rather different from the entire glucose distribution volume. Erythrocyte turnover, cell membrane permeability to glucose, hemoglobin glycation and deglycation, and a myriad of other processes will change glycated hemoglobin levels (18). Twin studies show heritable components contributing to A1C: when twins are concordant for diabetes, their A1C levels are, unsurprisingly, rather similar, but, interestingly, twins discordant for diabetes also show correlation of A1C levels, leading to suggestion of a strong nonglycemic hereditable component to A1C (19).

A large number of medical conditions are associated with alterations in the relationship between mean glycemia and A1C: hematological conditions, such as persistent fetal hemoglobin, hemoglobin S, C, or D, and the presence of carbamylated hemoglobin in uremia; illnesses characterized by hemolysis or other states with shortened erythrocyte life span; a variety of systemic conditions including certain forms of dyslipidemia, malignancies, and cirrhosis. The common condition of iron deficiency anemia can, for unexplained reasons, lead to an increase in A1C by 1–1.5% that subsequently falls following iron treatment (20–23). Given the frequency with which subjects with diabetes have other medical illnesses, the likelihood that such factors may alter A1C is widely underestimated. Interestingly, hyperglycemia may itself shorten erythrocyte life span (24), suggesting a mechanism by which glycemia need not to exhibit a direct linear relationship to the A1C level. Pregnancy is well recognized to be associated with a substantial reduction in A1C levels, perhaps as a function of hemodilution or increased erythrocyte turnover, although it has not been fully explained by either mechanism; during late pregnancy, A1C levels decrease by ~0.5% at every level of mean plasma glucose (25).

A recent study shows little rationale for the proposed threshold of 6.5% based on total retinopathy, albuminuria, or neuropathy. Interestingly, in that study, nonfasting ("random") glucose was as suitable as A1C for identifying subjects with diabetes (26). Analysis of U.S. National Health and Nutrition Examination Survey (NHANES) data revealed that 50–60% of patients with fasting plasma glucose ≥7 mmol/l had A1C <6.5%, suggesting that A1C might reduce the number of people diagnosed as having diabetes from that using current glycemic criteria (27). If because of anemia, renal disease, infection, ethnicity, age, or other patient medical characteristics or for economic reasons one uses glucose rather than A1C measurements, the likelihood of diabetes would presumably be greater, which is certainly not desirable.

Measuring fasting and 2-h glucose values to diagnose diabetes, then, has limitations, but there may be less risk that these measurements could lead to an individual being misdiagnosed as could occur with A1C based on age, ethnicity, renal disease, anemia, or hemoglobinopathy. These issues and the possible list of tests required in addition to the "simple" A1C make the idea of just fasting overnight for a glucose test an attractive option.

Indeed, as discussed above, it is reasonable to conclude that the use of A1C will lead to overdiagnosis among the elderly, blacks, subjects with iron deficiency, and individuals genetically predisposed to greater levels of hemoglobin glycation, whereas those with anemia, renal insufficiency, and many hemoglobinopathies, as well as those with other genetic variations, will be incorrectly told that they do not have diabetes. If A1C is used as the sole means of diagnosis (and of assessing glycemia) and if there is encouragement to limit glucose self-monitoring until a patient is treated with insulin, one must wonder how without concurrent hemoglobinopathy screening, testing for anemia and testing for renal impairment we will identify the incorrectly diagnosed and incorrectly treated patients. A further entirely distinct argument against the use of A1C for diagnosis is the lack of access to this test in many of the countries where diabetes is likely to increase most in prevalence over coming decades.

Should A1C be reported as eAG?

The closely related topic of routine reporting of eAG with A1C was debated at the ADA Scientific Sessions (and again in July at the American Association for Clinical Chemistry [AACC] Annual Meeting). First, the positive and negative positions were addressed from a clinical standpoint by Nathan and me, and then these sides were taken from the clinical chemistry perspective by David Sacks (Boston, MA) and Eric Kilpatrick (Hull, U.K.).

