Review

Glycated haemoglobin (HbA1c): today and tomorrow

Hémoglobine glyquée (HbA1c) : aujourd’hui et demain

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Available online 29 September 2007

Abstract

The assay of glycated haemoglobin (HbA1c) is a gold standard in bioanalysis, and is essential to ensure the optimal care of diabetic patients. Accordingly, the principal scientific societies in diabetology and clinical chemistry have made efforts to standardize this assay in order to select and validate certain analytical methods and achieve consistency in the results obtained therewith. However, clinicians have to be aware of the caution required when interpreting HbA1c assay results owing to modified lifetime and/or abnormal synthesis of haemoglobin. Although this biological examination has now become an essential part of diabetes monitoring, its status as a screening tool is still controversial, even after 30 years of debate. Other uses of HbA1c assay are currently being assessed in cardiology (coronary syndromes), vascular diseases (atheriopathy), nephrology (renal insufficiency), haematology (anaemia) and oncology (factors of predisposition).

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Mots clés : Hémoglobine glyquée ; Diabète ; Diagnostic ; Pronostic

Keywords: Glycated haemoglobin; Diabetes; Diagnosis; Prognosis

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0003-4266/S - see front matter © 2007 Published by Elsevier Masson SAS.
doi:10.1016/j.ando.2007.06.004
1. Introduction

At the time non-enzymatic glycation processes were discovered it was difficult to imagine the success that would follow on the development of a test based on the physiological process whereby glucose molecules bind to the amino-terminal valine of globin β chains. In the last 30 years the HbA1c assay has become extremely widespread and can now even be performed at the diabetic’s home or in the doctor’s surgery using small delocalized biological devices. This makes it more necessary than ever for practitioners to be fully aware of the main sources of error encountered when interpreting HbA1c assays. Here we review the current applications of this assay, both validated and controversial, and some of its possible future uses.

2. Standardization of methods

From the 1980s the assay of glycated haemoglobin became extremely popular, but the introduction of quality control showed widely diverging results according to the assay method used. A worldwide standardization programme was therefore initiated. In France, the recommendations drawn up by the Higher Health Authority (HAS) for the follow-up of diabetic patients, and by the French Agency for the Safety of Health Products (AFSSAPS) for the treatment of diabetes, require HbA1c to be assayed using a method certified by international standardization procedures. Two working groups have been involved in the international standardization effort:

- the first is the US National Glycohemoglobin Standardization Program (NGSP) group. This standardization has been used in the DCCT and UKPDS studies that have as a reference system cation exchange high performance liquid chromatography (HPLC) and purified HbA1c calibration standards. This group has a network of reference laboratories and proposes a protocol for the certification of methods. It was this group that specified the risk thresholds set at 7% for type 1 and 6.5% for type 2 diabetes;
- the second is the International Federation of Clinical Chemistry (IFCC) group. This standardization is both more recent and more specific. It gives a more restrictive definition of HbA1c, taking as reference structure globin β-chain glycated N-terminal hexapeptide. The reference assay method is HPLC coupled to either mass spectrometry or capillary electrophoresis. As this method is more specific for HbA1c, the values it gives are 1-2% lower than those found with the NGSP standardization. The two standardization programmes thus needed to be linked. 2004 the two groups NGSP and IFCC agreed on a ‘gold equation’ to interconvert values:

\[
\% \text{ HbA1c (NGSP)} = (0.915 \times \% \text{HbA1c (IFCC)}) + 2.15
\]

A working group formed by the European Association for the Study of Diabetes (EASD), the American Diabetes Association (ADA), the International Diabetes Federation (IDF) and representatives of the NGSP and IFCC issued the following prescriptions concerning HbA1c assay:

- the results are to be stated according to the current NGSP standard;
- the usual values and the NGSP critical thresholds are to remain valid;
- the IFCC standardization shall specify the reference materials and methods against which in vitro diagnostics suppliers are to standardize their products.

2.1. The situation in France

At the end of 2003 AFSSAPS conducted a large-scale inspection of the HbA1c assay methods commercialized in France, based on evaluation reports. A list of 16 reagents was published corresponding to items in the specifications (available on the AFSSAPS website). Bioanalysts must therefore choose from this list the method that is the most appropriate (allowing for haemoglobin variants) and presents the best precision (coefficient of variation CV for repeatability < 3% and for reproducibility < 5%).

