review

# Hemoglobin $A_{1c}$: Past, present and future

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Hemoglobin $A_{1c}$ ($HbA_{1c}$) has been used for decades to monitor the control of glycemia in diabetes. Although $HbA_{1c}$ is currently undergoing a reassessment, and major developments have been underway in recent years, $HbA_{1c}$ is not recommended at present for diabetes screening or diagnosis. The objective of this review is to summarize the recent developments and to review a potential diagnostic role for $HbA_{1c}$. Implementation of changes in $HbA_{1c}$ results and units of measurements have been suggested for the purpose of test standardization. These include lower reference ranges (by about 1.5-2 points) and measurement units expressed in percentage (%), as mg/dL (mmol/L) or mmol/mol (or a combination of these units). In diabetes screening and diagnosis, the current diagnostic guidelines use measurement of plasma glucose either fasting or after glucose load. These diagnostic methods have shortcomings warranting a potential diagnostic role for $HbA_{1c}$. While recent developments in $HbA_{1c}$ methodologies are acknowledged, it is not yet known which changes will be implemented, and how soon. Given the recent literature supporting $HbA_{1c}$ diagnostic abilities, and given the shortcomings of the current guidelines, it is possible that a diagnostic role for $HbA_{1c}$ may be considered in future practice guidelines, globally. Very recently, the first of such recommendations has been proposed by an expert panel, as announced by the US Endocrine Society.

The "worldwide explosion in the prevalence of type 2 diabetes mellitus[1]" has turned diabetes into a global epidemic.[2] Epidemiological data have shown that diabetes prevalence skyrocketed in recent years; for example, in the US, a 61% increase in the prevalence of diabetes between 1990 and 2001 has been reported.[2] The prevalence of pre-diabetes, defined as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), is also increasing globally.[1,3] Recent studies[2] have shown pre-diabetes which eventually progresses to diabetes in up to 70% of cases, to be a risk factor for cardiovascular disease.[2]

It follows that there is a critical need to develop effective methods to improve early detection and treatment of diabetes and pre-diabetes, in an effort to avert the well-known complications of diabetes. These micro- and macrovascular complications continue to claim more lives and to further exhaust national budgets. Control of hyperglycemia, as monitored by glycated hemoglobin ($HbA_{1c}$), has been recommended by various international diabetes organizations which recommend $HbA_{1c}$ management targets.[4] These targets vary from one organization to another, ranging roughly between 6.0% and 7.0%.[4]

It is notable, however, that $HbA_{1c}$ has been associated with controversies and confusion among patients and physicians alike. Among the scientific community, $HbA_{1c}$ has traditionally served as an indicator of glycemic control over the preceding 2- to 3- month period. In the real world, patients with diabetes measure their glucose levels at home obtaining results such as "120 or 200" (mg/dL), while physicians measure $HbA_{1c}$ with different results that many patients cannot fully comprehend, e.g., 7.6% or 8.8%. Among the diabetes scientific community, the main controversies about $HbA_{1c}$ concern standardization of the test and artifactual interferences with some assay methods.[5]

Another controversy about $HbA_{1c}$ is whether or not the test can be used for screening or diagnosis of diabetes. The current screening and diagnostic methods for diabetes have known shortcomings, which warrant the consideration of $HbA_{1c}$ as a possible alternative.[5-7]

These shortcomings are: 1) the fasting plasma glucose (FPG), the main screening method, suffers from inadequate sensitivity; 2) the oral glucose tolerance test (OGTT), a suggested alternative diagnostic test, is considered cumbersome and is not commonly used in clinical settings; 3) both tests require fasting, which may not be feasible, especially in busy clinical settings and in population screening.

In response to the aforementioned concerns, there have been major developments in $HbA_{1c}$ methodologies and terminologies over the last few years. Similarly, there have been developments regarding a potential diagnostic role for $HbA_{1c}$, revisiting this controversial issue. In the forthcoming sections, we will provide an overview of these developments and discuss the validity of $HbA_{1c}$ as a potential diagnostic test for diabetes.

