The Pros and Cons of Diagnosing Diabetes With A1C

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An International Expert Committee was convened in 2008 by the American Diabetes Association (ADA), the European Association for the Study of Diabetes, and the International Diabetes Federation to consider the means for diagnosing diabetes in nonpregnant individuals, with particular focus on the possibility to indicate A1C as an alternative if not a better tool (1). After reviewing the available literature and a thorough discussion on the advantages and the limits of previous diagnostic strategies (essentially based on fasting glucose assessment) and the considered alternative approach (based on A1C measurement), a consensus was reached that the latter (i.e., A1C) should be included among diagnostic tools for diabetes and, with the exception of a number of clinical conditions, should even be preferred in diabetes diagnosis in nonpregnant adults.

The main conclusion of the International Expert Committee was implemented in the most recent clinical recommendations issued by the ADA. However, in these guidelines, A1C is indicated as a diagnostic tool alternative but not superior to blood glucose, leaving to the health care professional the decision about what test to use in an individual.

The World Health Organization is currently examining the proposal made by the International Expert Committee and is carefully addressing the controversial issues still remaining, most of which have been the subject of letters to the editor and articles recently published in the literature. Nevertheless, the use of A1C for diagnosing diabetes is rapidly becoming a reality in many Western countries.

In the text that follows, one of us (E.B.) will present the main points supporting A1C (pros) and the other (J.T.) will illustrate the main counterpoints challenging A1C (cons) as the primary tool for diabetes diagnosis. The text has been prepared in full coordination and the final conclusions represent the opinion of both authors. Tables 1 and 2 summarize the pros and cons.

PROs

A1C captures chronic hyperglycemia better than two assessments of fasting or 2-h oral glucose tolerance test plasma glucose

Diabetes has been diagnosed for decades with fasting plasma glucose (FPG) assessment or, much less frequently, with an oral glucose tolerance test (OGTT). Hyperglycemia as the biochemical hallmark of diabetes is unquestionable. However, fasting and 2-h OGTT gauge just a moment of a single day. In addition, the two assessments required to confirm diagnosis might be fallacious in describing a chronic and complex clinical condition. In this respect, there is no doubt that a biochemical or clinical parameter describing the extent of a biological phenomenon over a long period provides a more robust indicator of glycemia than a parameter describing it in the short term or in a given moment only. Accordingly, there are some good examples in medicine: urinary albumin excretion rate provides more reliable information on the presence and the degree of microalbuminuria than spot urinary albumin-to-creatinine ratio; serum IGF-I is definitely more efficacious than serum growth hormone when monitoring patients with acromegaly, etc.

Labeling a person with a diagnosis of diabetes has several psychological and legal implications and requires a robust and reliable approach. The measurement of A1C equals the assessment of hundreds (virtually thousands) of fasting glucose levels and also captures postprandial glucose peaks; therefore, it is a more robust and reliable measurement than FPG and/or 2-h OGTT plasma glucose. This is particularly valid when FPG oscillates above and below the cut point of 126 mg/dL or 2-h plasma glucose (PG) oscillates above and below the cut point of 200 mg/dL. Of note, the 2-h PG had poor reproducibility. From a clinical standpoint, having an FPG of 120 or 130 mg/dL or having a 2-h PG of 185 or 215 is virtually the same, but from the patient's perspective (perception of having a disease, psychological well-being, health insurance, recognition of particular benefits, or imposition of certain limitations, etc.), it makes a substantial difference. Therefore, a diagnostic tool gauging chronic rather than spot hyperglycemia is certainly preferable.

A1C is better associated with chronic complications than FPG

Different from National Diabetes Data Group criteria, which were essentially based on distribution of glucose levels within the general population, the 1997 ADA criteria (and the subsequently recommended World Health Organization criteria) established diabetic glycemic levels by means of their association with retinopathy, the most exclusive and specific diabetes complication. Various observational studies documented that an increased prevalence of nonproliferative diabetic retinopathy can be observed with

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fasting glucose levels around 7.0 mmol/L (126 mg/dL) and 2-h PG around 11.1 mmol/L (200 mg/dL). Interestingly, the same studies documented that retinopathy increased with A1C levels around 6.5% (2–4). These results were confirmed in a more recent study including almost 30,000 subjects recruited in several countries. Such study clearly showed that prevalent retinopathy started to increase in the A1C category of 6.5–7.0% (5). Therefore, a cut point of A1C for diagnosing diabetes with an approach similar to the one used with FPG and 2-h PG is available (and indeed already was available in older studies).

