

Review

Glycated Haemoglobin: A Predictor of Vascular Risk?

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Abstract

Glycated haemoglobin (HbA_{1c}), a marker of average glycaemia during the previous six to eight weeks, is a predictor of microvascular complications in diabetic individuals. However, the role of HbA_{1c} as a predictor of macrovascular complications (e.g. myocardial infarction or stroke) in these patients is not clearly defined. In contrast, new evidence suggests that HbA_{1c} can predict the risk of cardiovascular disease in the general population. The potential applications of this test in vascular disease prevention are discussed.

Key words: *Diabetes mellitus, glucose, glycated haemoglobin, impaired fasting glucose, impaired glucose tolerance, vascular disease.*

Introduction

Glycated haemoglobin (HbA_{1c}), a marker of average glycaemia, is a predictor of microvascular complications in diabetic individuals.^{1,2} However, it is not yet clear whether the HbA_{1c} is an indicator of the risk of the macrovascular complications associated with diabetes mellitus.¹⁻³ In addition, the concentration of this long-term index of glycaemia has recently been shown to predict cardiovascular disease (CVD) risk in individuals without diabetes.³ This is an important finding because the comprehensive assessment of vascular risk will improve the targeting of preventive treatment.

Limitations of HbA_{1c} measurement

Haemoglobin is separated initially as HbA₀. This fraction is further separated into the following sub-fractions: HbA_{1a1}, HbA_{1a2}, HbA_{1b} and HbA_{1c}. Glucose is the carbohydrate in HbA_{1c}. Although the term glycated haemoglobin denotes total HbA₁, HbA_{1c} assays are the predominant way of estimating 'long-term' glycaemic control.^{4,5} The normal life span of red blood cells (RBC) is 120 days. During this period the process of glycation takes place. However, recent glycaemia has the greatest influence on HbA_{1c} values.⁶ Thus, approximately 50% of the total HbA_{1c} value results from glycation of Hb over the previous one month.⁵ Overall, HbA_{1c} is a marker of average glycaemia during the previous six to eight weeks.^{4,5}

There are "fast" or "slow" glycaters of haemoglobin. This effect probably depends on the variability of RBC

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survival time.⁷ This means that the value of HbA_{1c} tends to remain stable in the same person but it may vary considerably between individuals with the same degree of glucose impairment. For example, in those with the same degree of impaired glucose tolerance (IGT), HbA_{1c} values can fluctuate between 4% and 6% (typical reference range: 3.9 - 6.1 %).^{8,9}

Other limitations include the inaccuracy of HbA_{1c} assays in patients with abnormal haemoglobins or haemolytic diseases.⁵

HbA_{1c} as a risk factor for CVD in diabetic individuals

CVD is the main cause of mortality among Type 2 diabetic patients^{5,10,11}. Although HbA_{1c} is a well-established risk factor for microvascular complications in diabetes mellitus, there is no clear evidence regarding its predictive role for diabetic macrovascular complications.^{1,2} The Diabetes Control and Complications Trial¹ (DCCT) and the United Kingdom Prospective Diabetes Study² (UKPDS) evaluated the role of glycaemic control in Type 1 and 2 diabetes, respectively. These trials showed a non-significant reduction of CVD risk with more intensive glycaemic control (lower HbA_{1c}). In the DCCT,¹ the CVD risk reduction was 40% ($p = 0.08$). This reduction was not significant probably because the patients were young and accordingly there were few cardiovascular events. In contrast, in the UKPDS² there were more CVD events but the variation in HbA_{1c} values was smaller than in the DCCT (the intensive treatment group in the UKPDS had a HbA_{1c} <7% while the 'control' group had a HbA_{1c} between 7% - 9%). The risk reduction (16%) in UKPDS² failed to reach significance ($p = 0.052$) for myocardial infarction (MI). However, a recent meta-analysis¹² showed that when

the whole range of the HbA_{1c} concentrations in UKPDS was considered, there was a highly significant relation between HbA_{1c} and CVD risk.