## $HbA_{1c}$ Terminology and Methodology, Past and Present

*The chemistry and clinical interpretation of $HbA_{1c}$*

During unrelated work in the late 1960s, Rahbar discovered a glycated species of hemoglobin that he called the "diabetic hemoglobin" as reported by Miedema.[8] Different subtypes of these compounds have since been described. The collective overall entity, previously termed glycosylated hemoglobin, is referred to in modern laboratory terms as glycated hemoglobin (GHb), but that term or glycosylated hemoglobin is not used commonly at present in cinical settings and day-to-day communication among health care providers. Hemoglobin A1 (HbA1) is a derivative of adult hemoglobin (HbA), with monosaccharide (fructose or glucose) attachments. $HbA_{1c}$ is the major and the most extensively studied subtype of the three known HbA1 species (HbA1a, b and c). In strict chemical terms, the molecular structure of $HbA_{1c}$ is _-N-(1-deoxy)-fructosyl-hemoglobin[8] or N-(1-deoxyfructose-1-yl) hemoglobin beta chain.[9] $HbA_{1c}$ is formed via a posttranslational nonenzymatic attachment of glucose to hemoglobin[10] in an irreversible fashion and at a rate dependent on the ambient blood glucose during the lifespan (120 days) of the red blood cell.[8] Hence, $HbA_{1c}$ is traditionally looked at as an indicator of the mean blood glucose (MBG) in the preceding 2 to 3 months. However, it has been recently recognized that the MBG in the preceding 1 to 2 months is the major contributor to $HbA_{1c}$.[11-13] In this regard, it has been found that MBG in the preceding 30 days has the largest contribution to $HbA_{1c}$,[11] and that up to 70% is determined by the preceding 2-month MBG.[12] According to Tahara et al, monthly contributions of MBG to $HbA_{1c}$ are as follows: 50% from the most recent 30 days and 25% from each of the preceding 30 and 60 days.[13] This concept has been referred to as the "weighted" average of blood glucose as related to $HbA_{1c}$.[11,13,14] Furthermore, until recently it had not been established how variations in glucose profiles on a daily basis would influence $HbA_{1c}$; for example, fasting versus postprandial glucose levels. In a recent analysis of the Diabetes Control and Complications Trial (DCCT) cohort, Service and O'Brien concluded that the MBG contributed more to overall $HbA_{1c}$ than did variations in 7-point daily glucose measurements.[15]

At present, $HbA_{1c}$ is measured by three basic types of assay methods.[8,10] These include immunoassay and the two types of high performance light chromotagraphy (HPLC), the cation-exchange and the boronate affinity methods. The unit of $HbA_{1c}$ measurement is the percentage unit (%), i.e., the percentage of $HbA_{1c}$ to HbA. The reference range used by many laboratories is roughly 4.0% to 6.0%.

## $HbA_{1c}$ as the Time-Tested Cornerstone in Glucose Monitoring in Diabetes

Once it became known that $HbA_{1c}$ closely reflected the preceding glycemic average, it became the cornerstone of monitoring of glycemic control, in addition to the method for glucose self-monitoring by patients. Furthermore, almost all outcome studies on diabetes complications are now based on $HbA_{1c}$. The most famous of such studies, which displayed the relationship of $HbA_{1c}$ to diabetic complications, are the Diabetes Control and Complications Trial (DCCT),[16] and the United Kingdom[17] Prospective Diabetes Study. Both studies have established a direct link between $HbA_{1c}$ levels and retinopathy, nephropathy and neuropathy.[10] Various diabetes and other health organizations have since issued management guidelines defining $HbA_{1c}$ targets.[4,10] Thus, and soon after the publication of the DCCT, the American Diabetes Association (ADA) began in 1994 to recommend a $HbA_{1c}$ target of <7 % for patients with diabetes.[18] It is notable that subsequent ADA guidelines amended the earlier $HbA_{1c}$ target by calling for individualization of this target (by relaxing or tightening this target), considering age, comorbidities, life expectancy and hypoglycemia risks.[19] Other health organizations, worldwide, recommended similar $HbA_{1c}$ guidelines, overall.[20-22]

## Problems and Concerns About $HbA_{1c}$ Measurement and How These Were Addressed

The clinical use of $HbA_{1c}$ has encountered several road blocks since it became available. These obstacles have included:

*Standardization*

Measurement of glycated hemoglobin from different assay methods used by laboratories varied considerably,[10] with over 20 methods in clinical use as recently as 2004.[23] Early assay methods measured and reported different glycated fractions (total GHb, HbA1, and $HbA_{1c}$).[10] This heterogeneity in reported results caused concerns about reliability and reproducibility of $HbA_{1c}$. The call for test standardization was critical. In response, the DCCT method (Rex 70 ion-exchange HPLC) was recommended by the National Glycohemoglobin Standardization Program (NGSP) as the preferred method for US laboratories in the mid 1990s.[10,24] Compliance with this program was reported to be very satisfactory, as noted in Figure 1.[10] Outside the US, the NGSP standardization method has been adopted rather universally, but local (somewhat similar) standardization programs have recently been adopted in Sweden[25] and Japan.[26] At about the same time that the NGSP initiated its program, the International Federation of Clinical Chemistry (IFCC) developed the so called "definitive reference method", which was aimed toward global $HbA_{1c}$ standardization.[8,10,23] This method involves a sophisticated technical, 2-step procedure that further purifies the $HbA_{1c}$ assay by removing impurities from the tested blood samples.[8] It should be noticed that the NGSP and IFCC results are very tightly correlated (r=0.99), as noted in Figure 2.[10] The results are interchangeable by a master equation as follows (23-27): To convert $HbA_{1c}$ from IFCC units to NGSP units=(0.915×IFCC)+2.15. The IFCC results are about 1.9, and 1.3 points lower than the NGSP results at normal and elevated $HbA_{1c}$ values, respectively.[27]

*Interference with assays*

Concerns have been raised about the possible effects of hemoglobinopathies,[28,29] uremia[30] and ethnic variations[5,31] on $HbA_{1c}$ assays. Concerns about other possible interferences have been raised, particularly in regards to recent circulatory and hematological changes, such as in patients with recent blood regeneration.[32] These concerns were real and they certainly needed to be addressed. While interfering substances raise concerns about test reliability, recent technologies have introduced more accurate commercial analyzers into clinical use reportedly not affected by common hemoglobinopathies or uremeia.[33,34] It is prudent that physicians be aware of the functionality of analyzers used in their local laboratories. They should also be aware of recent circulatory changes that may influence $HbA_{1c}$, such as a recent blood transfusion or hemolytic anemia.[30]

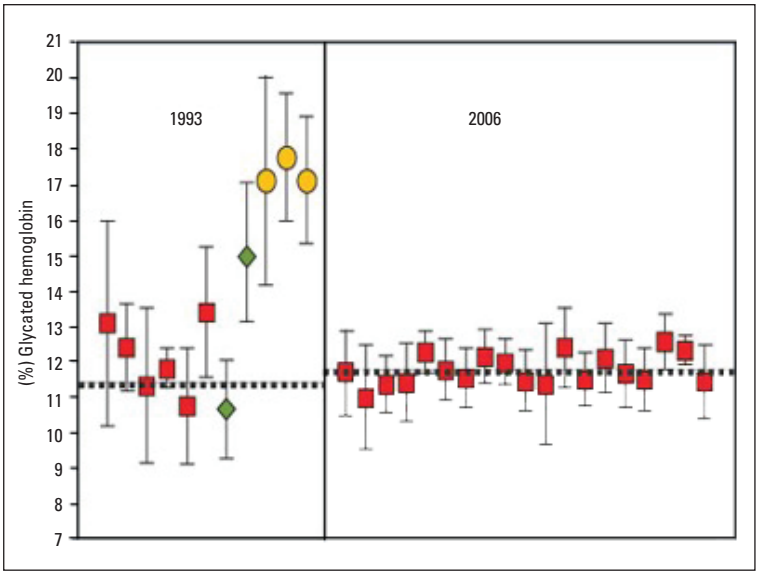


**Figure 1.** Glycated hemoglobin results from the College of American Pathologists in 1993 and 2006.[10] Each point and bar represent the mean ±2 standard deviation of results for a single method. Diamonds represent results reported as HbA1, squares represent results reported as $HbA_{1c}$, and circles represent results reported as total GHb. The dotted horizontal line represents the NGSP/DCCT target value. (Reproduced with permission: From the IVD (In Vitro Devices) Technology in Los Angeles, CA, and the University Of Missouri School Of Medicine in Columbia, MO).

