



CURRENT DIABETES PRACTICE

The official publication of the Council for the Advancement of Diabetes Research and Education

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– Pros and cons
- **SELF-MONITORING OF BLOOD GLUCOSE AND CONTINUOUS GLUCOSE MONITORING**

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ABOUT CADRE

CADRE is a nonprofit organization committed to reducing the burden of diabetes by providing healthcare professionals with scientific information and educational initiatives designed to translate research into effective clinical practice.

EDITORIAL

FROM THE EDITOR-IN-CHIEF

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Without accepting the fact that everything changes, we cannot find perfect composure. But unfortunately, although it is true, it is difficult for us to accept it. Because we cannot accept the truth of transience, we suffer.

Shunryu Suzuki

With this issue, *CADRE's Current Diabetes Practice* presents one of its most interesting and lively debates yet, on the pros and cons of adopting the A1C assay as a method for diabetes diagnosis. We would like to thank Drs. Richard Kahn and Zachary Bloomgarden for providing their perspectives on this issue.

As medical professionals and scientists, it is our responsibility to evaluate arguments presented both for and against change. In most fields today, major changes are accepted – even expected – on a regular basis. To be frank, however, the only people who really like change are babies with soiled diapers!

I was initially skeptical of the A1C assay's sensitivity for diagnosing diabetes. But after thoughtful consideration of the evidence, I have come to see the benefit in opting for change. That said, concerns about the assay's limitations in clinical practice are valid, and will have to be addressed before A1C can

be widely adopted as the preferred method for diabetes diagnosis.

Those who support using A1C as a diagnostic tool argue that it more accurately identifies the level of chronic hyperglycemia at which microvascular complications arise. The test is now standardized, has obvious advantages over oral glucose tolerance testing (OGTT), and is simple and convenient for patients. It is also the primary measure already used to evaluate glycemic control, make treatment decisions, and assess risk for long-term diabetes complications.

Detractors point out that A1C, as a diagnostic tool, has poor sensitivity and specificity, and fails to identify a substantial proportion of patients who would be diagnosed with diabetes (type 1 or type 2) by direct glucose measurement. In addition, certain hemoglobin traits can interfere with the assay, and A1C levels can be altered by age, ethnicity, and other non-glycemic factors, all of which have the potential to produce inaccurate and misleading results.

What is clear is that diabetes needs to be defined as a function of the risk for the development of long-term complications. This approach will provide clinicians with the information they need in order to know when to actively intervene. In the midst of discussing types of glucose measurement and their utility, we may have lost sight of this objective. Identifying overt diabetes is easy. Early diabetes (identified by either A1C or OGTT) presents a greater challenge. Well-controlled clinical trials are needed, in which patients with borderline diagnoses of type 1 or type 2 diabetes are treated and tracked over the long term for the development of diabetes-related complications.

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This new approach to diabetes diagnosis is one in a long line of glucose monitoring advances that have substantially improved the way we manage diabetes. In our other featured article, Dr. Satish Garg and colleagues discuss this historical perspective. In our search for a true “gold standard,” we abandoned urine glucose monitoring for blood glucose and A1C testing, and we may soon start to transition from reliance on self-monitoring of blood glucose to a greater emphasis on continuous glucose monitoring. All of these advances, which were undertaken with rigorous investigation and great care, make it possible for us to consider – even argue – about whether using A1C to diagnose diabetes is a good idea. And this is good news.

Dr. Schatz has no commercial relationships to disclose related to the content of this article.

In 2009, an Expert Committee concluded that the A1C test was an appropriate tool for diagnosing diabetes.

CONTROVERSIES IN CARE

DIAGNOSING DIABETES BY A1C TEST

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There is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things.

Niccolo Machiavelli
The Prince, 1632

In 2008, an International Expert Committee (IEC) chosen by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the International Diabetes Federation (IDF) was convened to review the current methods used to diagnose diabetes, and to discuss the possibility that the A1C test could be used to diagnose the disease. After numerous meetings and considerable discussion, the IEC unanimously agreed that:

- The A1C test is as good as any other test at defining the level of hyperglycemia at which diabetes-specific retinopathy occurs,
- The characteristics of the test (e.g. biologic variability, pre-analytic and analytic variability) greatly exceed other measures of glycemia used for diagnosis,
- The A1C test is sufficiently standardized and more clinically convenient than any other test, and
- The A1C test holds a central role as a measure of glycemic control and for monitoring treatment effectiveness.

For these reasons, the Committee concluded in their 2009 report that the A1C test was an appropriate diagnostic tool (click on the PubMed ID number to read more: [PMID 20011212](https://pubmed.ncbi.nlm.nih.gov/20011212/)). Further, on the basis of recently completed studies, the Committee

recommended that the A1C cutpoint defining diabetes should be $\geq 6.5\%$.

Since the 2009 IEC report appeared, numerous authors have supported its recommendations, provided a more in-depth analysis of why A1C testing is superior to other glucose measures, and discussed the pro's and con's of the A1C test to diagnose diabetes. At least two prominent organizations have endorsed the Committee's recommendation ([PMID 21193625](https://pubmed.ncbi.nlm.nih.gov/21193625/); [WHO Consultation](#)). Nonetheless, skeptics remain.

In addition, there appears to be some confusion about the merits of the test. This stems from innumerable studies within a countless number of different populations, comparing the prevalence of diabetes by all three recommended tests. These studies often report that the tests do not perform equally. That is, one test detects more cases than another, and whatever test is considered the gold standard—usually, the 2-hour oral glucose tolerance test (OGTT)—is, not surprisingly, the “winner.”

The skepticism and criticism regarding the utility of the A1C for diabetes diagnosis has many roots. First, it relies on a continuing distortion of the early studies that first defined diabetes, discussed in detail below. Second, critics conveniently ignore or downplay the well-known, major limitations of glucose testing itself. Finally, critics seem oblivious to the fact that we have totally accepted the A1C test as the core, definitive assay to guide treatment decisions. This should support its use in diagnosis. Alternately, if the problems with the A1C test are so important, we should have major concerns over its use in diabetes management. This article responds to the critics and attempts to explain the weaknesses in their arguments.

