Glycated haemoglobin in the year 2000

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The past decade has given us a better insight into the clinical uses and problems associated with glycated haemoglobin measurement. This article describes the recent studies that have helped clarify the role of glycated haemoglobin in the management of patients with diabetes.

There remain numerous analytical problems associated with glycated haemoglobin measurement, such as the lack of assay standardisation and the problems related to its measurement in particular patient groups with haemoglobinopathies, fetal haemoglobin, renal failure (who form haemoglobin derivatives), and haemolytic diseases. These analytical problems have been reviewed recently[1] and are not discussed at length here.

The term "glycated haemoglobin" is a generic one, which includes haemoglobin A_1 (HbA_1), HbA_{1c} and "total glycated haemoglobin". In recent years, improved analytical techniques have resulted in HbA_{1c} measurement supplanting HbA_1, to become the predominant measure of glycated haemoglobin, and all major clinical studies have used this assay. Therefore, I will concentrate on the HbA_{1c} or HbA_{1c} equivalent assays that are in routine use.

What is HbA_{1c}?

Carbohydrates (such as glucose) can bind non-enzymatically to proteins (such as haemoglobin) in a process known as glycation. The charge separated haemoglobins of normal adult HbA_0 are jointly known as HbA_1, which can be further separated into its constituent parts, HbA_{1a1}, HbA_{1a2}, HbA_{1b}, and HbA_{1c}. Glucose is the carbohydrate in the major fraction, HbA_{1c}, whereas other carbohydrates, some of which still need to be established with certainty, constitute the other fractions.[2] The predominant glycated haemoglobin, called HbA_{1c}, was first identified as a minor fraction of normal adult haemoglobin by ion exchange chromatography nearly four decades ago.[3] Early structural studies suggested this HbA_{1c} fraction exhibited glycation at the N-terminal valine of the haemoglobin β-chain.[4 5] Recently, in an effort to try and standardise the measurement, the International Federation of Clinical Chemistry (IFCC) has proposed that HbA_{1c} should be defined as glucose glycation at one or more of these sites on the haemoglobin molecule.[6] However, the application of new techniques to glycated haemoglobin measurement, such as electrospray mass spectrometry, has suggested that the assays used in the clinical studies described below, which were previously thought to measure only what the IFCC defines as HbA_{1c}, actually measure a mixture of species with both glycated α-chains and β-chains, non-glycated α-chains, and glycated β-chains and multiple glycated β-chains.[7 8] It

means that any future IFCC standardised assay will give lower results than those clinicians are used to.[6]

HbA_{1c} as an indicator of glycaemic control

Traditionally, HbA_{1c} has been thought to represent average glycaemia over the past six to eight weeks.[9] In fact, glycation of haemoglobin occurs over the entire 120 day life span of the red blood cell,[10] but within this 120 days recent glycaemia has the largest influence on the HbA_{1c} value.[11] Indeed, theoretical models and clinical studies suggest that a patient in stable control will have 50% of their HbA_{1c} formed in the month before sampling, 25% is in the month before that, and the remaining 25% in months two to four.[12] The advantage that HbA_{1c} can give as an assessment of average plasma glucose can also be perceived as a drawback because it does not give an indication of the stability of glycaemic control. Thus, in theory, one patient with wildly fluctuating glucose concentrations could have the same HbA_{1c} value as one whose glucose varies little throughout the day.

The evidence that HbA_{1c} measurement gives an indication of mean plasma glucose in the first place is not as strong as might be assumed. The initial clinical studies into HbA_{1c} in the 1970s could only compare it with the glycaemic assessment that was available at the time. Thus, it was compared with 24 hour glucose excretion rates,[13] "plasma glucose brackets",[14] daily mean plasma glucose,[15] and the area under the curve of the glucose tolerance test.[16] The best evidence that exists arises from the feasibility study of the diabetes control and complications trial (see below), which compared the average of multiple HbA_{1c} measurements to the average of laboratory measured blood glucose profiles over the period of one year.[17] Although there appeared to be an excellent association ($r = 0.80$), this hid the fact that an individual patient with a mean glucose of—for example, 10 mmol/litre, could have an HbA_{1c} that varied from anywhere between 7% and 11%. Indeed, it has been known for several years that in any diabetic population there is a proportion of people who appear to glycate haemoglobin at a faster or slower rate than most others.[18] Even within a non-diabetic reference range of 4–6%, subjects tend not to vary between 4% and 6%, but instead stay very close to their own "set point".[19 20] By inference, this means that two subjects with the same degree of glucose tolerance might well have HbA_{1c} values that vary by up to 2%. The reason for these differences between "high" and "low" glycators was originally thought to the result of interindividual differences in tissue glycation,