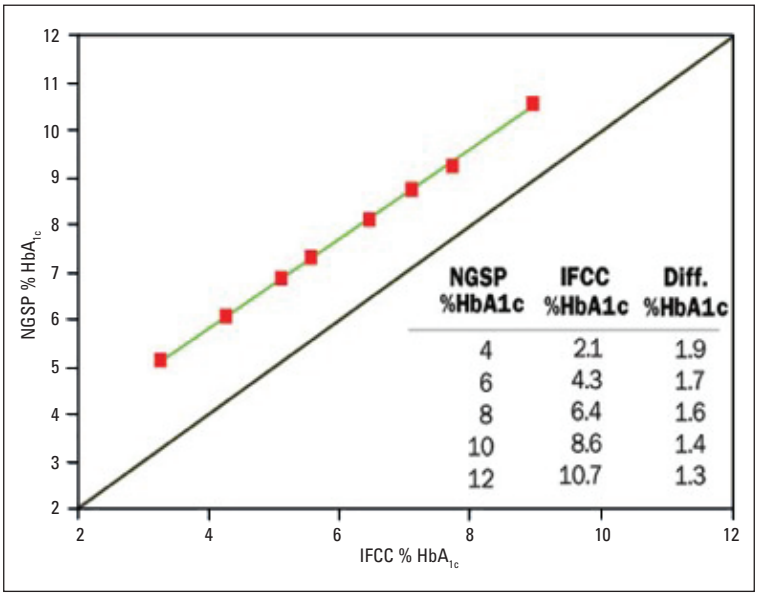


**Figure 2.** The relationship between $HbA_{1c}$ measured by the NGSP and IFCC networks.[10] The upper green line is the regression line. The solid line is y=x. (Reproduced with permission: From IVD (In Vitro Devices) Technology in Los Angeles, CA, and the University of Missouri School of Medicine in Columbia, MO).

Finally, in regards to the potential effects of race or ethnicity on $HbA_{1c}$ measurements, a recent study by Herman et al (n=3819) has addressed this issue.[31] In this study of individuals with IGT, mean $HbA_{1c}$ was found to be slightly higher in minority US individuals, with the highest differences observed between Caucasians and African Americans (5.8% vs 6.2%, respectively). Therefore, this should be taken into consideration when analyzing $HbA_{1c}$ results.

*Confusing terminologies and measurement units*

As anecdotally observed, the fact that the $HbA_{1c}$ test includes hemoglobin (literally and by name) has often created confusion among patients. While they understand that "diabetes is a disease of blood sugar", they wonder what hemoglobin (referred to as blood count by patients) has to do with diabetes? One of our patients once referred to $HbA_{1c}$ as "that sugar thing on the blood count"! Similarly, patients wonder what the percentage (%) unit appearing in $HbA_{1c}$ result means. Finally, patients often wonder "how come" a blood sugar of 130 on their glucose meters, for example, translates into 6.5% or 7% as reported by their physicians as $HbA_{1c}$ laboratory results! It seems, therefore, as if patients and their physicians are testing two different entities. For better education, in the quest for better patient participation in their disease management, there is no doubt that a common, easily understandable language of communication between patients and physicians, is highly desirable. To reconcile the concepts of what $HbA_{1c}$ actually measures and what patients measure at home, major developments in $HbA_{1c}$ have occurred in the recent few years. These developments will be covered in the next section.

## Summary of the Recent Developments in $HbA_{1c}$ Terminology, Methodology and Units of Measurements

*Technical and laboratory developments*

To capture the aforementioned developments in $HbA_{1c}$ testing, various national and international laboratory organizations participated in collaborating and then reporting these developments. After a series of expert consensus meetings[10] it was agreed that the proper scientific name for the measurement (test) should be "hemoglobin beta chain (blood) - N-(1-deoxyfructos-1-yl) hemoglobin beta chain; substance fraction millmole per mole". This change in $HbA_{1c}$ units, i.e., mmol/mol, will give totally different $HbA_{1c}$ numbers that are unfamiliar to clinicians, and therefore we opted not include these new units in this review. Readers can learn more about this in a brief and concise recent editorial by Panteghini and John.[35] Other changes agreed upon are summarized in the final consensus statement by the aforementioned organizations, and will be reviewed in a subsequent section.