The different methods of HbA1c assay are based on either:

- charge modification:
  - ion exchange chromatography;
  - high performance liquid chromatography;
  - electrophoresis;
- structure modification:
  - affinity chromatography (modification of cis-diol function);
  - immunoturbidimetry or inhibition of agglutination (β-glycated terminal).

National surveys on the use of the different methods of HbA1c assay during quality control operations revealed trends in the use of methods in French laboratories between 1999 and 2004:

- reagents assaying HbA1 or total glycated Hb had disappeared (8% in 1999 and 0% in 2004);
- 98% of laboratories assaying HbA1c were now using methods certified by international standardization bodies, against only 52% in 1999.

The most frequently used methods were immunological methods (48.3% of assays in 2004, but these do not detect haemoglobin variants) and ion exchange chromatography methods HPLC/LPLC (38% in 2004). These two methods present the lowest CV values (< 5%) [11].

2.2. Interpretation of results

As regards haemoglobin, the HbA1c value is determined by two physiological factors: a normal red cell lifetime of
120 days, and qualitatively and quantitatively normal synthesis of haemoglobin (97-99% HbA). If either of these factors varies the interpretation of the HbA1c value is unreliable.

2.2.1. Case of abnormal synthesis of haemoglobin

2.2.1.1. Presence of a variant of haemoglobin. More than 900 variants are currently known, and the number of heterozygote carriers is estimated at about 7% of the world’s population (i.e. some 400 million persons). Some variants are responsible for major public health problems such as HbS (which mainly affects populations of African origin) and HbE (populations from South-East Asia). Other rarer variants (e.g. HbC, O-Arab and D-Punjab) have minimal pathological effects, but when associated with HbS can lead to a major drepanocytic syndrome. It had to be noted, that the drepanocytic syndrome is the genetic disease most frequently detected at the birth in France (affecting 1 child out of 2700). Several of these variants were discovered on HbA1c assay. The interference caused varies according to the type of variant and the assay method used.

With HPLC, interference occurs when the variant or its glycated form are not well enough separated from HbA or HbA1c. For a large number of variants, their presence leads to an overestimation of HbA1c values with this assay method.

With immunoanalysis, the method does not screen for variants, and HbA1c values are generally underestimated. In heterozygote patients, interference is only analytical, but it is nevertheless useful to detect the presence of a variant of haemoglobin when interpreting the result of an HbA1c assay (Figs. 1 and 2). The epidemiological studies conducted by UKPDS and DCCT concern only patients who are AA homozygotes.

In the case of homozygote haemoglobin abnormalities, the absence of HbA implies an absence of HbA1c, making assay results impossible to interpret.

Fig. 1. Chromatograph of a diabetic patient with an abnormal haemoglobin (HbA / HbS).

Fig. 1. Chromatographie d’un patient diabétique présentant une hémoglobine anormale de type HbA–HbS.
2.2.1.2. Elevated haemoglobin F. Quantitative haemoglobin abnormalities can also affect HbA1c values. For example, in the course of myeloma, lymphoma or β thalassaemia, haemoglobin F (normally < 1%) can increase and cause a spurious fall in HbA1c values, especially with the immunological assay method.

2.2.1.3. Presence of carbamylated haemoglobin. Another source of error in the interpretation of HbA1c levels is the presence of carbamylated haemoglobin in some patients. This forms in the red cells of patients with renal insufficiency and elevated urea concentrations (> 15 mmol/L). It is considered that 1 mmol/L of urea is associated with the formation of 0.063% of carbamylated haemoglobin in vivo. In patients with severe renal insufficiency the level of carbamylated Hb can approach 3% [20]. The results of charge-based separation methods can be adversely affected, as the isoelectric point of carbamylated haemoglobin is very close to that of labile glycated haemoglobin. Currently, the HPLC assays well separate the carbamylated and A1c forms of haemoglobin. Immunological methods are also unaffected by carbamylated haemoglobin [2].