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but recent data suggest that much of these differencies can be explained by the fact that high glycators seem to have red blood cells that survive for longer than low glycators.[21] Even if there is to be a change in the HbA_{1c} set point, then it seems likely to be related to changes in red blood cell life rather than glycaemia or glycation rates.[22]

Of course, measures of glycaemic control other than glycated haemoglobin exist, such as serum fructosamine[23] and 1,5-anhydroglucitol.[24] Unfortunately, none of them has been investigated in as much detail as glycated haemoglobin and, crucially, none was measured alongside HbA_{1c} in the two major complications studies described below. Thus, we seem destined never to know whether tests such as fructosamine can predict the risk of diabetes complications any differently to HbA_{1c}.

HbA_{1c} and diabetes complications

After the clinical studies of the 1970s,[13–16] the next logical step was taken to use HbA_{1c} to evaluate whether improving glycaemic control in diabetic patients could lead to a reduction in the long term small vessel (microvascular) and large vessel (macrovascular) complications of diabetes. Two seminal studies, the diabetes control and complications trial (DCCT)[25] and the United Kingdom prospective diabetes study (UKPDS),[26] set out to establish the effect on microvascular complications in patients with type 1 (insulin dependent) and type 2 (non-insulin dependent) diabetes, respectively. It was hoped that these studies could also shed light on whether macrovascular complications could be avoided by this means.

MICROVASCULAR COMPLICATIONS

The microvascular (small vessel) complications of diabetes comprise retinopathy, nephropathy, and most probably neuropathy. Patients with diabetes who develop these conditions constitute a large proportion of all subjects who develop blindness, renal failure, and/or require limb amputation. To see the effect that improving glycaemic control might have on the development and progression of these complications, the DCCT study recruited 1441 young patients (mean age, 27 years) with type 1 diabetes, half of whom were assigned to what was "conventional" treatment in the USA at that time (one or two daily insulin injections and daily urine/blood glucose monitoring), whereas the other half were allocated to "intensive" treatment (three or more insulin injections/day or an external pump, and multiple daily blood glucose measurements), where the aim was to achieve as near normal blood glucose concentrations as possible. Haemoglobin A_{1C} measurement was the cornerstone of glycaemic assessment in these patients. Compared with a non-diabetic reference interval of 4.05% to 6.05%, the intensively treated group achieved a median HbA_{1c} value of 7%, whereas in the conventionally treated group 9% was obtained throughout the study period. After a mean follow up period of 6.5 years, the risk of developing retinopathy in the intensively treated group was reduced by 76%, the risk of developing proteinuria was reduced by 54%, and the risk of clinical neuropathy was reduced by 60%.[25] Benefits extended to the slowing of retinopathy progression in patients who already had mild eye disease at study entry.

Subsequent detailed analysis showed that HbA_{1c} measurement could be used as a tool to stratify the risk of a patient developing microvascular complications because there was an exponential rise in the rate of these complications with increasing HbA_{1c} values.[27] This applied to all values of abnormal HbA_{1c} and not just to the values of 7% and 9%. Further examination also showed that there was an apparent absence of a "glycaemic threshold"— short of normal glycaemia—below which small vessel complications did not occur.[28] Nevertheless, as with all exponential relations, there was a law of diminishing returns, whereby the absolute benefit of reducing HbA_{1c} was diminished as the starting value decreased. For example, the absolute reduction in retinopathy risk of a patient falling from a HbA_{1c} of 7% to 5.2% is the same as another patient falling from 10% to 9.7%.[29] Striving for good glycaemic control by aiming for as low an HbA_{1c} as possible is also not without risks because the rate of severe hypoglycaemia in this study was found to increase exponentially as the HbA_{1c} concentration fell.[30] Indeed, for many patients with diabetes, the fear of experiencing an acute complication, such as hypoglycaemia, is greater than the possible increased risk of developing long term small vessel complications through having chronically high HbA_{1c} values.