How Do We Know When Diabetes is Diabetes?

The basis for the 2009 IEC report was a 1997 publication from an earlier Expert Committee ([PMID 9203460](https://pubmed.ncbi.nlm.nih.gov/9203460/)). Almost immediately following its release, this reports' recommendations were adopted

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worldwide. To understand how present-day critics have erred, it is important to understand the background and contribution of the 1997 report.

The 1997 report made two fundamental points that are particularly relevant to any discussion of the methodology used to diagnose diabetes. First, it stated that the premise for designating a specific level of hyperglycemia as “diabetes” should be based on the relationship between glycemia and the presence of long-term complications. The report pointed out that arriving at a cutpoint for diabetes diagnosis based on a statistical value (for example, the presumed bi-modal distribution of glucose values in a population), or based on a glucose value at which symptoms first appear, was an error. If the major problem with hyperglycemia was that it caused severe, long-term adverse outcomes that seriously affected morbidity and mortality, it seemed appropriate to diagnose abnormal hyperglycemia as the glycemic level at which these complications were likely to develop. Hence, the test used to diagnose the disease and the point at which diabetes existed should relate as closely as possible to the risk of developing complications.

Moreover, the report pointed out that the thresholds designated for diabetes diagnosis prior to 1997 (≥ 140 mg/dL using the fasting plasma glucose test [FPG] or ≥ 200 mg/dL using the OGTT) were entirely arbitrary. The National Diabetes Data Group, which provided us with those numbers, said this explicitly in their initial paper ([PMID 510803](#)). With time, however, this seems to have been forgotten. In addition, when the FPG or OGTT were initially designated as suitable for diagnosing diabetes, it was acknowledged that there was no distinction between the tests in their ability to separate people with diabetes from those without—yet another point that has been lost over the years.

Why is this history worth mentioning? To this day, the innumerable papers that compare the various diagnostic tests’ ability to detect diabetes assume erroneously that, sometime in the distant past, and surely on the basis of

solid data, the OGTT was designated the gold standard assay for diabetes diagnosis. This means that other tests are de facto unlikely to detect as many cases. Therefore, the assumption for the primacy of the OGTT not only lacks scientific evidence, but the very paper that ushered in its use in diagnosis explicitly acknowledged its lack of superiority. Even now, it is difficult to identify any scientific study that has found the OGTT *better* than the FPG or A1C in predicting diabetes complications or identifying those with complications.

The second fundamental contribution of the 1997 report to highlight that, when the prevalence of retinopathy (the most sensitive and specific chronic complication arising from hyperglycemia) was graphed against glycemia deciles in three distinct populations, the deciles at which retinopathy began to increase were *virtually the same* regardless of whether the glycemic measure applied was the FPG, OGTT, or the A1C. The implication of this observation was that the pre-1997 designated FPG cutpoint of 140 mg/dL was set too high, and that a threshold corresponding to an increase in retinopathy prevalence called for a lower cutpoint. A new threshold of ≥ 126 mg/dL (still in effect today) was chosen so that the corresponding value in the metric system would be an even 7.0 mmol/l.

Of note, the OGTT value that corresponded to an increase in retinopathy prevalence was much higher than the earlier-designated 200 mg/dL threshold. However, the 1997 report did not change that cutpoint because they thought it would be “very disruptive” to the research community. Thus, not only was the OGTT cutpoint of 200 mg/dL decided arbitrarily, based largely on the statistical distribution of glucose values in a population, it did not come close to identifying the point at which microvascular complications developed. What all this tells us is that it is wrong to use an OGTT value of 200 mg/dL as a meaningful threshold, even though this practice is well accepted. The many authors that use this value as a basis to assess the attributes of other

tests have been misled, and hence, their conclusions are misleading.

The 1997 report also tells us that, when the diagnostic methods are compared for the ability to detect retinopathy, they all perform about equally. That conclusion has since been confirmed in many studies ([PMID 20978099](#); [19875604](#)). Does perform “about equally” mean that the receiver operating characteristic curves are superimposable? They are not, probably due to both intrinsic measurement errors and because each test measures different metabolic characteristics ([PMID 10535454](#), [21346184](#)). Nevertheless, what appears certain is that there is no clinically significant difference between the tests’ ability to identify individuals who will develop diabetes-specific complications.

There is no distinction between FPG and OGTT in the ability to separate people with diabetes from those without diabetes.

If diabetes is defined by a test that itself has no basis for being a gold standard, the above information means that it is inappropriate to compare tests to see which one identifies more individuals with diabetes. Presenting one test, or any cutpoint, as somehow better or inferior because it results in a higher or lower prevalence of affected individuals misses the point. Why do we try to identify cases in the first place? It is not because we want the problem of diabetes to be viewed as important because of the high number of people affected, it is so we can know at what point to start treatment to prevent serious downstream complications.

Does the A1C Test Have Too Many Limitations?

No diagnostic test in all of medicine is flawless; each has drawbacks independent of sensitivity, specificity, and predictive value. The limitations of the A1C are carefully described in the 2009 IEC report and have been discussed many times since ([PMID 21525453](#), [19502545](#)). However, these limitations

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in no way preclude the use of the assay to diagnose diabetes. For example, although A1C levels may be elevated in some racial groups or in the elderly, this does not necessarily mean that such individuals would be falsely diagnosed and inappropriately started on therapy. Additionally, it is far from proven that the relationship between mean blood glucose levels and A1C in older patients actually reflects an abnormality of concern. The assertion that various clinical factors such as some anemias, chronic infections, or certain hemoglobinopathies are fatal flaws that negate the use of the test is a gross simplification and exaggeration. The vast majority of interfering conditions can be overcome by modern methods to measure A1C, or are easily appreciated by most clinicians. For the overwhelming majority of persons at risk for diabetes, the A1C works beautifully. The problems that might require a different assay affect a very small proportion of the world's population. In the U.S., the test would be contraindicated in a very small proportion of the population. Certainly, in many parts of the world, the cost of the A1C test could be an issue, but it is far less costly than the OGTT.