It is well known that cardiovascular disease (CVD) is the most frequent chronic complication of diabetes, with incidence rates 5- to 10-fold higher than with microvascular disease. For this reason, the association of A1C with CVD can be considered a major issue when discussing the potential use of A1C for diagnosing diabetes. In this regard, it is worth mentioning that, in the general population, FPG is a poor marker of future CVD events, whereas 2-h OGTT and A1C are good predictors (6,7).

Fasting is not needed for A1C assessment and no acute perturbations (e.g., stress, diet, exercise) affect A1C

Plasma glucose levels are not stable but rather vary throughout the day, mainly in postprandial periods. Although it is believed that fasting glucose levels are reproducible across days, a number of acute perturbations of glucose homeostasis have been described. Acute stress can increase endogenous glucose production substantially and impair glucose utilization. People who are worried about blood sampling or experience a stressful situation in the hours preceding blood sampling can have an increase in fasting glucose concentration. On the contrary, exercise can decrease glucose levels, and an evening or early-morning session of physical exercise can affect the level of fasting glycemia. Moreover, most individuals do not pay attention to the request or are not asked to consume a diet with at least 200 g carbohydrate in the days before testing glucose. Some individuals do not abstain from food in the 8 h before testing, thus arriving to the laboratory in the postabsorptive rather than fasting condition. In addition, smoking or taking certain medications can adversely affect fasting glucose. The lack of appropriate preparation for glucose testing makes FPG less reliable for diabetes diagnosis, with results sometimes falsely elevated and sometimes apparently normal. On the contrary, A1C is not influenced by acute perturbations or insufficient fasting. Indeed, A1C can be measured anytime, irrespective of fasting or feeding.

A1C has a greater pre-analytical stability than plasma glucose

Even when preparation to glucose testing is optimal, plasma glucose values may still be misleading because of pre-analytical instability. In fact, tubes for blood collection do not always contain antiglycolytic substances, and even when they do, significant glucose consumption occurs in blood cells in the first 1–2 h after sampling because glycolysis is inhibited in its more distal steps by NaF or other preservatives. As long as the sample is not processed and plasma and blood cells are separated by centrifugation, a significant glucose loss is observed. In this regard, it must be emphasized that, quite often, blood samples reach the laboratory and are processed hours after withdrawal. Consistently, glucose concentration decreases 5–7% (on average ~0.5 mmol/L) per hour and even more rapidly in cases of high ambient temperature (8,9). In such cases, glucose levels can show results lower than they are and diabetes diagnosis can be missed. It has been estimated that pre-analytical variability of FPG is 5–10%. On the contrary, pre-analytical variability of A1C is negligible. As for analytical variability, it is superimposable for glucose and A1C, being ~2%.

Standardization of A1C assay is not inferior to standardization of glucose assay

One of the main concerns surrounding A1C and raising perplexities on its use for diabetes diagnosis is the poor standardization of the assay. Quite surprisingly, the same concerns and perplexities do not extend to A1C use for diabetes monitoring despite the understanding that only when A1C is aligned to the Diabetes Control and Complications Trial (DCCT)/UK Prospective Diabetes Study (UKPDS) standard should the recommended target be pursued (in general <7%). A great effort was made in the U.S. and other countries to make reproducible A1C across laboratories with an effective standardization program. Such a program has been recently completed and is being implemented worldwide to provide more reliable information to physicians who monitor diabetic patients (10). The standardization is expected to minimize laboratory biases and is a prerequisite to use A1C not only for monitoring but also for diagnosing diabetes.

Although it is generally believed that glucose assay is highly reproducible across laboratories, this is not true. A recent survey conducted in 6,000 U.S. laboratories clearly documented a significant bias in glucose assessment in as many as 41% of them, yielding a misclassification of glucose tolerance in 12% of subjects (11). Therefore, the argument that A1C cannot be used for diabetes diagnosis because of poor standardization is no longer tenable.