Randie Little (Columbia, MO), moderating the debate, discussed the change in methodology of A1C standardization adopted in 2001 by the IFCC, with synthesis of an NH_2-terminal valine- glycated HbA_1 B-chain. This "truer" A1C comprises only approximately three quarters of what has previously been considered A1C with biologically derived standards. There is potential for confusion if the resulting lower A1C levels are expressed as percentages, although the intent of the IFCC is to express A1C in mmol/mol, with normal levels up to ~45. In 2004, an ADA/EASD/International Diabetes Federation (IDF) workshop suggested a compromise approach between the "true" lower A1C and the now considered inaccurate older A1C standard, which includes other hemoglobin-derived compounds. The workshop recommended that A1C be reported with eAG.

Nathan took the position that such eAG reporting with A1C will serve a useful purpose. He began by commenting

that "diabetes has always been sugar-centric" and noted that what was subsequently found to be glycated hemoglobin was first described as a minor hemoglobin fraction in 1958 (28); Rahbar found an increase in levels with diabetes a decade later (29). The 1997 ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, the Diabetes Control and Complications Trial (DCCT), and the UK Prospective Diabetes Study (UKPDS) intervention trials, he said, "cement A1C as the means by which we measure our targets." The goal of treatment is, he continued, an A1C <7%, observing that "we're guiding people based on A1C." This led him to question the use of both glucose and A1C, two different measures, in treating diabetes, suggesting that this might be confusing for patients, and he suggested that the use of eAG would allow all values discussed with patients to be expressed in the same units, which he considered desirable. Such conversions have been proposed by a number of investigators, beginning with a European study (30) and one he carried out (31) more than 25 years ago, with robust correlation of A1C with mean self-monitored blood glucose (SMBG). These considerations led to the A1C-derived average glucose (ADAG) study of more than 500 type 1 and type 2 diabetic and nondiabetic subjects, 83% of whom were Caucasian, 8% black, and 8% Hispanic, who performed continuous glucose monitoring (CGM) 2–3 days monthly as well as pre- and postprandial SMBG for 4 months, giving ~2,500 CGM and 230 SMBG values per patient. Both forms of monitoring gave similar findings, with CGM leading to the following formula: [average glucose] = 2.87 × A1C − 46.7, with r^2 0.84 (32). Nathan suggested that the correlation might have been even higher, but that there are always measurement errors and incomplete glucose monitoring, and he acknowledged that there may be variability among individuals in rates of erythrocyte formation and hemoglobin glycation. He commented that the study was carried out in a fashion designed to minimize variability and noted that "we had screened . . . to try to strip the population of these errors." He agreed that the study was therefore somewhat limited because there were few people of non-Caucasian ethnicity and no data in children, pregnancy, or renal disease and that "we also had people who were generally more stable." He concluded that the use of eAG would be greatly advantageous in helping more people to understand their level of glycemia and noted that only a quarter of diabetic individuals think that they know what their A1C is, and few of these are correct (33).

I argued the contrary position that eAG has certain conceptual weaknesses that make its use not desirable (9). This is not, then, an argument that A1C does not vary with different levels of glycemia but, rather, that there are weaknesses of A1C in predicting eAG. A1C is affected by a variety of hematological and general medical illnesses, as discussed above, with A1C underestimating glycemia in subjects with HIV infection (34) and on hemodialysis (35).

I mentioned that Nathan is the senior author of an important analysis of two large epidemiological studies showing that, controlling for glycemia, A1C increases with increasing age, with a 0.4% rise between 40 and 70 years of age (36). In a study by Kilpatrick et al. (37) of both A1C and fructosamine, a measure of glycated albumin, in subjects ranging in age from 20 to 80 years, A1C increased by ~30%, but fructosamine levels failed to change with age, further suggesting that increasing glycemia is not the explanation for the age-related increase in A1C. Another factor is ethnicity. In multivariate analysis of the 15,934 nondiabetic participants in the 1999–2006 NHANES, correcting for age, sex, BMI, cigarette use, alcohol use, hypercholesterolemia, hypertension, education, cardiovascular disease, and C-reactive protein, non-Hispanic blacks had 2.4-fold increase in likelihood of A1C >6% among subjects with fasting glucose <100 mg/dl (38). Among subjects with IGT in the Diabetes Prevention Program, which Nathan chaired, mean A1C was 5.78% for whites and 6.18% for blacks, adjusted for age, sex, systolic blood pressure, diastolic blood pressure, BMI, fasting and postload glucose, corrected insulin response, and insulin resistance (39).