Finally, it is unclear why the concern over A1C testing to diagnose diabetes has not translated into concern that use of the A1C test to monitor treatment might be equally problematic. Since the early 1990s, the A1C has been the primary indicator of glycemic control, the primary measure that guides pharmacotherapeutic decision-making, and the only well-studied and proven marker of risk for diabetic complications. The A1C test is also universally considered one of the best, if not *the* best, measure of the quality of healthcare provided to people with diabetes. If the assay were as flawed as some have suggested, why aren't we seriously discussing and putting limitations on its use in the routine medical management of diabetes?

All told, the A1C test has shortcomings, but they are not so serious or pervasive to prohibit or discourage its widespread adoption.

Aside From the Diagnosis and Treatment of Diabetes, How Does the A1C Test Compare to Other Glucose Measurements?

It is well recognized that postprandial hyperglycemia, best measured by the OGTT, is the most sensitive indicator of risk for developing diabetes and the earliest marker of insulin resistance and beta-cell failure, the two hallmarks of type 2 diabetes. This would suggest that performing an OGTT could not only diagnose diabetes, but also identify those with early signs of metabolic dysfunction. On the other hand, an A1C or FPG above normal, but below the diabetic threshold, also denotes an elevated risk for developing diabetes ([PMID 9387611](#)). What is unclear is whether, in the long run, the better sensitivity of the OGTT makes any difference in our ability to reduce the rate at which complications develop.

What we lack (and may never have) is a clinical trial that randomizes subjects with a modest glucose tolerance abnormality to either intensive treatment to delay the onset of diabetes, or to no treatment until A1C becomes elevated. In other words, we need a well-controlled trial that tells us whether it is really worth knowing when the first appearance of a metabolic abnormality occurs (based on OGTT), versus waiting until it becomes more pronounced and thereby detectable by A1C. Until we know more about the benefits of identifying very early glucose abnormalities, the better sensitivity of the OGTT does not mean it is ultimately the test of choice to prevent the long-term complications of diabetes.

Some reports suggest that an OGTT indicating impaired glucose tolerance (IGT) is a better predictor of mortality and future cardiovascular disease (CVD) events than the FPG or A1C ([PMID 20807875](#)). Other studies show that an abnormal A1C level, below that diagnostic of diabetes, is more strongly associated with well-known CVD risk factors and is an excellent predictor of cardiac events, kidney disease, cancer, and all-cause mortality in people without diabetes ([PMID 20573754](#), [20886203](#)). Taken together, these suggest that a

compelling reason is yet to be provided as to why the A1C should not be the test of choice to ascertain risk for diabetes, risk for other diseases, and of course, to diagnose diabetes.

Conclusion

As with any new development in medicine or in society, there are individuals who claim the new order is unnecessary, a mistake, or will make life much more troublesome. Civilization needs and must welcome such critics because they challenge the proponents of change to justify their beliefs. Those in favor of A1C testing to diagnose diabetes have risen to the occasion by clearly documenting all the tests' advantages and limitations. As most clinicians and diabetes-related organizations have concluded, the use of A1C testing to diagnose diabetes is well-founded. In the absence of new data suggesting a previously undocumented problem, it is time to stop quibbling and move on to matters of greater importance.

Dr. Kahn has no commercial relationships to disclose related to the content of this article.

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LIMITATIONS IN THE USE OF A1C FOR DIAGNOSIS AND TREATMENT OF DIABETES

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The measurement of glycated hemoglobin (A1C) provides an assessment of long-term (~3 months) glycemic exposure and is regularly used in diabetes management. Recently, it has also been recommended by the American Diabetes Association (ADA) and the International Expert Committee (IEC) for use in the diagnosis of diabetes (click on the PubMed ID number to read more: [PMID 20067953](#); [20042772](#); [19502545](#)).

To use this approach most effectively, however, it is important for physicians to understand the potential for variability in A1C levels. Multiple factors can influence individual A1C levels, including ethnic variations, and genetic, hematologic, and illness-related conditions. Thus, while A1C is useful in diabetes treatment decision-making, its limitations as a diagnostic tool should be closely considered. Likewise, practitioners using mean blood glucose (MBG, a range meant to correspond to A1C) need to understand its potential for variability at the individual level.

A number of factors can influence A1C levels (Figure 1). Erythrocyte lifespan is one factor; as erythrocytes age, A1C increases. An individual's erythrocyte lifespan can vary based on genetics or the presence of disease, as well as external factors such as surgery or the presence of certain drugs. Another factor that may affect A1C is hemoglobinopathy, or changes in the molecular structure of hemoglobin (such as HbAS [sickle cell]). Further, multiple variations can exist among hemoglobin molecules, some of which may affect glycation or interfere with

measurement assays. Finally, the greatest proportion of A1C variation appears to be due to differences in the glycation of serum proteins. Glycation rate is related not only to glucose levels, but can be affected by intracellular pH and variations in the degree of glucose entry into the erythrocytes. ([PMID 20923515](#)).

A number of studies suggest that, beyond blood glucose levels, multiple factors affect A1C. For example:

- A study of 38 monozygotic (MZ; both with and without diabetes) and 41 dizygotic (DZ; all without diabetes) twin pairs found within-pair A1C correlations in pairs concordant and pairs discordant for diabetes; this suggests that genetic factors control hemoglobin glycation, independent of blood glucose levels ([PMID 11723071](#)).
- A cross-sectional study of 8,296 participants (≥20 years of age), using data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002, found that low levels of endogenous iron were associated with increased A1C levels, while low endogenous hemoglobin was associated with decreased A1C. These data further illustrate the complex effects of hematologic factors on hemoglobin glycation ([PMID 20942846](#)).
- Another cross-sectional study of 5,743 individuals without diabetes

from the Framingham Offspring Study (FOS) and NHANES found a significant relationship between age and A1C. Specifically, multivariable linear regression analysis found that, for each year of life, there was a 0.014- and 0.010-unit increase, respectively, in A1C. This was independent of multiple factors, including glucose levels and glucose tolerance ([PMID 18628569](#)).