## Clinical Developments (The International $HbA_{1c}$-MBG Study)

To better understand the relationship of $HbA_{1c}$ and glucose levels, an international, multicenter, prospective study was designed. This landmark study was sponsored by major national and international diabetes organizations.[35] The main purpose of the study was to firmly define the relationship between $HbA_{1c}$ and MBG. Although this correlation had long been observed in the literature, the concern was that this correlation was not "exceptionally robust", and that prior studies had not utilized frequent glucose measurements.[36]

The most important message from the study sponsors during the conduct of the study is that the ultimate purpose of the study was to alleviate the patient confusion about $HbA_{1c}$ terminology and measurement units.[36] Thus, if a tight correlation between $HbA_{1c}$ and MBG is confirmed, then $HbA_{1c}$ can be expressed in glucose units, the so called estimated average glucose (eAG), or $A_{1c}$-derived average glucose (ADAG).

The study was launched in 2004, and utilized monthly $HbA_{1c}$, continuous glucose monitoring systems and 7-point capillary (fingerstick) glucose profiles, and has just been published.[37] The study enrolled 507 subjects: 268 with type 1 diabetes mellitus, 159 with type 2 diabetes mellitus and 80 non-diabetic controls. As expected, the study confirmed the tight correlation between $HbA_{1c}$ and average glucose, per linear regression analysis ($P$<.0001).

The firmly established tight correlation between HbA1c and a average glucose across the spectrum of glycemia (from normal to extreme hyperglycemia) allowed calculation of an estimated average glucose (eAG) from $HbA_{1c}$ results.[37] Thus this calculation can be used to express the results of HbA1c measurements into glucose units that patients are more familiar with, i.e., the same units they get from their glucose meters. An easy formula[37] was derived from the study results as follows: $eAG\ (mg/dl) = 28.7 \times HbA_{1c}\% - 46.7$.

It is notable that of the anticipated changes in $HbA_{1c}$ measurement, the idea of co-reporting eAG with $HbA_{1c}$ is not totally new in clinical practice. In fact, many laboratories have been doing that for some time,[38] and many physicians have been giving their patients $HbA_{1c}$-derived glucose equivalents.[36]

## The International Consensus Statement Summarizing the Recent Developments

Following the aforementioned developments, a consensus statement was published jointly by major national and international diabetes and laboratory organizations (ADA, EASD [The European Association for the Study of Diabetes], IFCC [The International Federation of Clinical Chemistry and Laboratory Medicine], IDF [The International Diabetes Federation]). The statement was intended to educate the public on recent developments and anticipated changes in $HbA_{1c}$. The statement included five recommendations:[36]

1. $HbA_{1c}$ test results should be standardized worldwide, including the reference system and results reporting.
2. The new IFCC reference system for $HbA_{1c}$ represents the only valid anchor to implement standardization of the measurement.
3. $HbA_{1c}$ results are to be reported worldwide in IFCC units (mmol/mol) and derived NGSP units (%), using the IFCC-NGSP master equation.
4. If the ongoing "average plasma glucose study" fulfills its a priori-specified criteria, an ADAG value calculated from the $A_{1c}$ result will also be reported as an interpretation of the $A_{1c}$ results (As noted above, the study has already been completed and published).
5. Glycemic goals appearing in clinical guidelines should be expressed in IFCC units (i.e., mmol/mol), derived NGSP (i.e., %) units, and as ADAG (i.e., mg/dl or mmol/L).

## The Role of $HbA_{1c}$ in Screening and Diagnosis of Diabetes and Pre-diabetes

### *$HbA_{1c}$ and MBG correlation from a diagnostic perspective: Review of the literature on the diagnostic validity of $HbA_{1c}$*

Evidence had shown a satisfactory correlation between MBG and $HbA_{1c}$[39-42] in the hyperglycemic range. It is expected that such evidence will be firmly substantiated by the International $HbA_{1c}$-MBG Study which was recently published.[37] The next question, in regards to the diagnostic issue, was: Does $HbA_{1c}$ follow glycemia as it transits from normal to pre-diabetes and then to diabetes? Research has shown this to be the case indeed. Correlation between $HbA_{1c}$ and MBG did hold true in cohort large studies, including two separate analyses from the population-based NHANES (National Health and Examination Survey), the NHANES III and the IV.[43,44] Certainly, the latest international $HbA_{1c}$-MBG[37] substantiated this (tight) correlation across the glycemic spectrum.