After the report of the DCCT study in 1993 it was hoped, but could not be assumed, that the results from this trial into type 1 diabetes would be equally applicable to the patients with type 2 disease, who represent most of the diabetic population.[31] It took the publication of the UKPDS in 1998 to confirm that HbA_{1c} could also be used to indicate the risk of developing small vessel complications in this group of patients.[26] This study involved 3867 older subjects (mean age, 54 years), who were either assigned to intensive treatment, with the aim of achieving a fasting plasma glucose of 6 mmol/litre, or conventional treatment, with an aim to remain free from hyperglycaemic symptoms and/or keep the fasting glucose below 15 mmol/litre. Again, the cornerstone of treatment evaluation was by means of HbA_{1c} measurement, using the same assay as had been used in the DCCT. The separation between the groups this time was not as impressive as in the DCCT (HbA_{1c} 7.0% *v* 7.9% over 10 years), but there was still a 25% risk reduction in microvascular endpoints, which was in keeping with what the DCCT would have predicted.

The UKPDS might also have inadvertently given an indication as to whether the stability of glycaemic control, and not just the mean plasma glucose, influences the risk of small vessel disease because some patients were treated with insulin, whereas others received sulphonylurea drugs. Because patients treated with insulin tend to have greater glucose oscillations than non-insulin treated ones,[32] it might

have been expected that the risk of complications at any given HbA_{1c} value would have been different between the two groups. In reality, no such differencies appeared to exist.

These two recent studies proved the usefulness of HbA_{1c} measurement in predicting the risk of developing microvascular complications and, as a consequence, have led to the widespread recommendation of its increased use.[31 33–35] However, it must be emphasised that hyperglycaemia as measured by HbA_{1c} is not the sole contributor to this risk because other factors can also have an important effect. In the UKPDS—for example, a reduction in blood pressure from a reading of 154/87 to 144/82 was found to be associated with a 37% decrease in microvascular endpoints.[36] There was also a clustering of microvascular disease in families participating in the DCCT, suggesting an additional genetic influence on complication development and progression.[37]

MACROVASCULAR DISEASE
Although diabetic microvascular complications form a large proportion of the excess morbidity and mortality associated with diabetes, the main cause remains the effects of large vessel (macrovascular) disease. Diabetes is associated with a two to threefold increased risk of coronary heart disease in men, and a four to fivefold increased risk in premenopausal women.[38] The DCCT and UKPDS trials did not primarily set out to establish whether a relation between HbA_{1c} and heart disease existed, but subgroup analysis has nevertheless been performed to examine this question. In the DCCT, the cardiovascular event rate was low because of the age of the patients recruited, but there was still an excess of macrovascular events in the conventional compared with the intensive group (40 v 23), although this just failed to reach significance ($p = 0.08$).[39] In the UKPDS, the event rate was higher, but the HbA_{1c} separation between the two groups lower, and again the findings were statistically suggestive but not conclusive ($p = 0.052$ for myocardial infarction).[26] However, recent analysis has shown that when the whole range of UKPDS patient HbA_{1c} concentrations is taken into account there is a highly significant relation between HbA_{1c} and coronary heart disease risk in these patients.[40] Thus, HbA_{1c} appears to give an indication of macrovascular risk (additional to hypertension, smoking, etc) in patients with diabetes, and might go some way to indicating the excess risk of coronary events associated with the disease.