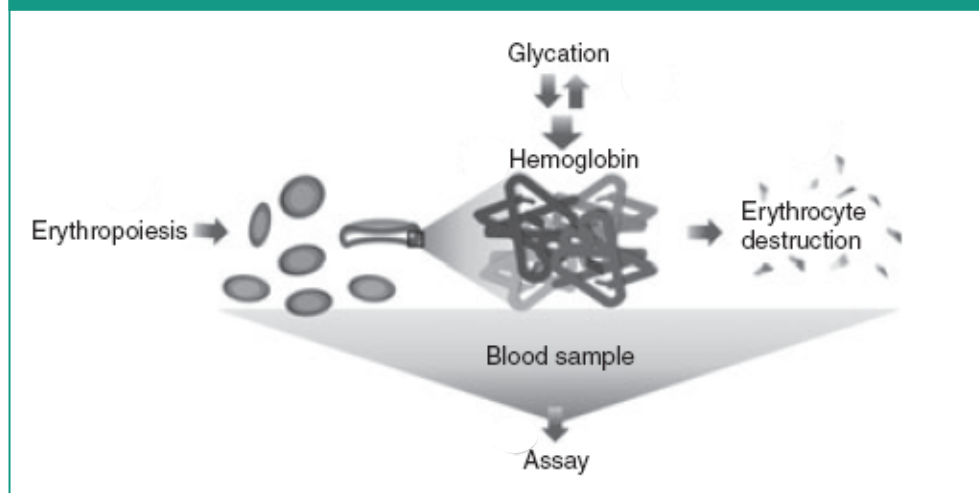
In addition, several studies suggest that race may be a factor in A1C levels, and that “normal” levels may vary. For example, a 2007 study using baseline data from 3,819 patients (≥25 years of age) with impaired glucose tolerance (IGT) in the Diabetes Prevention Program (DPP), found that non-Caucasian ethnic groups had significantly higher A1C levels compared with Caucasians, with African-Americans having the highest mean levels ([PMID 17536077](#)). Similarly, a Danish study that compared A1C levels between native Greenlander Inuits (n=917), Inuits living in Denmark (n=256), and Danes (n=6,784), found increased A1C levels among Inuits living both outside of and in Denmark ([PMID 20739381](#)).

Using A1C Levels For Treatment Decisionmaking

A substantial body of evidence exists to indicate that, in type 2 diabetes (T2DM), baseline patient A1C levels

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Figure 1. Factors influencing A1C



From Gallagher EJ, et al. *J Diabetes*. 2009;1:9-17; used with permission.

are strongly predictive of potential treatment efficacy, as assessed by A1C-lowering.

For example, multiple studies encompassing all major diabetes medication classes have found that higher A1C levels at baseline correlate with greater overall on-treatment A1C reductions. A 2006 meta-regression that drew data from 61 studies involving 5 major oral agent classes (alpha-glucosidase inhibitors, meglitinides, metformin, sulfonylureas, and thiazolidinediones) found a significant correlation between mean baseline A1C levels (range: 6.0% to 11.8%) and mean A1C decrease (range: -0.2 to -1.2; $P < 0.0001$), independent of treatment ([PMID 16936168](#)). A 2010 meta-analysis of data from 59 studies of 10 categories of glucose-lowering therapies (the 5 noted above, plus the incretin therapies and injected and inhaled insulin) similarly found a significant relationship between baseline A1C (6.4% to 11.7%) and absolute A1C reductions (+0.58 to -2.6; $P < 0.0001$) ([PMID 20536494](#)). In each of these studies, a lower baseline A1C was associated with lower overall A1C reductions, while a higher baseline A1C was associated with a greater reduction. Thus, regardless of medication choice, baseline A1C is an important predictive factor of medication effect.

In response to this research, current diabetes management guidelines, such as those from the American Association of Clinical Endocrinologists (AACE) suggest strongly that baseline A1C is critical in treatment decision-making. The AACE algorithm suggests targeting therapy (monotherapy, dual therapy, insulin) depending on initial A1C levels.

A1C and Mean Blood Glucose

MBG, or estimated average (mean) blood glucose, provides an estimated blood glucose range that corresponds with a patient's A1C level. The goal of MBG is to simplify provider/patient communication about glycemia by using the same units of measure (mg/dL) applied to discuss daily self-monitoring of blood glucose (SMBG) ([PMID 18540046](#)).

However, a recent study of 623 insulin-treated patients with T2DM that compared SMBG and A1C measurements found a correlation between MBG and A1C, but with considerable inter-subject variability. For example, among patients with A1C levels 6.5% to 7.5%, the average MBG was 142 mg/dL, but 10% of patients had MBG < 115 mg/dL and 10% had MBG > 171 mg/dL ([PMID 20923490](#)). Another study of children with type 1 diabetes (T1DM) found that, although there was a linear relationship between A1C and total MBG, substantial variability did exist based on individual patients' daily glycemic variability. For example, at an A1C of 10%, MBG ranged from 100 to 300 mg/dL ([PMID 12200073](#)). When participants were separated into high, moderate, and low glycation groups, all groups were found to have significantly different A1C levels ($P < 0.01$) but similar MBG ranges, again suggesting that factors independent of glycemic control may weaken the population-level relationship between A1C and MBG.

A number of studies suggest that, beyond blood glucose control, multiple factors affect A1C. These include ethnicity, heritability, and iron deficiency.