It is notable that the diagnostic role of $HbA_{1c}$ is not a new research endeavor. As a matter of fact, this issue was addressed soon after GHb discovery, but has remained controversial.[43] In a brief search of the literature since the late 1970s, we came across numerous studies that addressed the validity of $HbA_{1c}$ for screening and diagnosis, in both type 2 diabetes [45-61] and gestational diabetes mellitus (GDM).[62-71] These studies were heterogeneous in design and yielded no consensus on the diagnostic validity of $HbA_{1c}$, overall. An extensive literature search for all relevant studies or appraisal of these studies is beyond the scope of this review. However, we identified published reports that reviewed the available studies in an in-depth scrutiny.

In the case of type 2 diabetes, Perry and associates discussed the ongoing debate about $HbA_{1c}$ diagnostic usefulness, and analyzed large population studies, as compared to their study, the Early Diabetes Intervention Program (EDIP).[54] They reported that two large epidemiological studies showed poor sensitivities of $HbA_{1c}$, as compared to FPG alone. This was in contrast to the findings of the EDIP study,[54] as well as the findings of two other large, population-based studies which showed improved sensitivity of combined $HbA_{1c}$ and FPG; their own study yielded a sensitivity of 61% for the combined tests versus 45% for FPG alone.[54] Ko et al reported similar advantages of combined $HbA_{1c}$ and FPG in diabetes screening.[51]

Acknowledging that several studies on $HbA_{1c}$ diagnostic validity were done prior to test standardization, Bennett et al recently published a systematic review of studies done between 1998 and 2004.[5] They evaluated primary cross-sectional studies on the accuracy of $HbA_{1c}$ (at a cut-off point of 6.1%) for the detection of type 2 diabetes using the OGTT as the reference standard and FPG (at a cut-off point of 6.1 mmol/L) as a comparison. They cited a total of 63 studies, and included 9 that fulfilled their strict inclusion criteria; 6 were Asian studies and the rest were from Europe and the US. The findings of the systematic review showed that both $HbA_{1c}$ and FPG are equally effective screening tools for the detection of type 2 diabetes, but both were not effective for detection of IGT (sensitivities ~ 50%). At certain cut-off points of $HbA_{1c}$ (6.1%) and FPG (6.1 mmol/L), sensitivities and specificities were 78% to 81% and 79% to 84% for $HbA_{1c}$, and 48% to 64% and 94% to 98%, respectively.[5] The investigators concluded that both $HbA_{1c}$ and FPG were equally effective screening tools.

Overall, Bennett et al concluded that while $HbA_{1c}$ may be more expensive than FPG at present, $HbA_{1c}$ provides less intra-individual variability and better predicts diabetic complications, and thus provides a more

favorable argument for cost-effectiveness. Additional benefits of $HbA_{1c}$ included the convenience of non-fasting, availability of point-of-care capillary assays, and the potential for mass population screening given the availability of transporting capillary samples from remote areas to central laboratories.[5] While the investigators emphasized the several advantages of $HbA_{1c}$ over FPG and OGTT, they also recapitulated the possible influences of hemoglobinopathies, uremia, and medications on $HbA_{1c}$ measurements.[5]

Not included in the systematic review were several studies that addressed the use of $HbA_{1c}$ in the retrospective opportunistic detection of undiagnosed diabetes in inpatient and outpatient settings.[50-57,60,72] The most impressive report is the recent analysis of the NHANES 1999-2004 cohort reported by Buell et al in late 2007.[44] In this study (n=4935; 3280 normal, 1485 with IFG, and 170 with diabetes), a cut-point $HbA_{1c}$ of 5.8% was shown to have a sensitivity and specificity of 86% and 92%, respectively, for diagnosing diabetes.[44]