2.2.2. Other interference

Other physiological factors can affect HbA1c values in patients with renal insufficiency:

- in patients under haemodialysis, the lifetime of red cells is shorter;
- erythropoietin treatment causes a shift to younger red cells.

If red cells have a lifetime of less than 120 days, the balance between synthesis/breakdown and non-enzymatic glycation is modified. As the glycation process is cumulative and starts...
during the erythropoietic stages, the HbA1c levels in older red cells are higher than in the younger ones. Any haemolytic situation, any haemorrhage or severe damage to blood, any treatment stimulating haemoglobin synthesis and any recent transfusion procedure will cause HbA1c levels to fall.

The result obtained must also be interpreted with care in patients with liver disorders: the lifetime of red cells can be modified by cirrhosis (haemolysis, increased splenic sequestration of red cells, modified erythropoiesis) or by treatment with ribavirin in HCV patients (haemolysis).

In pregnant women, haemodilution and lower fasting glycaemia can explain why the usual values of HbA1c tend to be 0.3-0.7% lower than in non-pregnant women [5]. In this case it is preferable to use fructosamine assay (assay of all the glycated serum proteins except for haemoglobin, using a colorimetric method) [13].

A recent study did not support the reported effects of vitamin C, vitamin E or aspirin (acetylated haemoglobin was not detected in patients chronically taking 1 g of aspirin per day) [3].

In sum, many diseases and situations can make it difficult to interpret glycated haemoglobin levels reliably. However, if the assay method is always the same, patients can act as their own controls in monitoring HbA1c trends.

3. Clinical utility of HbA1c assay

3.1. Information supplied by HbA1c levels

Optimal control of glycaemia in type 2 diabetes is recommended to delay or forestall the onset and (or) slow the progression of microvascular and cardiovascular complications. Monitoring of plasma glucose control in type 2 diabetes is based on the assay of HbA1c performed every 3-4 months. Surveys conducted by various sickness insurance schemes show that patient monitoring has improved.

- In the Champagne-Ardenne Region, 43% type 2 diabetes patients were reimbursed for HbA1c assays in 1998. This figure was 60.5% in 1999 [19];
- in the Ile-de-France Region, 42.1% of the diabetic population has an HbA1c assay in 1999. This figure was 59% in 2000 [8];
- in the Nord-Pas-de-Calais Region, the indicators in place for the past four years make it possible to record a marked improvement in type 2 diabetes care in general practice; 71% of diabetic patients now have at least one HbA1c assay every 6 months, against only 41% at the beginning of 1999. Another encouraging finding is that the number of diabetics who are not monitored has dropped from 19.8% to 8.7% [7].

Plasma glucose targets are translated into HbA1c targets. They must be individualized according to the patient’s age, comorbidity and the psychosocial context. They are set in the professional recommendations and references issued by the French healthcare evaluation body ANAES [14]. The foremost public healthcare aim is to help to significantly improve plasma glucose balance in all type 2 diabetes patients, so that most of them maintain an HbA1c level < 7%. Today fewer than half do so.

The working group’s recommendation is at the outset to seek and lastingly maintain the near-normalization of plasma glucose by targeting an HbA1c value of < 6.5%. Diet and physical activity are the two main components in the initial treatment of diabetes.

It is considered that a level of glycated haemoglobin of 7% reflects an average plasma glucose level of about 1.5 g/L over the preceding 60-90 days or so. We can consider that beyond 6% HbA1c, an increase of 1% corresponds to an average increase of 0.3 g/L in glycaemia [28] (Fig. 3).

3.2. The place of HbA1c in screening for diabetes

The French General Directorate for Health’s May 1999 circular (DGS/DH 99/264) concerning the organization of care for type 2 diabetes advocates, among other recommendations, screening for diabetes. The American Diabetes Association advocates simply measuring fasting glycaemia in place of the WHO criteria of 1985 [33] which included a glucose tolerance test, for which reserves were expressed by epidemiologists, including in the US. The essential criticism of this measurement is its low sensitivity. Half of the non-identified subjects, despite plasma glucose levels above 2.0 g/L two hours after oral glucose loading, were negative for fasting glycaemia, which was under the threshold value of 1.26 g/L (trial con-

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Fig. 3. Relationships between HbA1c values (%) and mean of glycaemia on 2 or 3 months (from Rohlfing et al. [28]).