Relationship of A1C to Retinopathy

While there is a demonstrated correlation between A1C and retinopathy development, it is not clear that A1C is the best predictor of such complications. A 2003 report from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus compared several studies, including one of Pima Indians, one of Egyptians, and one of the U.S. population (NHANES III); this research found that fasting plasma glucose (FPG), 2-hr postprandial glucose (PPG), and A1C all similarly predicted retinopathy ([PMID 12502614](#)). A more recent study (2009) of data from the NHANES 2005-2006, evaluated 1,066 adults aged ≥ 40 years and found a relationship between A1C and

retinopathy. Rates of retinopathy increased steeply once A1C levels exceeded 5.5%; after this point, retinopathy prevalence rose 12.7% for each 1% increase in A1C ([PMID 19875604](#)). A Singaporean study, however, suggests that the classification used to define retinopathy (labeled in this study as any, moderate, or mild) affects the strength of the relationship. Specifically, in this group of 3,280 ethnic Malay individuals, there was a good relationship between A1C and moderate retinopathy, while study patients with "mild" retinopathy had the lowest prevalence rates per A1C group. Furthermore, an analysis of the strength of the relationship between A1C and neuropathy, and between A1C and nephropathy, found an association that was considerably weaker than that identified for retinopathy ([PMID 19387611](#)).

Use of A1C to Diagnose Prediabetes

The ADA considers an A1C of 5.7% to 6.4%, impaired fasting glucose (IFG, FPG of 100 to 125 mg/dL), or IGT (a 2-hr PPG measurement of 140 to 199 mg/dL on an oral glucose tolerance test [OGTT]) indicative of prediabetes. The IEC criteria regards an A1C of 6.0% to 6.4% as indicating risk for diabetes ([PMID 20042772](#); [19502545](#)).

However, a number of studies suggest that the use of A1C for prediabetes diagnosis is not as sensitive as OGTT. For example, a study utilizing 3 datasets from the Screening for Impaired Glucose Tolerance (SIGT) study, NHANES III, and NHANES 2005-2006 ($N = 4,706$ for all 3 combined), found that, when compared with OGTT, the use of A1C levels to identify prediabetes had incorrect identification rates (false-positive or false-negative) of 90% and 71% using IEC or ADA criteria, respectively ([PMID 20639452](#)). Another prospective, population-based study of 593 Finnish patients found that 65.7% of patients who developed diabetes within 10 years had ≥ 1 marker of prediabetes at baseline (IGT, IFG, or A1C). IGT alone better predicted diabetes (with 23.4% of patients eventually developing diabetes) compared

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with either A1C (14.1%) or IFG (6.3%). However, all 3 tests missed a large percentage of eventual diabetes cases ([PMID 20573752](#)).

A study of a multiethnic cohort of 1,156 obese children and adolescents found poor agreement between A1C values and OGTT status. Of the 247 patients whose A1C indicated they were at risk for diabetes, only 103 (47%) were categorized as such according to OGTT, suggesting that A1C alone is a poor diagnostic tool for identifying prediabetes in this population ([PMID 21515842](#)). Additionally, the Insulin Resistance Atherosclerosis Study (IRAS) found that 385 of 719 patients (53.5%) without diabetes were at risk of diabetes according to OGTT; however, only 23.6% of these individuals would have been identified by A1C assay alone ([PMID 20573754](#)).

Several other studies have similarly found that A1C is a poor single indicator of prediabetes. For example, in one analysis of data from the NHANES 2005-2008, depending on the measure used, substantial variability existed in establishing prediabetes. In this study, crude prediabetes prevalence was 14.2% when defined as A1C 5.7% to 6.4%. When defined as IFG (FPG 100 to 125 mg/dL or 110 to 125 mg/dL), prevalence was 26.2% or 7.0%, respectively; when defined as IGT (OGTT 140 to 199 mg/dL), prevalence was 13.7%. With all measures combined, the prevalence of patients at risk of diabetes was 36.7%, but study authors emphasized how difficult it was to identify prediabetes given the discordance between individual tests ([PMID 21270196](#)).

There also appears to be considerable overlap between normal glucose tolerance (NGT), IGT, and IFG. A recent study of German patients (N=2036) found that, in patients with newly identified NGT, IGT/IFG, or diabetes, the range of A1C values varied widely, from 3.5% to 7.1%, 4.1% to 7.1%, and 4.6% to 10.2%, respectively ([PMID 21264802](#)). Last, a recent longitudinal cohort study in Japan of 6,241 patients with no prior

prediabetes or diabetes diagnosis also found that A1C alone was a poor indicator of prediabetes. Of 2,092 patients diagnosed with prediabetes by either IFG or A1C (according to current ADA criteria), only 20% (n=412) were identified using A1C without IFG. The authors estimated that using A1C alone would have missed 61% of diagnoses. Expressed another way, of the 338 patients who developed diabetes over the 4.7 mean follow-up years, 9%, 32%, and 46% were originally identified as having prediabetes by A1C alone, IFG alone, or combined tests, respectively ([PMID 21705064](#)).

Using A1C to Diagnose Diabetes

The ADA criteria allow for an A1C cut-point of 6.5% as a single diagnostic tool for diabetes ([PMID 20042772](#)). In contrast, AACE recommends that A1C not be used as a primary diagnostic test; instead, it should be considered an optional diagnostic tool or, better, a screening test that may suggest the need for additional glucose measurements ([PMID 20350901](#)).

A number of studies indicate problems with the use of A1C as a diagnostic tool for diabetes. In the IRAS study, discussed previously, only one-third (32.3%) of patients identified as having diabetes according to OGTT were detected using A1C alone. The combination of IFG/IGT identified the greatest proportion (97.1%) of diabetes cases ([PMID 20573754](#)). An analysis of NHANES 2003-2006 data showed that A1C alone identified only 30% of patients with previously undiagnosed diabetes. In contrast, OGTT alone identified 90% of those with undiagnosed diabetes ([PMID 20067953](#)). A study conducted in the Netherlands examined the correlation between A1C and OGTT and found that an A1C cut-point of >6.0% resulted in a high number of missed or incorrect diagnoses ([PMID 19808928](#)). In a cohort of older patients (mean age 69.4 years) in the Rancho Bernardo Study, an A1C cut-point of 6.5% for T2DM diagnosis was found to have poor sensitivity/specificity (44%/79%). A cut-point of 6.15% had greater overall sensitivity/specificity

(63%/60%), but still missed one-third of patients with diabetes and misclassified one-third of those without. When stratified by age quartiles, the sensitivity/specificity of the 6.5% A1C cut-point improved substantially to 52%/95% in younger patients, but remained poor for the oldest patients ([PMID 19837792](#)). This confirms findings, discussed previously, indicating that A1C tends to increase with age.