The final question in regards to the diagnostic validity of $HbA_{1c}$ is: What is a reliable $HbA_{1c}$ cut-point for screening and diagnosis? We found out that various cut-points have been utilized, and these ranged from 5.8% to 6.2%.[5,43,44,54] Bennett et al concluded in their systematic review that this value was noted to be 6.1% in most reviewed studies. However, they emphasized that there was an argument for a population-specific, demographic-adjusted optimum $HbA_{1c}$ diagnostic cut-off point.[5] Obviously, this cut-off is arbitrary and will encounter pitfalls in terms of false positives and false negatives; an ideal diagnostic test for diabetes, with high sensitivity and specificity, is desirable but is yet to be found. However, $HbA_{1c}$ has a good biological variability as compared to FPG (2% vs 14%) and is free of laboratory variability.[6]

Unlike the case with type 2 diabetes, where reasonable evidence exists to suggest a diagnostic role for $HbA_{1c}$, it seems that the current literature is not conclusive for GDM. Several studies were published about $HbA_{1c}$ in GDM,[62-71] but except for few recent studies[69-71] the majority of these studies were done 2 to 3 decades ago. With drawbacks in designs and $HbA_{1c}$ methodologies and conflicting conclusions, no consensus could be reached from these studies. Well-designed prespective studies are therefore warranted to settle this issue.

## The Current Guidelines for Diabetes Screening and Diagnosis and the Prospective of $HbA_{1c}$ Diagnostic Use

At the moment, none of the health organizations in the USA, or elsewhere, recommend $HbA_{1c}$ for screening or diagnosis of either type 2 diabetes or GDM.[19,20,74]According to current ADA guidelines,[19] adopted almost globally at present, screening and diagnosis of type 2 diabetes and GDM are based on glucose measurement; these include: a) casual plasma glucose (with symptoms), fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) for type 2 diabetes on at least two occasions; b) 1-hour glucose challenge test (GCT) for screening, and 3-hour OGTT for diagnosis of GDM. Random blood sugar (RBS) is not recommended by ADA for screening or diagnosis,[19] and is not standardized. However, these recommended guidelines for diabetes screening are not usually followed in routine clinical practice.[6,72] Ealovega and associates evaluated retrospective opportunistic screening for diabetes in a large managed care system (n=5752), to evaluate how physicians acted on abnormal glycemic tests done either for targeted screening purposes or as part of routine tests. While 69% of the patients in the system were screened, the most commonly used test was RBS (95%), followed by FPG (3%), $HbA_{1c}$ (2%), whole blood glucose measurement (1%), and GTT (< 1%). Unfortunately, follow up on these tests was uncommon, and therefore the yield from these opportunistic screening efforts was low.[72] Finally, a survey was conducted by an independent survey company at the 2005 American College of Physicians Annual Meeting.[6] Of 258 physicians attending the meeting who were surveyed, 93% reported that they routinely screened for diabetes. $HbA_{1c}$ was the screening or diagnostic method in 49% and 59% of the time, respectively. Interestingly, 49% of these physicians thought that $HbA_{1c}$ was an approved test for screening.[6]

For GDM, GCT is generally adopted in the US as a screening test. It has been noticed that in other places physicians use other screening methods. For example, in the Netherlands, both RBS and GCT are almost equally used in screening for GDM.[75] We have also observed use of RBS for screening in pregnancy elsewhere.[76]

## Problems with the current diagnostic guidelines

For type 2 diabetes and GDM, the current diagnostic methods are suboptimal. The FPG has been shown to have poor sensitivity, missing a significant proportion of subjects with OGTT-confirmed diabetes, ranging from 33% to 50%[5,54,77] in the case of type 2 diabetes. The OGTT on the other hand has been regarded as inconvenient and cumbersome, and not well-reproducible.[5,54] From anecdotal observation, the OGTT is particularly inconvenient for pregnant women, mainly due to the unpleasant taste of the glucose load used in the test. Furthermore, both of these glucose tests re-

quire fasting; this requirement is less easily achievable in busy practices and, in particular, in settings of population screening. Therefore it is not surprising that these "established diagnostic criteria for diabetes are not followed in the community".[6] Given the aforementioned arguments, we believe that $HbA_{1c}$ may provide a reasonable alternative or adjunct in the screening and diagnosis of diabetes. In the case of GDM in particular, we believe that $HbA_{1c}$ provides a more tolerable alternative than the unpleasant glucose load tests, if research confirms its diagnostic validity.