Fig. 3. Relations entre les valeurs d’hémoglobine glyquée HbA1c (%) et la moyenne glycémique mesurée sur deux à trois mois (d’après Rohlfing et al. [28]).
ducted in subjects from the general population and occupational groups) [32].

The emergence of the HbA1c assay results from the need to have an indicator that is convenient, like fasting glycaemia, while at the same time has the high sensitivity of glycaemia 2 h after loading, which has a low reproducibility. Its evaluation may be more significantly representative than the artificial conditions of glucose loading [26]. It is well established that in some subjects, such as obese persons, diabetes is better diagnosed by fasting glycaemia, whereas in the elderly, for example, the glucose tolerance test is more significant. The fasting glycaemia cut-off value was set at 7 mmol/L, which corresponds to a value of 11.1 mmol/L 2 h after glucose loading. Almost one third of Europeans diagnosed on the basis of a 2 h glycaemia value of > 11.1 mmol/L have a fasting glycaemia of < 6 mmol/L simply because the population studied is less obese than that used to set the new diagnostic criteria. The HbA1c level may also vary according to the age, weight and ethnic origin of the population studied [17]. Many studies have nevertheless been conducted with the respect of such recommendations. They have confirmed that an elevated HbA1c value is relatively specific to glucose intolerance, but is poorly sensitive. In other words an elevated HbA1c value may indicate installed or developing glucose intolerance, but a normal value does not rule out this possibility [15]. This is consistent with studies conducted on the biological variation of HbA1c [29] which have shown that non-diabetic subjects mostly have HbA1c levels in the 4-6% range. Consequently, subjects with a baseline HbA1c value of 4% can increase their glycaemia level by 50% before they exceed that of non-diabetic subjects with a level of 6%. It is therefore not surprising that there is an overlap between values of HbA1c for diabetic and non-diabetic patients. Similarly, it is possible for a patient with an HbA1c value of about 5.5-6% to be developing diabetes: the average normal HbA1c values may correspond to a mixed population containing normal subjects and subjects whose level is increasing relative to their baseline [18].

In the face of these difficulties various authors including Geberhiwot have envisaged coupling HbA1c with fasting glycaemia for diabetes screening. A study has even been conducted in patients with risk factors such as:

- the existence of diabetes in a first-degree relative: father, mother, sibling or child;
- excess body mass defined by a body-mass index (mass in kg divided by the square of height in m) greater than 25 kg/m² or waist circumference of ≥ 90 cm for women or ≥ 100 cm for men;
- for women, a child weighing more than 4 kg at birth or gestational diabetes;
- hypertriglyceridaemia (≥ 1.75 g/L = 2 mmol/L);
- arterial hypertension (treated or ≥ 140/90 mm Hg), but with a fasting glycaemia of < 6 mmol/L.

In 580 patients with at least two risk factors, a glycated haemoglobin test and a glucose tolerance test were performed. Of these patients, 225 had a fasting glycaemia of < 6 mmol/L and were included: 23.1% had an abnormal glucose tolerance test result (45 had impaired tolerance and 7 were diabetic). The subjects with impaired tolerance all had higher HbA1c levels than normal individuals. An HbA1c level of 5.6% gives a sensitivity of 72% and a specificity of 77% for a 2 h glucose level of > 7.8 mmol/L. It seems therefore that fasting glycaemia associated with measurement of HbA1c in patients at risk is a good way to identify patients who need a glucose tolerance test [9].

Edelman undertook to measure the incidence of new cases of diabetes in patients enrolled in a health scheme to determine whether the HbA1c level allowed a stratification of the risk of developing diabetes in three years [6]. A total of 1253 non-diabetic patients aged 45-64 years were included, with a first measurement of HbA1c. All the patients with HbA1c > 6% had fasting glycaemia. The patients were then followed up annually for three years. After initial screening the new cases of diabetes were defined by HbA1c > 7% or a fasting glycaemia of > 7 mmol/L during the follow-up. There were 73 new cases of diabetes in the 3 years of follow-up, with an annual incidence of 2.2%. The annual incidence for patients with HbA1c > 5.5% was 0.8%. For HbA1c between 5.6% and 6%, the incidence was 2.5% and for values between 6.1% and 6.9% it was 7%. When the weight factor was added, an annual incidence of 4.1% was found for obese patients with HbA1c values between 5.6% and 6%. The ability of HbA1c to predict the onset of diabetes is still unknown, but this study suggests that for patients associated with risk factors, the HbA1c results could be used to adapt patient follow-up: closer for patients with HbA1c levels of > 2 standard deviations above the mean, and at wider intervals for patients with levels of < 1 standard deviation above the mean.