Biological variability of A1C is lower than that for FPG

When the same subjects have two assessments of the available glucose-related parameters, the correlation is stronger among the individual A1C measurements than among the FPG or 2-h PG measurements. The coefficients of variation of A1C, FPG, and 2-h PG are 3.6, 5.7, and 16.6%, respectively (12). This reflects of course both biological and analytical variability. However, although the latter was similar for A1C and FPG (~2%), biological variability of A1C was severalfold lower than that of FPG (<1 vs. ~4%) (13). This finding confirms that the two required assessments of FPG to diagnose diabetes can provide quite unreliable information, whereas A1C, especially if measured twice as recommended, provides more robust clinical information.

Individual susceptibility to glycation might be an additional benefit of A1C assessment

It is a common clinical finding that many subjects have an A1C value lower or higher than expected when examining their daily glycemic profiles. Using the DCCT database, McCarter et al. (14) calculated the hemoglobin glycation index (HGI) as the difference between observed and predicted A1C level and identified categories of patients with low, moderate, or high HGI. Most interestingly, they found that subjects with high HGI had a greater risk of developing retinopathy and nephropathy, even when they had good glucose control, and that subjects with lower HGI had a low incidence of microangiopathy despite high mean blood glucose levels. This finding demonstrates that A1C assessment might provide not

only information on chronic hyperglycemia but also a measure of whole-body susceptibility of protein glycation and, therefore, risks of diabetes complications that are more strictly related to this pathogenic mechanism.

Using the same biomarker for diagnosing and monitoring diabetes might be an advantage

A1C is used to monitor diabetes and to establish the degree of metabolic control. Deviation from individualized A1C targets prompts physicians to modify treatment strategies with lifestyle intervention and/or drug titration or changes. The use of A1C for diagnosing diabetes has the advantage that, in subjects with A1C ≥6.5% (i.e., diabetes), baseline A1C is already measured and deviation from target is immediately available (no A1C measurement as a second step after FPG assessment). In subjects with A1C of 6.00–6.49% (i.e., high risk of diabetes), an effective prevention strategy can be immediately undertaken with the awareness that a single A1C is definitely more reliable than a single FPG to stratify the risk of the disease. Yet, in subjects with A1C of 5.50–5.99% plus other diabetes risk factors (e.g., central obesity, atherogenic dyslipidemia, hypertension, and/or metabolic syndrome), counseling can be immediately offered because diabetes risk is substantial, and single A1C assessment is definitely more reliable than single FPG to capture chronically high-normal glucose levels.

Pertinent to this issue is the firm belief that the implementation of the standardization of A1C assay would proceed more rapidly worldwide if A1C were to also be used for diagnosing diabetes. A1C assessment is crucial for diabetes monitoring, and establishing the individual A1C target definitely requires that the parameter is International Federation of Clinical Chemistry (IFCC) standardized and DCCT aligned. In fact, the A1C target and the deviation from it in the single patient remain totally uncertain when the laboratory provides A1C data that are not aligned to standard.

Cost of the assay: savings or no savings?

One of the major concerns raised by critics of the use of A1C for diagnosing diabetes is the higher cost of the assay when compared with FPG. There is no doubt that from an analytical point of view (cost of reagents and equipment), FPG is cheaper than A1C. However, other considerations about cost should be made. FPG assessment requires overnight fasting, whereas A1C can be assessed any time. This means that a person could go or could be driven by a relative/friend to the laboratory, even during lunch or in the late afternoon, avoiding loss of work hours. It is also possible to collect blood for A1C assessment in the evening and hand it to the laboratory in the following days. Yet, in subjects with FPG ≥7 mmol/L (≥126 mg/dL), A1C assessment would be needed the next few days as a second step in a newly diagnosed diabetes workup. On the contrary, when A1C assessment yields a value ≥6.5%, the second step required to initiate diabetes monitoring after diagnosis would be completed, with a substantial savings of both analytical and nonanalytical costs. On the other hand, when using FPG to screen for diabetes and finding a value in the range of 5.6–6.9 mmol/L (100–125 mg/dL; impaired fasting glucose), an OGTT is frequently prescribed (mainly in Europe and less frequently in the U.S.) to establish glucose tolerance. This test requires hours in the laboratory, with additional analytical and nonanalytical costs. In such cases, which represent a sizable portion of the general population, A1C rather than FPG would provide an immediate diabetes diagnosis or a valuable risk stratification (15) without supplementary testing.