In the IRAS study, only one-third (32.3%) of patients identified by OGTT as having diabetes were detected using A1C alone.

Another common measure of glucose, FPG, also lacks consistent agreement with A1C. An analysis of 6,890 adult participants without self-reported diabetes from the NHANES 1999-2006 cohort found that 1.8% had A1C \geq 6.5% and FPG \geq 126mg/dL, 0.5% had A1C \geq 6.5% and FPG <126 mg/dL, and 1.8% had A1C <6.5% and FPG \geq 126mg/dL. Although the study authors called this “reasonable agreement” between the two parameters, based on these data, nearly one-half of individuals with FPG \geq 126 mg/dL would be classified as not having diabetes because their A1C level was <6.5%, while 22% of individuals with an A1C \geq 6.5% had FPG <126 mg/dL and would be misdiagnosed as having diabetes ([PMID 19808920](#)). This again suggests that A1C alone may not reliably diagnose diabetes.

Finally, an analysis of NHANES III data on the effect of race and age on A1C found that, among those with A1C levels of 6.5% to 6.9%, fewer than one-quarter of whites and Mexican Americans, but more than two-thirds of African Americans, did not have diabetes based on OGTT ([PMID 20061043](#)).

Conclusion

Because A1C is influenced by a large variety of non-glycemic factors, including age, ethnicity, heritability, and iron

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deficiency, physicians need to be aware of the potential for inaccuracies when using this measure to diagnose diabetes or prediabetes. Evidence indicates that A1C is a useful tool for treatment decision-making, and practitioners should understand the relationship between A1C levels (both baseline and on-treatment measurements) and expected treatment outcomes. However, when A1C is used for diagnostic purposes, it is important that physicians understand the test's potential variability. Although the ADA and IEC recommend the use of A1C as a diagnostic test ([PMID 20042772](#);

[19502545](#)), available research indicates that identified A1C cutoffs may result in both positive and negative misdiagnoses.

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PRACTICE POINTERS

SELF-MONITORING OF BLOOD GLUCOSE AND CONTINUOUS GLUCOSE MONITORING IN PATIENTS WITH DIABETES MELLITUS

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In 2011, the U.S. Centers for Disease Control reported that 25.8 million U.S. residents have diabetes. This figure is projected to increase to 44.1 million by the year 2034. Further, the healthcare costs of diabetes are estimated at \$218 billion annually; this figure is projected to increase to \$336 billion by the year 2034. However, the achievement and maintenance of proper glucose control has been shown to decrease micro- and macrovascular complications of diabetes, decrease healthcare costs, and improve patients' quality of life.

Current diabetes management guidelines place substantial emphasis on A1C values as a reflection of glucose control. The Diabetes Complications and Control Trial (DCCT) found a linear correlation between mean plasma glucose (MPG) and A1C; consequently,

recommendations have been made that providers should have a clear understanding of the relationship between MPG and A1C, to enable them to set appropriate glucose targets (click on the PubMed ID number to read more: [PMID 11815495](#)).

There is concern, however, that while A1C and MPG provide a good expression of mean glucose levels, they do not provide an adequate representation of glucose variability, a possible risk factor for the development of microvascular complications ([PMID 21266647](#); [19966012](#)). For example, despite having satisfactory glucose levels overall, many patients experience post-meal hyperglycemic and/or hypoglycemic episodes ([PMID 11679447](#)). As shown in Figure 1 on the next page, two patients with the same A1C and MPG can have substantially different glucose variability. Compared with Patient B's glucose levels, Patient A has a much larger standard deviation and interquartile range, and a higher degree of glucose variability. As a result, it can be argued that Patient B, who has less glucose variability, has better glycemic control.

The best way to delay the onset and severity of diabetic complications is with intensive insulin therapy, delivered ideally either by continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI), both of which should be accompanied by frequent blood glucose (BG) testing. Self-monitored BG (SMBG) and con-

tinuous glucose monitoring (CGM) have made BG monitoring more accurate, convenient and easier to perform.

This article provides a brief overview of glucose measurement and monitoring technology for diabetes management, from its early days, through present circumstances, to future directions.

SMUG

Self-monitored urine glucose (SMUG) was one of the first methods available to measure glucose. It involved collecting spot urine and placing a test strip into the sample. Due to the inaccuracy and inconvenience of SMUG testing, it has widely been replaced by SMBG.

SMBG

SMBG meters were first developed in the 1970s. Over the years, meters have become smaller and more accurate, and test strips have been developed that require smaller amounts of blood. According to international standards, all glucose meters on the market for patient use must adhere to the following guidelines: ≥95% of BG results should fall within ±15 mg/dL of the reference method at BG concentrations <75 mg/dL, and within ±20% at BG concentrations ≥75 mg/dL. However, a 2010 study found that 11 out of 27 meters did not meet these requirements ([PMID 20151773](#)). In March 2010, the U.S. Food and Drug Administration/Center for Devices and Radiological Health held a public meeting to discuss the accuracy of

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available BG meters. To provide one example of how real-world factors can affect meter accuracy, a study comparing BG measurements from first-drop blood samples obtained under various states of hand cleanliness found that 11% of participants had a $\geq 10\%$ difference in BG concentrations depending on whether their hands were washed or unwashed. In washed vs. fruit-exposed hands, a $\geq 10\%$ difference occurred in 88% of participants ([PMID 21289231](#)). To improve SMBG accuracy, researchers recommended that, if handwashing is not possible and the patient's hands are not visibly soiled or contaminated by recent contact with sugar-containing foods, the patient should wipe away the first drop of blood and use a second drop for the test.