Given these caveats, I asked whether it is possible to predict true mean or average glucose with a high degree of accuracy in a given person based on the A1C measurement. I reviewed Nathan's original study from 1984 (5). Twenty-one diabetic subjects measured capillary glucose at least four times daily, both pre- and postprandially, for 2 months prior to A1C determination; the regression equation generated was used to show that 24% of practitioners' estimates of mean glucose differed by >75 mg/dl from the estimate derived from A1C. However, the study was not able to answer the question whether a substantial number of subjects differ in average glucose from those A1C-derived estimates. In the analysis of 623 insulin-treated type 2 diabetic subjects who measured capillary glucose before and after breakfast, lunch, and dinner and at bedtime on 3 days during the 2 weeks prior to measurement of A1C, there was the expected excellent correlation of the two measures, but frequency analysis of glucose group versus A1C showed important differences between the measures. For example, of 224 patients with mean plasma glucose 110–140 mg/dl, 10% had A1C <6.0% and 10% had A1C >8.1%. Conversely, comparing A1C grouping with mean glucose, of 260 patients with A1C 6.5–7.5%, 10% had mean glucose <115 mg/dl and 10% had mean glucose >171 mg/dl (D. Shrom, E. Choi, L. Ilag, Z.T.B., unpublished data). Approximately 20% of eAG values, then, differed rather substantially from measured mean glucose values in the patients.

The dilemma is the high interpatient variability of hemoglobin glycation, which is quite different from the high degree of tracking of mean blood glucose with A1C for each individual studied at multiple levels of glycemia (40). A related phenomenon of greater variability in groups of diabetic patients, but much stronger correlation within individuals, has been shown in the relationship between A1C and fructosamine (41). This phenomenon of variable degrees of hemoglobin glycation is well demonstrated in the DCCT 1-day, seven-sample capillary glucose versus A1C database of some 250,000 blood glucose and 72,000 A1C values, where participants could be divided into high, medium, and low glycators (42). Although studies of CGM might be expected to be more accurate, analysis of a pediatric population showed that while there was a strong correlation of A1C with mean glucose in the group, the use of A1C to estimate mean glucose in individuals would lead to error (43). Although the ADAG study group, as Nathan discussed, did find strong correlation between A1C and average glucose based either on self-monitored capillary glucose or CGM analysis and although this study was hailed editorially as "a key reference regarding the relationship between A1C and average glucose" (44), I explained some important features of the study design that could bias it to overly support the relationship. Subjects with hemoglo-

binopathy, anemia, reticulocytosis, blood loss, and chronic renal or liver disease or those receiving high-dose vitamin C, transfusion, or erythropoietin treatment were excluded. Furthermore, of those entering the study, 23% subsequently were deleted from analysis for conditions that might increase the discordance between A1C and glycemia. Representation of a variety of ethnic groups was limited. Precisely those subjects most important for clinicians to identify, then, were not included. Furthermore, there were limited data for subjects with average glucose >10 mmol/l. I speculated that the discrepancy between A1C and mean glucose might be clinically detrimental, potentially explaining the treatment effect on mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (45), because "high glycators" might, if assigned to a treatment protocol dictating additional medication for A1C regardless of glycemia, develop hypoglycemia with consequent adverse outcome. In a recent case report, a "low glycator" was allowed to have substantially poorer actual glycemic control than would be desirable because of misleadingly "good" levels of A1C (46).