Impact of changing the diagnostic laboratory parameter on epidemiology of diabetes

A further critique to the program of moving from FPG to A1C for diabetes diagnosis comes from people who state that epidemiology of the disease is based on FPG and that the scenario would change if A1C were used instead of FPG. A recent report based on the U.S. population (16) showed that the use of A1C rather than FPG would not significantly change diabetes prevalence and that the categorization would not change in as many as 97.7% of subjects. Moreover, this study showed that half of the subjects with FPG ≥7 mmol/L (≥126 mg/dL) had an A1C value in the 6.00–6.49% range, thus deserving strict monitoring and an intervention. In this regard, however, it should be emphasized that any comparison of A1C with FPG (or 2-h OGTT PG) is equivocal because a true gold standard is not available. FPG, which in classic studies relating glucose parameters (including A1C) to retinopathy was measured just one time and with less than optimal pre-analytical and analytical procedures, cannot be taken as the gold standard. Therefore, any study examining sensitivity and specificity of A1C for diagnosing diabetes suffers from these limitations and is questionable. At present, the gold standard is probably the combination of FPG, 2-h PG, and A1C assessments with optimal pre-analytical, analytical, and standardized procedures and confirmatory testing for all parameters. This is not feasible on a large-scale basis and cannot be recommended. A1C seems to be a reasonable approach for all reasons discussed above (summarized in Table 1).

CONs

Diabetes is clinically defined by high blood glucose and not by glycation of proteins

The introduction of A1C as the diagnostic tool for diabetes, in particular, if this parameter is considered the primary tool, will lead to a major change in the pathophysiological paradigm that defines the syndrome called "diabetes." So far, diabetes has been defined as "a clinical condition of elevated glucose concentration in blood". High A1C represents high

Table 1—*Reasons to prefer A1C compared with plasma glucose determination for diagnosing diabetes*

Chronic hyperglycemia is captured by A1C but not by FPG (even when repeated twice).
Microangiopathic complications (retinopathy) are associated with A1C as strongly as with FPG.
A1C is better related to cardiovascular disease than FPG.
Fasting is not needed for A1C assessment.
No acute perturbations (e.g., stress, diet, exercise, smoking) affect A1C.
A1C has a greater pre-analytical stability than blood glucose.
A1C has an analytical variability not inferior to blood glucose.
Standardization of A1C assay is not inferior to blood glucose assay.
Biological variability of A1C is lower than FPG and 2-h OGTT PG.
Individual susceptibility to protein glycation might be caught by A1C.
A1C can be used concomitantly for diagnosing and initiating diabetes monitoring.
Diabetes assessment with A1C assay is not necessarily greater than with glucose assessment.

glycation of proteins in the body, which is a substantially different biochemical abnormality, although it is certainly secondary to high blood glucose. In medicine, it is important to pay attention to primary phenomena before emphasizing the secondary ones. Moreover, high A1C is only observed subsequently to an increase in blood glucose, but there are few data on how long the delay is. Regardless of the length of this delay (weeks, months), diagnosis of diabetes using A1C would occur later than with blood glucose assessment. In many cases, such a delay might have negative clinical consequences.

A1C is a poor marker of important pathophysiological abnormalities featuring diabetes

OGTT and 2-h post-glucose levels do reflect the pathophysiology behind diabetes better than any other glycemic parameter, since they provide information on what occurs in the postprandial state, when glucose levels are at the highest levels during the day and when the health of the pancreatic β-cell is essential. On the contrary, fasting glucose is the least informative among glycemic parameters, since in most subjects, it corresponds to the lowest glucose level during the day and it reflects the long nocturnal period when there is no intake of food and no particular stress for β-cells. However, humans spend most of their time in postprandial or postabsorptive states that are deranged in diabetes. A1C is a poor indicator of what occurs in the postprandial state. A1C captures only chronic hyperglycemia, but it will miss acute hyperglycemia. Normal blood glucose levels 2 h after glucose load indicates a good β-cell capacity, whereas high 2-h OGTT glucose levels document an impairment of β-cell function (17). This means that only 2-h OGTT PG can provide reliable information on the key pathophysiological defect of diabetes, also providing advice regarding the correct therapy to overcome it. This can be compared with ambulatory blood pressure monitoring (ABPM), where the main features predicting cardiovascular events are not only the long-term average blood pressure but the daily variation in blood pressure (especially the lack of a physiological nocturnal dip). Thus, ABPM is clinically useful in finding out blood pressure patterns, not estimating the long-term average. Recently, the Insulin Resistance Atherosclerosis Study (IRAS) showed that A1C is a weaker correlate of insulin resistance and insulin secretion in studies of metabolism compared with FPG and 2-h PG (18).