## Point-of-Care $HbA_{1c}$ Assays: Another Technological Improvement in $HbA_{1c}$ Methodology

$HbA_{1c}$ can now be reliably measured by portable capillary devices at physicians' offices,[78-81] and immediate feedback can thus be provided to patients. This point-of-care technology has been shown to improve management outcomes in patients with diabetes. The advantages of sharing the results of $HbA_{1c}$ with patients at the time of their visit include better motivation by patients, and better chances that patient take more active roles in their diabetes management . In addition to its role in diabetes management, we believe that this new point-of-care technology, especially the most recent improved devices (small, cheap, simple and fast) will be helpful should $HbA_{1c}$ attain a diagnostic role in diabetes.[5,81] This will be of particular importance in population-based diabetes screening globally, especially the advantage of transporting capillary samples from remote areas.[5]

## The Future of $HbA_{1c}$ Diagnostic Potential

During the 2007 ADA annual meeting, the NGSP's Clinical Advisory Committee posted on the NGSP web site a summary of discussions on the status of the use of $HbA_{1c}$ in diabetes screening.[82] It was reported that: "only in Japan was $HbA_{1c}$ used for screening or diagnosis of diabetes at present". The consensus was that: "many physicians are already using $HbA_{1c}$ for the screening and/or diagnosis of diabetes, but different cutoff levels are being used." The consensus ascribed multiple advantages, and fewer disadvantages, to $HbA_{1c}$ as a diagnostic test.[82] Whether the ADA, or other diabetes organizations, will be revisiting their diagnostic guidelines in regards to $HbA_{1c}$ remains to be seen. The US Endocrine Society announced in a press release that an expert panel recommended new diagnostic guidelines for diabetes. These recommendations, recently published,[6] noted that the current ADA diagnostic guidelines were made over a decade ago, dismissing $HbA_{1c}$ as a diagnostic tool based on inadequate test standardization. Given recent evidence, the expert panel believed that it was time to revisit using $HbA_{1c}$ and include it in screening and diagnosis of diabetes.[6] These new guidelines recommended incorporating $HbA_{1c}$ into the current criteria for screening and diagnosing diabetes, besides FPG and OGTT. The guidelines recommended a screening $HbA_{1c}$ cut-point of 6.0% as a threshold for close follow up, and diagnostic cut-point of 6.5%, if supported by any glucose test. The guidelines recommended, and for the first time, adding RBS for screening purposes, at a cut-point of 130 mg/dl.

## Conclusions

In conclusion, $HbA_{1c}$ has been and continues to be used to monitor the control of glycemia in diabetes management. While $HbA_{1c}$ testing will probably not be abandoned, it is expected to undergo some changes in terms of terminologies and measurement units. It is anticipated that laboratories around the world will either use NGSP % or IFCC (mmol/mol or %) plus MBG (to be called eAG or ADAG) in communicating $HbA_{1c}$ results. In the US, it is anticipated that laboratories will probably continue to report NGSP $HbA_{1c}$ % units, and probably not IFCC (in % units) new units, which are about 2 points lower and may thus cause confusion. Similarly it is not anticipated that the IFCC molar units (mmol/mol), which are quite unfamiliar to clinicians, will be adopted in the US, to avoid further confusion, but this remains to be seen. Changes in other countries that may want to report the IFCC units are expected to be very slow in view of anticipated technical difficulties in achieving such a major transition.

Furthermore, it is anticipated that diabetes organizations may consider adding $HbA_{1c}$ at an appropriate cut-point value as a screening tool for diabetes. This has been rationalized by improved test standardization, and by the observation that a lot of physicians already use $HbA_{1c}$ for screening of type 2 diabetes, and probably for diagnosis confirmation in some cases. The ES has announced in a press release that an expert panel recommended using $HbA_{1c}$ in diabetes screening and diagnosis. Whether other diabetes organizations will follow suit remains to be seen.

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