I concluded that A1C certainly reflects the phenomenon of hemoglobin glycation being proportional to mean glycemia and that the measurement is, of course, useful in understanding the glycemic exposure of subjects with diabetes, but that one should not expect all subjects to glycate hemoglobin to the same degree for a given level of glycemia, suggesting that it will be important to develop and validate new approaches to understanding glycemic exposure of subjects with diabetes. Any highly homogeneous population will be likely to show higher correlation between A1C and average glucose than is seen in the overall population of diabetic patients treated in clinical practice. Alternative A1C-derived indexes that include age, ethnicity, anemia, and renal function might, in fact, make A1C more useful and more clinically relevant. I further commented that these considerations call into question our current reliance on A1C as a "goal" and certainly lead one to be circumspect in recommending that it be used alone in diagnosis of diabetes in divergent populations, of varying age and ethnicity, and with underlying medical conditions affecting erythrocytes. Furthermore, these arguments suggest that glycemic self-monitoring of diabetic subjects not requiring insulin treatment would be likely to add considerably to A1C measurement in endeavoring to optimize the control of their diabetes.

Sacks reviewed the correlation of A1C with average glucose and suggested that laboratory information systems can be used to perform a variety of calculations, such as the estimated glomerular filtration rate. In a CAP survey of ~3,000 laboratories in April 2009, 16.7% reported eAG, with 28.8% using the equation derived from the ADAG study, 22.6% using an equation derived from the DCCT A1C versus glucose dataset, and the remainder using other equations. He noted that the AACC recommendations in January 2009 "call on all labs in the U.S. to report eAG along with A1C" and suggested this to be reasonable for three reasons: first, because "healthcare providers find it useful," second, because the "ADA believes eAG facilitates communication," and, third, because its use is strongly supported by diabetes educators. He did not show information in support of these views.

Kilpatrick suggested that eAG is no more than "a consensus compromise" of multiple groups endeavoring to communicate the new methodology of A1C measurement. He reviewed the acceptance criteria used in the ADAG study that 90% of patients should have mean glucose within 15% of the eAG based on A1C, pointing out that these limits are "too wide." If we accept that 90% of patients said to have an eAG of 200 have actual mean glucose as low as 170 mg/dl or as high as 230 mg/dl (this in itself allows variability exceeding 25%), the mathematics of normal distributions (which are somewhat inaccurate for glycemia) would lead the 99% confidence limits to be within 24%, allowing a range from 152 to 248 mg/dl. Kilpatrick reviewed his analysis of variability of glycated hemoglobin in nondiabetic individuals, occurring in a fashion unrelated to mean glycemia (47). While individuals are quite consistent, the interindividual variability of the A1C in subjects not having diabetes suggested that A1C in diabetic subjects with similar mean glycemia would likely vary by 1–2%. Furthermore, he showed evidence of imprecision of A1C measurement between laboratories both in the U.K. and in the U.S., based on a CAP report from May 2009, so that the 99% confidence limits of an eAG of 200 might in actuality be from 135 to 265 mg/dl.

Kilpatrick contrasted the use of calculated LDL cholesterol and estimated glomerular filtration rate, both of which add to the measures in question, with that of eAG, which, he stated, "adds nothing . . . it is simply a play on numbers." Furthermore, he suggested that many patients will not understand eAG and noted that in the U.K. only 20% of patients self-monitor and that the vast majority of these test only before meals, leading to measurements ~10% lower. This is important because the eAG of 154 for a person with A1C 7% is similar to the preprandial mean glucose for a person with A1C 8%. Diabetic patients, he predicted, will ask, "Should I trust the lab or my meter?" He pointed out that the ADAG study excluded 23% of patients, included few nondiabetic subjects, and lacked sufficient numbers of subjects of differing ethnicity and urged that before its equation is used a sturdy confirmation dataset be assembled. "We are all aware that A1C is not perfect," he concluded, but he urged the audience that it appears incorrect and is certainly premature to introduce eAG into clinical discourse. Following an audience comment after the debate, Robert Cohen (Cincinnati, OH) noted that there is substantial variability in erythrocyte life span among individuals without hematological illness (48), as well as in erythrocyte glucose permeability (49), factors which are likely to underlie the variable relationship between A1C and mean glucose (50).