A1C has a poor sensitivity in diabetes diagnosis and would change the epidemiology of diabetes

Diabetes diagnosis based on A1C misses a large proportion of asymptomatic early cases of diabetes that can only be identified by the OGTT. According to a recent Chinese study, A1C sensitivity is inferior compared with fasting blood glucose at the population level (19). Also, people with impaired glucose tolerance (IGT), in whom the efficacy of diabetes prevention has been unequivocally proven (20), cannot be detected by A1C.

Epidemiological studies carried out in the general population showed that A1C and plasma glucose (FPG and/or 2-h OGTT) identify partially different groups of diabetic subjects (21). A1C ≥6.5% identifies ~30–40% of previously undiagnosed patients with diabetes (16). A larger percentage is detected by FPG (~50%) and 2-h PG (~90%). These findings are based on several recent studies, including the 2003–2006 NHANES (30% of diabetic individuals detected by A1C ≥6.5%, 46% by FPG ≥126 mg/dL, and 90% by 2-h PG ≥200 mg/dL) (18) and the IRAS (32, 45, and 87%, respectively) (18). In Qingdao, China, the ≥6.5% A1C cut point detects 30% of individuals with diabetes according to 2003 ADA criteria (19). In Chennai, India, however, A1C ≥6.5% detects 78% of individuals with newly diagnosed diabetes according to these criteria (22). In the IRAS, A1C of 5.7–6.4% predicted type 2 diabetes better with increasing BMI, and there were significant ethnic differences in the performance of A1C of 5.7–6.4% to detect diabetes (18). The ethnic differences in A1C compared with glucose measurements were also well demonstrated in the Diabetes Prevention Program population (23) and in a recent multiethnic database by Christensen et al. (24) that showed that there are no systematic interpretations as to why a shift to an A1C-based diagnosis for diabetes has substantially different consequences for diabetes prevalence across ethnic groups and populations.

2-h Glucose level and IGT are stronger predictors of CVD than A1C

Because high glucose is toxic and causes many types of tissue damage, any indicator of hyperglycemia is predictive of diabetes complications. In the general population, FPG is a poor marker of mortality and future CVD events, whereas 2-h PG and A1C are better predictors (8,10,25–27). When analyzed jointly, only 2-h PG remains a statistically significant predictor of mortality and CVD (28,29). The findings regarding associations of FPG, 2-h PG, and A1C with retinopathy from the Pima Indians in the ADA 1997 report describing diagnostic thresholds of each glycemic parameter were derived by univariate analyses, and the multivariate analysis aiming at identifying the best glycemic parameters for diagnosis has never been reported. One of the main issues is that people with IGT have ~40% increased mortality compared with normoglycemic people, and these individuals cannot be identified by measuring FPG or A1C. In addition, lifestyle intervention has been shown to prevent the progression from IGT to diabetes and also reduce their mortality risk to the level observed among normoglycemic people (30,31). Such prevention trial evidence does not exist for A1C or FPG, and this evidence should not be forgotten when deciding the approaches to identify intermediate hyperglycemia. Moreover, these results indicate that early intervention is effective in reducing mortality in people with IGT, and therefore, we should attempt to make the diagnosis of hyperglycemia as early as possible.

Fasting is not essential to identify perturbation in glucose metabolism

Measuring blood glucose in the fasting state in nondiabetic individuals is probably the least efficient way to identify early signs of perturbations in glucose metabolism. Because excessive postprandial glucose excursions are marking the first signs of abnormal glucose regulation and they also seem to best predict cardiovascular outcome, fasting is not really the central issue. It is likely that fasting has been overemphasized in diagnosing type 2 diabetes. We may pay attention to approaches used in the diagnosis of high blood pressure that also vary markedly during the day, but despite this variation, we are able to identify individuals with hypertension, even though measurements are not restricted to certain hours of the day but are done at any time.