In conclusion, the evidence suggests but does not confirm a role for HbA_{1c} as a predictor of CVD in the diabetic population. As far as macrovascular complications are concerned, diabetic patients are more likely to benefit from tight blood pressure control and the modification of the other major risk factors (e.g. dyslipidaemia and smoking) than from improved glycaemic control.^{1,2,5,13}

HbA_{1c} and CVD risk in non-diabetic individuals

Several studies assessed the relationship between HbA_{1c} values and the risk of vascular disease.^{3,14-22}

The European Prospective Investigation of Cancer and Nutrition study³ (EPIC-Norfolk) included 4662 men (aged 45 - 79 years) from the general population. They were followed up between 1995 and 1999. The primary endpoints were CVD, ischaemic heart disease (IHD) and all cause mortality. There were 1204 men with a HbA_{1c} <5%, 1606 with a HbA_{1c} between 5 - 5.4%, 1611 with a HbA_{1c} 5.5 - 6.9%, 81 with a HbA_{1c} >7% and 160 known diabetic patients. A multivariate analysis showed that a 1% increase in the HbA_{1c} value was associated with a 29% increase [95% confidence interval (CI): 14% - 45%] in all cause mortality, a 38% increase in CVD mortality (CI: 18% - 61%) and a 44% increase in IHD mortality (CI: 21% - 71%). After excluding known diabetic patients or those with a HbA_{1c} >7% and those with known IHD or stroke, the relative risk (1.46; CI 1.0 - 2.1) of all cause mortality for a 1% increase in the HbA_{1c} value remained significant ($p =$

0.05).

The relevance of the EPIC-Norfolk study³ is that a wide range of HbA_{1c} values in non-diabetic individuals was assessed. The increase in CVD mortality according to HbA_{1c} values seems to follow a stepwise pattern.³ The relative risk for CVD among men with HbA_{1c} 5% - 6.9% (n=3217) was approximately 2.5 compared with those with HbA_{1c} values <5%. Compared to HbA_{1c} values <5%, the relative risk of men with HbA_{1c} >7% was 5 but this comparison is limited by the small number of subjects with the higher HbA_{1c} (n = 81 vs 1204). Finally, the relative risk of men with diabetes (n = 160) was 8.1 compared to those with HbA_{1c} values <5%.

Since the EPIC-Norfolk study included only men, a gender-dependent relationship between HbA_{1c} and CVD could not be assessed. This is an important question that still needs to be answered. Thus, a recent meta-analysis²² (10 prospective studies) revealed that compared to non-diabetic individuals, the relative risk of IHD was higher for diabetic women (2.58) than for diabetic men (1.85). This gender-based difference in risk was significant (p = 0.045).

These results of the EPIC-Norfolk study are in accordance with a combined analysis of the Whitehall, the Paris Prospective and the Helsinki Policemen studies.¹⁴ Similarly, in the Framingham study, the risk of IHD showed a continuous increase across the spectrum of non-diabetic glucose tolerance¹⁵. Moreover, in two prospective studies,^{16,17} HbA_{1c} was a predictor of CVD in non-diabetic individuals. However, these two studies^{16,17} focused on the upper end of the distribution of HbA_{1c} values. This means that patients with undiagnosed diabetes could have been included.

The predictive value of HbA_{1c} for macrovascular disease is further supported by its correlation with the carotid intima-media thickness (IMT), a well-established and modifiable marker of atherosclerosis.¹⁸⁻²¹

Drugs and HbA_{1c}

Improved glycaemic control in diabetic individuals (Type 1 and 2) is clearly necessary to reduce the risk of microvascular complications.^{1,2} However, an added benefit may be that this policy will also result in a reduction in macrovascular complications. Similarly, in non-diabetic individuals the benefit from improved insulin sensitivity (as represented by 'lower' HbA_{1c} values) could be a reduction in CVD risk³. It follows that drugs that improve insulin sensitivity may provide an additional benefit.²³⁻³³

Fibrates are useful in mixed dyslipidaemias and they may also exert a small beneficial effect on insulin sensitivity.^{23,24,25} One fibrate, gemfibrozil, significantly reduced (22 %; p = 0.006) the risk of vascular events in a secondary prevention trial that included diabetic individuals (at least 25% of the trial population) and patients with the features of the insulin resistance syndrome.²⁶