Despite the potential for inaccurate glucose measurements, SMBG testing is clearly associated with improved A1C levels in patients with type 1 diabetes (T1DM) and patients with insulin-treated type 2 diabetes (T2DM) ([PMID 20377657](#); [20307405](#)). Patients who do not require insulin may also benefit from SMBG. The Structured Testing Program (STeP) study looked at insulin-naïve individuals with T2DM over a 12-month period and found a 0.9% A1C reduction in the group that received a structured SMBG testing plan, compared to those without a structured plan. In addition, improvements in glucose variability were noted in the group using the structured testing plan ([PMID 21270183](#)).

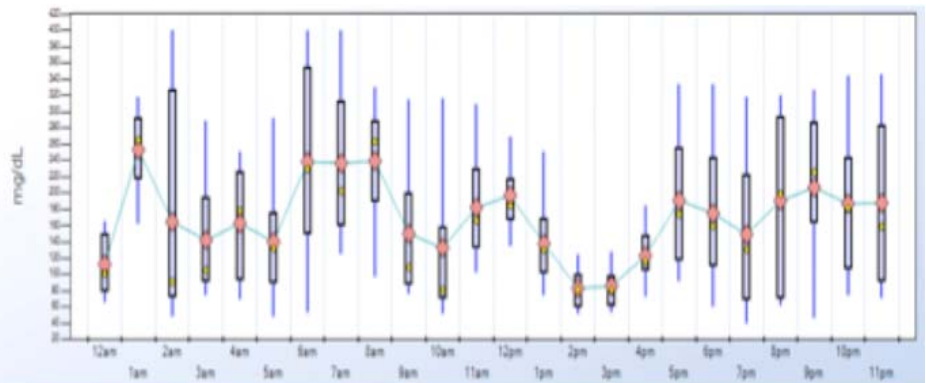
Regardless, the efficacy of SMBG depends on the patient's willingness and ability to perform several fingersticks throughout the day. In addition, even when SMBG frequency is high, it still provides only a few snapshots from a complex and variable environment, and provides no information about glucose levels when a patient is sleeping ([PMID 19560388](#)). For a more continuous view of BG, we must consider the increased use of CGM.

CGM

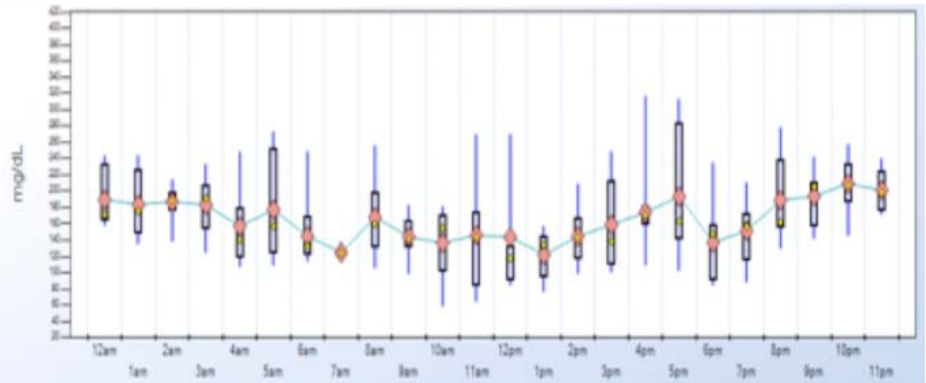
Continuous glucose monitors are the newest BG monitoring devices; they are

Figure 1. Glucose variability in two patients with the same A1C and MPG

Patient A



Patient B



From the clinical practice records of Dr. Garg; used with permission.

used primarily in patients with T1DM or insulin-requiring T2DM. In the past 15 years, many CGM systems have been developed for use in daily diabetes management. Real-time CGM allows patients to continuously see glucose values and improve glucose control by reducing both hyper- and hypoglycemic excursions — and thus increasing the amount of time spent in the euglycemic range. All CGM systems provide interstitial glucose level readings at 1- to 5-minute intervals (Table 1, next page). Compared with the isolated values

obtained using SMBG, this allows for an accurate representation of overall glucose trends ([PMID 21278138](#)). The American Association of Clinical Endocrinologists (AAACE) recently published guidelines ([PMID 21356637](#)) recommending CGM use in:

- Adults with T1DM who have hypoglycemic unawareness or frequent hypoglycemia,
- Adults with A1C levels over target or excess glucose variability, and
- Patients who require A1C reduction without increased hypoglycemia, and/or who are pregnant or planning pregnancy.

These recommendations were based, in part, on the results of a clinical trial that showed significant A1C reductions of 0.53% ($p < 0.001$) in adult patients (≥ 25 years of age) using CGM compared to those using SMBG ([PMID 18779236](#)).

Despite the potential for inaccurate glucose measurements, SMBG testing is clearly associated with improved A1C levels in patients with T1DM and with insulin-treated T2DM. Patients who do not require insulin may also benefit from SMBG.

Continued

Table 1. U.S. Food and Drug Administration-approved personal continuous glucose monitoring devices

Features	Abbott FreeStyle Navigator	DexCom SEVEN PLUS	Medtronic Guardian Real-Time	MiniMed Paradigm REAL-Time Revel System
Approved age group	≥18 years	≥18 years	≥7 years	≥7 years
Integration with pump	No	No	Yes	Yes
Integration with glucometer	Yes	No	No	Yes
Predictive alarm	Yes	No	Yes	Yes
Rate of change alarm	Yes	Yes	Yes	Yes
Sensor wear (days)	5	7 (10 – 14)*	3 (5 – 6)*	3 (5 – 6)*
Frequency of glucose measurements (minutes)	1	5	5	5

* Numbers in parentheses indicate off-label use from the authors' clinical experience

Reprinted from Blevins TC, et al. AACE Consensus Panel on Continuous Glucose Monitoring. *Endocr Pract.* 2010;16:734-735, with permission from the American Association of Clinical Endocrinologists.