Although HbA1c does not contribute any more than traditional epidemiological factors, it may nevertheless supply a more accurate and significant indication for the patient and an additional motivation for a change in diet and lifestyle [27]. The reason why the use of HbA1c for diabetes screening is still controversial, some 30 years after its usefulness for monitoring plasma glucose balance was recognized, is also because of analytical limitations. We have seen that the harmonisation and standardization of methods is underway, but the difficulties of interpretation due to the presence of variants or anaemia strongly impede the implementation of this test for screening. Finally, even if we accept a coefficient of variation of < 3% for the HbA1c assay, a difference of 0.7% can occur in the same subject with a level of 6%. Given these difficulties, it is hard to imagine how HbA1c could ever supersede the assay of plasma glucose in the diagnosis of diabetes. For proof, the department of technological and economic evaluation of the ANAES concluded in his report on the principles of the following of diabetes of the type 2 (February 2003): "The measurement of glycated haemoglobin, marker of effectiveness and follow-up of treatment of the diabetes, is a simple test, non-constraining and well accepted by patients". It will still be necessary to
await the standardization of the methods to confirm them rather favourable results of the diagnostic performance observed with current data and to recommend it for following. Moreover, its cost is currently higher than that of measurements of glycaemia (quotiation with the nomenclature of the acts of medical biology (NABM): B10 for glycaemia either 2.68 € and B60 for glycated haemoglobin or 16.1 €).

3.3. Other current or potential uses of glycated haemoglobin assay

3.3.1. In cardiology

Diabetes is associated with a markedly higher fatality rate after myocardial infarction.

In acute coronary syndromes, glucose metabolism is modified and a stress-related hyperglycaemia is frequent among non-diabetics. Studies have been undertaken to determine the contribution of glycaemia levels on admission and HbA1c levels on vital prognosis after myocardial infarct [10].

Twenty years ago in patients admitted for myocardial infarct non-diagnosed diabetes was defined for individuals with HbA1c > 3 standard deviations above the mean. This was supported by the fact that in infarct patients with a very high HbA1c (> 7.8%) 86% of the survivors were found to be diabetic. A glycaemia value of > 11 mmol/L on admission had a positive predictivity of only 33% for diabetes [25].

The results of several studies show an independent relation between glycaemia on admission and morbidity/mortality in both diabetic and non-diabetic patients. Hyperglycaemia on admission is associated with a shorter survival time and more extensive necrosis [4]. In type 2 diabetes patients, the long-term glycaemia state (and therefore HbA1c levels) can predict admission plasma glucose and prognosis [21].

A recent study was made of 332 patients admitted to intensive care with confirmed diagnosis of acute coronary syndrome. If these patients are classified according to their glycaemia on admission it was found a fatality rate of 9% in those with plasma glucose in the range 7.8-11 mmol/L. In type 2 diabetes patients, the long-term glycaemia state (and therefore HbA1c levels) can predict admission plasma glucose and prognosis [21].

3.3.2. In vascular pathology

The relation between HbA1c and peripheral arterial disorders was observed in adult Americans participating in the National Health and Nutrition Examination Survey (NHANES) in 1999-2002 (4528 participants) [23].

Of these, 5.1% of patients presented arterial disorders. In non-diabetic individuals (classified according to their HbA1c values: < 5.3%, 5.3-5.4%, 5.5-5.6% and 5.7-6%) a significantly increased risk of arterial disorders was found in patients with HbA1c levels in the range 5.7-6%. This elevation was not found to a significant degree for HbA1c levels between 5.3% and 5.4% or between 5.5 and 5.6%.