Targets for patients with diabetes
The publication of the DCCT and UKPDS has led to a reappraisal of the glycaemic control targets that should be aimed for in the treatment of patients with type 1 and type 2 diabetes. Previously, some guidelines tried to account for the lack of standardisation in glycated haemoglobin measurement by comparing patients using the number of standard deviations (SDs) their HbA_{1c} result lay from their particular assay's non-diabetic mean value.[41] However, the SD targets were necessarily rather arbitrary, and the use of SDs could lead to discrepancies in patient classification, depending on which glycated haemoglobin assay was used.[42]

The DCCT and the UKPDS has allowed a more "evidence based" approach to be taken to the recommendations, and the fact that they both used the same HbA_{1c} method has allowed SD targets to be dispensed with. The European diabetes policy group guidelines (as part of the International Diabetes Federation) now recommend that both patients with type 1 and type 2 diabetes aim for a DCCT or DCCT equivalent assay value of $\leqslant 7.5\%$ to reduce the risk of microvascular complications.[43 44] In the USA, it is recommended that a value of $< 7.0\%$ be achieved, with values $> 8\%$ suggesting that additional action should be taken.[45] As mentioned above, the absolute value of these targets might change if the proposed HbA_{1c} IFCC standard becomes adopted, but many clinicians seem to favour continuing with the current de facto DCCT standard.

HbA1c as a screening test for diabetes
There remains considerable interest in extending the use of glycated haemoglobin measurement to include the diagnosis as well as simply the monitoring of diabetes. Using the 1985 WHO oral glucose tolerance test (OGTT) criteria for diagnosing diabetes,[46] a meta-analysis of 34 studies has found HbA_{1c} to be limited as a screening test because of the large number of subjects who have either impaired glucose tolerance or frank diabetes, but have HbA_{1c} values that are within the non-diabetic reference interval.[47] Thus, a raised HbA_{1c} would appear to be specific for diagnosing diabetes, but the test is not particularly sensitive. Even when using the proposed new diabetes diagnostic criteria[48 49]—which define diabetes as a fasting plasma glucose value $\geqslant 7$ mmol/litre—the same limitation in diagnosing type 2 diabetes is found.[50]

Some authors support the idea that HbA_{1c} testing is likely to be a more physiological assessment of glucose intolerance than the artificial conditions of the OGTT, and so believe this should be the preferred diagnostic test. Certain studies have shown HbA_{1c} to be as good a predictor of microvascular disease as fasting or two hour post-OGTT glucose values,[51 52] although not all studies have reached this conclusion.[53] One group took a more pragmatic approach to diagnosis, stating that subjects with a HbA_{1c} below 7.0% are not likely to require pharmacological treatment of their condition and so need not be classified as diabetic, although the meta-analysis from which the value of 7% was derived did not convincingly take account of differences in HbA_{1c} methods between constituent studies.[47]

I believe it is unlikely that HbA_{1c} will ever be a reliable test for the diagnosis of type 2 diabetes for the following reason. If hyperglycaemia, rather than glycation, is the true cause of diabetic complications (and it continues to be the means of diagnosing diabetes) then HbA_{1c} is fundamentally limited by the fact that

two individuals with the same degree of glucose tolerance can have HbA$_{1c}$ values that differ by nearly 2%.[20] Thus, a subject with a HbA$_{1c}$ value of 4% would need to increase his/her glycation rate by 50% to match another non-diabetic subject with a HbA$_{1c}$ value of 6%. It is therefore not surprising that there can be overlap between the HbA$_{1c}$ values of patients with diabetes and those of subjects without the disease. Even if glycation is thought to be the underlying reason for complications, we have to be sure that glycation of haemoglobin gives an accurate reflection of glycation in small vessels. Because it is known that HbA$_{1c}$ values can be affected by factors that are independent of glycaemia or glycation rates,[18 21 54] then this assumption cannot be presumed.

Currently, guidance from the USA recommends against using HbA$_{1c}$ in the diagnosis of type 2 diabetes,[55] but recent European recommendations find a role for the test although, curiously, this is only if confirmatory glucose testing is also performed.[44]

Conclusions

Within the past 10 years, studies using HbA$_{1c}$ have answered positively the fundamental question as to whether glycaemic control influences the outcome of patients with diabetes. Therefore, despite its inherent limitations, HbA$_{1c}$ seems destined to continue to be the most valuable of the glycaemic risk markers.

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