A recent study evaluating CGM in patients with T1DM receiving insulin therapy via MDI or CSII showed similar and statistically significant A1C decreases in both groups 3 months after screening (approximately -0.7% to -0.8%). Of note, glucose variability indices were more improved in the CSII group. In addition, during the unblinded phase, both groups experienced a similar reduction in time spent in both hypo- and hyperglycemic ranges, and an improvement in time spent in target glucose ranges ([PMID 21278138](#)).

CGM in Children and During Pregnancy

There is a strong argument for the utility of CGM in children and during pregnancy complicated by diabetes. Hypoglycemia is a significant burden for all patients with T1DM, but even more so for children, whose food intake cannot be predicted. A recent CGM study in children found hypoglycemic episodes of <30 minutes in duration in 6 out of 27 patients (22%) and episodes lasting >30 minutes in an additional 17 patients ([PMID 12203949](#); [12203948](#)). Such data, not readily available without CGM, can enable providers to

update insulin regimens in order to increase glycemic control, decrease glucose variability, and improve diabetes care. Unfortunately, however, the majority of CGM devices are not FDA-approved for use in children.

In addition, to decrease the high risk of negative outcomes associated with pregnancies complicated by diabetes (including preeclampsia, cesarean section, fetal macrosomia, and congenital anomalies), glycemic control and near-normal A1C values are imperative for pregnant mothers with diabetes. A pilot study of 8 pregnant women (6 with T1DM, 2 with gestational diabetes) treated with MDI found that treatment adjustments based on CGM data resulted in decreased rates of undetected hyperglycemia and nocturnal hypoglycemia ([PMID 12823237](#)).

CGM in Cystic Fibrosis and Glycogen Storage Diseases

Factors affecting glycemia in patients with cystic fibrosis (CF) range from mal-absorption, abnormal glucose tolerance, the caloric burden of supplemental nutrition, and the metabolic effects of infection and drugs used to treat CF.

A recent study of CGM in patients with CF showed that 36% of those not yet diagnosed with CF-related diabetes had abnormal glycemic profiles with hyperglycemic excursions >200 mg/dL ([PMID 18415892](#)). This suggests that CGM may be useful for early detection of hyperglycemia in patients with CF.

In glycogen storage diseases (GSD), the lack of the enzyme glucose 6-phosphatase or translocase results in recurring episodes of asymptomatic hypoglycemia, particularly nocturnal hypoglycemia. During 48 hours of CGM wear, up to 220 minutes of hypoglycemia were discovered in 4 out of 6 patients with GSD type 1; information obtained enabled patients to modify their dietary intake to avoid future glucose excursions ([PMID 11916320](#)).

Issues With CGM Adoption

It is important to note that all CGM devices have been approved only as adjunctive devices; prior to taking corrective action based on CGM results, patients must use SMBG. SMBG results are also essential to help calibrate the CGM device. We hope this will not be required in the future.

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Other limiting factors to the adoption of CGM in clinical practice are cost, reimbursement challenges, issues with device calibration and lag time, lack of patient/provider education, and low staff availability to educate patients.

The Future of Diabetes Technology

In the future, CGM is likely to be used in conjunction with insulin pump therapy (closed-loop or semi-closed-loop) (PMID 20587585; 18644063). Early experience in Europe with closed-loop systems in patients with T1DM has shown decreases in hypoglycemic excursions (PMID 20138357).

Another emerging technology worth keeping an eye on are smart phone applications that allow patients to enter BG information manually. Several companies are working to develop a meter that integrates with mobile phone technology; an example is the iBGStar glucose meter that connects with the iPhone® (recently approved in parts of Europe; not FDA approved). This technology enables the auto-

matic input of BG values into the phone's application.

Implementing these technologies will require commitment on the part of providers, educators, and patients alike to create the best outcomes for diabetes management. The outcome for patients who can master these technologies and use them regularly will very likely be better glucose control.

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FROM THE CADRE ARCHIVES

An excerpt from "Current Developments in Glucose Sensors/Monitoring" by Howard Wolpert, MD, which appeared in *CADRE's Current Diabetes Practice*, Vol. 7, Issue 2:

Setting Alarms

Alarms for hypo- and hyperglycemia are a very important feature of real-time CGM devices. To ensure the patient derives full benefit from this technology, the alarm thresholds must be individualized. Table 3 outlines important considerations in optimizing alarm settings and preventing patients from developing alarm burnout. For individuals without

a history of problematic hypoglycemia, the low threshold may initially be set at 55 to 60 mg/dL, and the high threshold may be set at ≥ 250 mg/dL. This ensures that intrusive and irritating alarms will be reduced and risk for alarm burnout will be minimized while the patient initially masters use of the sensor and learns to smooth out glucose excursions. Over time, alarm

settings can be brought closer to target glucose levels, which may assist with further tightening of glycemic control. In the context of discussing alarm thresholds with patients, it is often worthwhile to emphasize that it is less important if the alarm went off at the "right" number than if the alarm provided timely warning of low and high glucose levels.

Table 3. Trade-offs in setting continuous glucose monitor alarm thresholds

	Set alarms at the "ideal" level (Example: low = 80 mg/dL, high = 180 mg/dL)	Set alarm thresholds more widely (Example: low = 55 mg/dL, high = 250 mg/dL)
Pros	<ul style="list-style-type: none"> • Patient will be warned of most low and high blood glucose readings 	<ul style="list-style-type: none"> • Fewer false alarms • Fewer irritating and intrusive alarms • Less risk for alarm burnout
Cons	<ul style="list-style-type: none"> • Frequent false alarms • Frustration and irritation • Disruption of sleep • Increased risk for alarm burnout with an associated tendency to ignore sensor alarms 	<ul style="list-style-type: none"> • Patient will not be warned of all high and low blood glucose readings