Peripheral arterial disorders are twice as frequent in diabetics as in non-diabetics. Prospective trials have been conducted to seek a relation between HbA1c levels and the occurrence of peripheral arterial disorders in diabetic patients. The results suggest that dysglycaemia is associated with an increased risk of peripheral arterial disorders independently of already known risk factors. This relation is particularly marked for severe peripheral disorders (claudication, disorders requiring hospitalization, etc.).

Patients with HbA1c > 7.5% are five times more likely to suffer claudication and five times more likely to be admitted to hospital for arterial problems than patients with HbA1c < 6%. Better glycaemia control would thus substantially reduce the risk of developing peripheral arterial disorders [30].

3.3.3. In nephrology

In the general population, hyperglycaemia (without diabetes) is a vital risk factor. It is very frequent among persons with chronic renal insufficiency. HbA1c is itself associated with increased fatality rates in non-diabetic patients with chronic renal insufficiency, and so it could be an important tool for stratifying the risk in this population [22].

A Japanese team [24] has recently published results on glycaemic balance in haemodialysed patients. Diabetic patients under haemodialysis were monitored after inclusion in a group linked to their average HbA1c level in the three months preceding the trial. Three groups were set up: HbA1c < 6.5%, 6.5% < HbA1c < 8% and HbA1c > 8%. The survival curve of the patients with poor glycaemic balance was markedly lower that for the euglycaemic patients. This cohort analysis suggests that HbA1c should be kept below 8% in haemodialysed diabetic patients (as advocated by the National Kidney Foundation Task Force on Cardiovascular Disease), a value higher than that recommended by the American Diabetes Association (7%) in view of the population concerned. This average level provides a reasonable protection against metabolic disorders, risks of infection and hypoglycaemia, which is frequent in these patients.

In a recent study [12] the possibility of using HbA1c to predict the onset of post renal transplant diabetes was examined. Among 200 non-diabetic patients grafted, 10.1% presented an increased HbA1c post-transplant. This test appears to be more sensitive than fasting glycaemia for screening post-transplant diabetes, especially in Afro-Americans.

3.3.4. In haematology

A Turkish team has suggested that HbA1c could be used to differentiate between iron-deficiency anaemia and minor thalassaemia. HbA1c levels were measured in 40 patients with minor thalassaemia, 20 patients with iron-deficiency anaemia and 38 healthy non-diabetic subjects. Average HbA1c level was lowest in the thalassaemia group. There was no significant difference between the iron-deficient patients and the healthy controls. A cut-off value for HbA1c of 5% gave a sensitivity of
95% and a specificity of 75% for differentiating the two conditions. The positive predictivity was 96.6%, and the negative predictivity was 67.9% [1]. Further studies are obviously necessary to validate these findings, but the first results are interesting.

3.3.5. In oncology

Diabetes seems to be associated with an increased risk of colorectal cancer. In a study conducted in 2004 Khaw [16] showed that an increase of 1% in glycated haemoglobin levels was associated with a 33% increase in the risk of developing colorectal cancer. One of the explanations proposed is the fact that both disorders reflect a diet rich in fat and poor in fibre, together with low physical activity. Greater attention is being paid to the role of insulin and insulin-like growth factors, which are probably involved in cancer formation, as they have effects on the epithelial cells of the colon.

HbA1c could be a good marker of metabolic processes influencing insulin levels and insulin-like growth factors.

If these results are confirmed, this association could open the way to efficacious preventive strategies.

4. Conclusion

The contribution of clinical bioanalysis is essential for the care of diabetic patients. HbA1c has become a gold standard for assessing the risk of microangiopathic complications and the positive impact of treatments designed to lower glycaemia and forestall complications such as retinopathy and nephropathy.

The practice of assay methods has changed profoundly in recent years. The least reliable methods have been superseded by standardized procedures. Assays based on chromatographic or immunological techniques have strongly contributed to improving the quality of the results supplied to the clinician.

Outside the monitoring of blood glucose balance, there is no current consensus for the use of glycated haemoglobin assay to screen for diabetes. However, many studies have been initiated to exploit the significance of abnormal HbA1c values. Hence once the problems linked to standardization have been solved, the use of this assay may well see many new developments in the years to come.

References