Statins (e.g. pravastatin and simvastatin) reduce the risk of vascular events in diabetic individuals and in those with impaired fasting glucose (IFG) (reviewed in reference 31). This benefit can be attributed to improving the lipid profile.³¹ However, a recent study showed that simvastatin (compared with cholestyramine) improved 24hr albumin excretion and diastolic blood pressure in diabetic individuals independently of changes in low density lipoprotein cholesterol (LDL) levels.³² Another

study has shown that atorvastatin decreased insulin resistance in non-insulin dependent (Type 2) diabetic patients.³³ Clearly more research is required to define the role of statins in diabetic individuals and patients with IFG. Antihypertensive agents (e.g. doxazosin) that increase insulin sensitivity may also be useful in these patient populations.^{27,28}

There is also evidence showing that hormone replacement therapy (HRT) improves long-term glucose homeostasis (as indicated by HbA_{1c} measurements).³⁰ However, this finding requires confirmation.

Whether improving insulin sensitivity also influences plasma fibrinogen levels remains to be established²⁹. However, such an effect could be important because fibrinogen is an independent and powerful predictor of vascular risk.²⁹

The use of HbA_{1c} as a predictor of cardiovascular risk: Future prospects

There is still a need to confirm that HbA_{1c} measurements can predict the risk of macrovascular events in both diabetic and non-diabetic individuals. The need to use HbA_{1c} measurements to assess cardiovascular risk in non-diabetic individuals may lead to the development of ultrasensitive assays. This is because small changes in this variable (possibly below an HbA_{1c} value of 5%) may be relevant (see comments, above, regarding the EPIC-Norfolk study³).

It will also be necessary to assess if HbA_{1c} is a stronger and more cost-effective predictor of cardiovascular risk than making a diagnosis of IGT or IFG using simple glucose measurements. A fasting glucose is currently recommended as part of the assessment of cardiovascular risk.³⁴ However, for

screening purposes, the need for fasting may be a disadvantage for glucose measurement but not when using HbA_{1c} assays.

Glycation of proteins and atherosclerosis

Whether glycaemia and/or the glycosylation by-products contribute to the pathogenesis of the cardiovascular complications in diabetic and non-diabetic individuals has not yet been clarified⁵. Although a detailed discussion of this topic is beyond the scope of this review it is of interest that the glycation of various lipoproteins [e.g. LDL and lipoprotein (a)] has been implicated in the pathogenesis of vascular disease.^{35,36} In addition, glycated human oxyHb inhibited nitric oxide (NO)-mediated vasorelaxation of human blood vessels.³⁷

A detailed discussion of the prognostic value of microalbuminuria in diabetic and non-diabetic individuals is beyond the scope of this review. However, it is worth mentioning that microalbuminuria is more likely to represent established endothelial dysfunction³⁸⁻⁴² rather than to be an early predictor of vascular risk like minimally raised HbA_{1c} levels.³ The presence of established vascular damage might also explain why the predictive power of microalbuminuria can be more significant than that of HbA_{1c} levels.^{3,39-42} Nevertheless, there is evidence of an association between microalbuminuria and HbA_{1c} measurements in diabetic and non-diabetic individuals.³⁸⁻⁴² Tight glycaemic control may retard the progression of microalbuminuria in patients with Type 2 diabetes.⁴² However, this effect is not necessarily associated with less deterioration of glomerular function or a decrease in the risk of macrovascular events⁴². Microalbuminuria can be induced in patients with peripheral vascular disease

after exercise.⁴³ However, the effect of different levels of HbA_{1c} on this phenomenon has not been investigated.

Conclusion

Current evidence suggests that HbA_{1c} could be used, together with other variables, to assess cardiovascular risk in diabetic and non-diabetic individuals. Reducing blood HbA_{1c} levels, in

conjunction with other interventions, should prove beneficial in decreasing the risk of vascular events in all populations. However, both these statements need to be confirmed by future trials. There is still a need to compare the predictive value and cost-effectiveness of HbA_{1c} and fasting glucose measurements in non-diabetic individuals.

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