Standardization of A1C assay is very poor and standardization of glucose assay is easier to implement

Inaccuracies in measurement and poor standardization of A1C assays are still

a common problem, even in Western countries. Although a less than perfect standardization also exists for plasma glucose, this assay might be more easily aligned to a standard than A1C. Such programs now exist in the U.S., Japan, and Sweden, but there is still a long way to a global standardization of the A1C assays. Actually, all glycemic assessments require confirmation to make the diagnosis of diabetes correctly, mainly to avoid errors in sample handling and laboratory procedures.

Table 2—*Reasons not to prefer A1C compared with plasma glucose determination for diagnosing diabetes*

Diabetes is clinically defined by high blood glucose and not by glycation of proteins.
A1C is a poor marker of important pathophysiological abnormalities featuring diabetes.
A1C has a poor sensitivity in diabetes diagnosis and would change the epidemiology of diabetes.
2-h glucose level and IGT are stronger predictors of CVD than A1C.
Fasting is not essential to identify perturbation in glucose metabolism.
Standardization of A1C assay is poor, even in Western countries, and standardization of glucose assay would be easier to implement.
In many subjects, A1C assay is unreliable and cannot be used.
A1C has significant differences in various ethnic groups, which are poorly understood and characterized.
Within-days biological variability of plasma glucose might unveil disturbance of glucose metabolism.
Individual susceptibility to glycation of hemoglobin is not relevant to diabetes diagnosis.
Using the same biomarker for diagnosing and monitoring diabetes might have negative effects.
Cost of the assay: glucose is unquestionably cheaper than A1C, and A1C assay is not available on a large scale in most of the countries.
A1C levels vary not only according to glycemia, but also to erythrocyte turnover rates (e.g., hemoglobinopathies, malaria, anemia, blood loss) as well as other factors.
Correlation between A1C and FPG is ~0.85%, which means that as many as 30% of the variation in FPG is not explained by A1C and vice versa.
Nothing is known about changes in A1C during the development of diabetes.
A1C levels of 6.0–6.5% do not predict diabetes as effectively as FPG and 2-h PG (OGTT).
Sensitivity of A1C to detect diabetes defined by the OGTT is <50%; thus, the majority of diabetic individuals will remain undiagnosed if A1C is used.
The levels of A1C predicting future retinopathy, nephropathy, etc., in the population is not well established (<6.5%?).
No diabetes prevention trials have selected their populations based on A1C.
Using A1C will delay the diagnosis of diabetes in ~60% of incident cases.

A1C assay is unreliable and cannot be used in many subjects

Abnormal hemoglobin traits are not uncommon in many regions of the world, and they significantly interfere with A1C assay (32), leading to spurious results. Also, there are several clinical conditions that influence erythrocyte turnover (e.g., malaria, chronic anemia, major blood loss, hemolysis, uremia, pregnancy, smoking, and various infections) that are responsible for misleading A1C data. Still, we are aware of ethnic differences in the relation between blood glucose and A1C levels (33) as well as an effect of aging. If different cut points regarding all these conditions need to be considered, A1C cannot be easily used to diagnose diabetes.

Within-day biological variability of plasma glucose might unveil disturbance of glucose metabolism

Biological variability in plasma glucose reflects our daily patterns of diet, physical and mental activity, sleep, etc., and also depends on possible pathophysiological processes that may underlie type 2 diabetes. By definition, postprandial, and also 2-h PG, vary more than FPG. In this regard, A1C, which does not have any substantial biological variability, provides little information on pathophysiological processes leading to type 2 diabetes. The variability in A1C is entirely due to other phenomena, not pathophysiological disturbances.

Individual susceptibility to glycation of hemoglobin is not relevant to diabetes diagnosis

The HGI was calculated in patients with type 1 diabetes from the DCCT (17). This parameter is not relevant to the diagnosis of diabetes in the general population, in which 99% of subjects have A1C levels definitely lower than patients with type 1 diabetes. Subjects with high HGI had a greater risk of developing retinopathy and nephropathy, even when they had good glucose control (i.e., FPG was not very high), whereas subjects with lower HGI had a very low incidence of microangiopathy despite high mean blood glucose levels. This finding indicates that postprandial glucose excursions must have been very high in the former and very low in the latter. A1C reflects high mean exposure to glucose but not glucose fluctuations during the day. Unfortunately, in this analysis with HGI, postprandial glucose excursions and daily glucose variability were not taken into account.