Other A1C topics at the ADA Scientific Sessions

At a National Glycohemoglobin Standardization Program review at the ADA Scientific Sessions, Little discussed interesting observations based on CAP surveys of A1C assay performance. Average CV decreased from 6 to 7% in 2003 to current mean levels around 4%. An important statistical notion is that of critical difference—the difference for a given patient between two test results that should be considered significant. For A1C, at an average method CV of 4%, the critical difference is 0.8%, suggesting that the typical approach of clinicians in considering relatively small changes to be of consequence may not be statistically accurate. In fact, even if an A1C method had a 1% CV, the critical difference would still be an A1C change of at least 0.3%. In grading of the CAP A1C survey, the acceptable limit in 2009 is ± 10%, although the plan is to reduce this to ± 6% over

coming years. Other characteristics of A1C assays were discussed at the session. Many methods do not show assay interference with hemoglobin variants, but 6.5% of labs use methods for which A1C of samples with hemoglobin S or C is incorrect by >10%, 20% of labs use methods in which hemoglobin E causes interference, and 6% of labs use methods in which hemoglobin D causes interference. It should be noted that the CAP surveys do not include information on "point of care" A1C methods, as this is a "waived" test for quality standardization; the use of such methods may, if accuracy is limited, further limit the value of A1C.

Several studies presented at the ADA Scientific Sessions added further relevant information. Kim et al. (abstract 991) reported confirmatory information from analysis of the 1999–2006 NHANES data for 10,296 women, 14.4% with iron deficiency and 4.1% with iron deficiency anemia; iron deficiency reduced the prevalence of A1C <5.5%, and the investigators suggested that it may affect the structure of the hemoglobin molecule, making it easier to glycate and hence elevating A1C in a glucose-independent fashion. Davidson and Schriger (abstract 965) studied the effects of age and race/ethnicity on A1C levels in 2,712 white, Mexican American, and black subjects from the NHANES III population. Among those who did not meet fasting and 2-h glucose criteria for diabetes, 22% of non-Hispanic white and 22% of Hispanic subjects, but 68% of non-Hispanic black subjects, had A1C of 6.5–6.9% with 5, 0, and 10%, respectively, having A1C >7%. A1C increased by 7 and 10% per decade of age in subjects with normal glucose tolerance and IGT/IFG, respectively.

Gong et al. (abstract 981) presented data from a longitudinal study of 1,838 adult Pima Indians who did not have diabetes at baseline. Diabetes, as defined by fasting glucose ≥126 mg/dl, 2-h glucose ≥200 mg/dl, A1C ≥6.5%, or drug treatment for diabetes, developed in 454 subjects over a mean of 7.3 years; the researchers reported no difference among A1C, fasting glucose, and 2-h glucose in predicting subsequent diabetes development, although none had high areas under the receiver operating characteristic curve at 0.68 for A1C, 0.68 for fasting plasma glucose, and 0.71 for 2-h plasma glucose. Thus, in a homogeneous population and one in which A1C is included in the criteria for diabetes, A1C may be as useful as indexes of glycemia in assessment of subsequent diabetes risk. Whether such information can be extrapolated to populations of varying ethnicity and other clinical characteristics is, of course, an important concern.

Summary

A1C does reflect the phenomenon of greater hemoglobin glycation at higher mean glycemia and is certainly useful as an objective measure of long-term glycemia in subjects with diabetes. The related concepts that A1C can be used rather than the results of actual patient glucose measurements in accurately ascertaining mean glycemia and that A1C might be useful in the diagnosis of diabetes are therefore highly appealing. One should not, however, expect all subjects to glycate hemoglobin to the same degree for a given level of glycemia, given that a number of lines of evidence indicate that in clinical populations there is heterogeneity in the degree to which this occurs. A1C may not, then, be sufficiently accurate to allow its clinical use in the diagnosis of diabetes in populations of varying age and ethnic background and with illnesses affecting erythrocyte turnover. Moreover, caution appears reasonable before adoption of terminology such as eAG. We need to develop and validate new approaches to understanding glycemic exposure of subjects with diabetes and to develop better approaches to assessment of glycemia among subjects at risk of diabetes. As an example, individuals with increasing fasting glucose when monitored over time appear to be at particularly high risk of developing diabetes (51), and this may be a promising approach to diagnosis.

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