Using the same biomarker for diagnosing and monitoring diabetes might not have positive effects only

This approach may be useful, but it also may lead to problems in two ways. First, people who have diabetes (based on their glucose values) will remain undiagnosed and untreated, since they are considered "nondiabetic" according to their A1C. Also, if the intermediate level of A1C (6.00–6.49 or 5.70–6.49%) was used to predict diabetes, it performed less well than impaired fasting glucose and/or IGT (18). Whereas the 6.5% A1C threshold misses a large percentage of previously undiagnosed diabetes, its clinical consequences remain unknown. It is important to recognize this problem. One obvious consequence is that with a less sensitive test, individuals who fall below the threshold are not considered in cardiovascular management algorithms as high-risk individuals and are probably treated less effectively for other risk factors.

Second, a large proportion of newly diagnosed diabetic patients based on current glucose criteria have A1C <6.5%. In the Finnish Diabetes Prevention Study, the sensitivity of A1C ≥6.5% to diagnose diabetes was only 39%, i.e., 61% of newly diagnosed case subjects had A1C <6.5% (34). If this same threshold were to be used for treatment, these patients would not be accepted to be treated, even though their glucose levels were twice the glucose threshold for diabetes. This would also mean that in 61% of high-risk people who were regularly monitored for diabetes, the actual diagnosis would have been delayed—for how long, we do not know, since diabetic people were referred to antidiabetic therapy based on their high glucose values.

Cost of the assay: glucose is unquestionably cheaper than A1C

Whichever way we calculate the assay costs, A1C assay is more expensive than glucose assay, and it will thus remain so despite the speculative claim that the cost of A1C assay will become less expensive when used more extensively. In addition, many individuals at high risk of diabetes would need other laboratory tests that require fasting (e.g., lipid profile, hepatic profile, etc.), and therefore adding a glucose determination to the panel is not really a major issue. Also, the vast majority of laboratories in primary care collect samples in the morning, and they do not operate after "working hours." This makes the claim that A1C can be measured "any time of the day" rather theoretical.

In a large part of the world, A1C is not available, and its cost is so high that it is meaningless to even discuss whether it should be given a priority over simple and inexpensive glucose measurements. This step would divide the world into two categories: developed societies in which diabetes diagnosis is made with A1C and less developed societies (between and within countries) in which diabetes diagnosis is made with plasma glucose: such a division should be avoided. It would add to the inequities in health and health care.

CONCLUSIONS—There is no doubt that hyperglycemia is the biochemical hallmark of diabetes and is a prerequisite for diagnosis. In this respect, moving from blood glucose to A1C might sound like a sort of heresy. There is also no doubt that all epidemiological data based on blood glucose assessment might be considered less important if the disease were mainly diagnosed with A1C. This might create confusion, disappointment, anxiety, and concern in all who lived a glucocentric existence. Partly rewarding would be the fact that, in several clinical conditions, A1C could not be used and blood glucose assessment would remain the standard diagnostic procedure. In all other conditions (most subjects), A1C could become the reference method, provided that its assay be aligned to international standards. Also mandatory is that the cost of assay declines and becomes affordable in less developed societies. Longitudinal studies should also reassure us about the relative benignity of clinical conditions in which A1C is below the diagnostic threshold of 6.5% but FPG and/or 2-h OGTT PG are above the thresholds of 7 or 11 mmol/L, respectively. This is currently one of the most relevant worries related to potentially missing diagnosis.

Glucose assessment is familiar and cheaper, but A1C seems to provide several advantages, especially in a scenario in which OGTT is rarely used and never repeated as a confirmatory testing. Perhaps accepting a double diagnostic approach in which both blood glucose and A1C do coexist as diagnostic tools is reasonable. In the meantime, epidemiological and clinical studies will hopefully provide further data to better understand whether the current recommendations to replace FPG with A1C are well founded.

We agree that the research and debate on the pros and cons of using A1C versus glucose assay as a diagnostic tool for diabetes should continue in a constructive manner until a larger and truly evidence-based consensus is reached.

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