HbA_{1c}: a useful cardiovascular risk marker in those without diabetes?

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Abbreviation

ARIC Atherosclerosis Risk in Communities

The apparent link between different measures of glycaemia and the occurrence of cardiovascular events has led to important developments in recent months. The presence of diabetes remains a well-documented cardiovascular risk factor, as shown in numerous studies [1]. However, it is the proposed association between dysglycaemia and cardiovascular events in those who do not have diabetes that has yielded new insights.

A recent analysis from the Reykjavik Prospective Study, in which participants were followed up for 24 years, found that the risk of coronary events was 3% higher for every 1 mmol/l higher postprandial glucose level (1 h measure) after adjusting for numerous established risk factors in those without diabetes [2]. In the same paper, a meta-analysis of 15 cohorts with over 100,000 participants without diabetes produced a 5% higher coronary risk for every 1 mmol/l higher postprandial glucose level. Links between fasting glucose in the non-diabetic range and

cardiovascular disease appear weaker. Data from the Emerging Risk Factors Collaboration concluded that there is a non-linear association between fasting plasma glucose and risk of cardiovascular disease, with the lowest risk in those with fasting glucose 3.9–5.6 mmol/l and higher risks either side of this, albeit modestly so [1]. HbA_{1c} reflects glycaemia over the preceding months, predominantly postprandial glycaemia. It has produced the most promising results of any measure of glycaemia as regards its association with cardiovascular risk. In the meta-analysis by Sarwar and colleagues, a 1% higher HbA_{1c} level was associated with a 20% higher coronary risk, appreciably better than either fasting or postprandial glucose [2]. Furthermore, in the Atherosclerosis Risk in Communities (ARIC) study, participants with no history of diabetes and with a baseline HbA_{1c} level of 5.5–5.9%, 6.0–6.4% and ≥6.5% had a 23%, 78% and 95% higher risk of coronary events, respectively, compared with those with an HbA_{1c} level of 5.0–5.4% in a multivariable-adjusted model, findings that were not attenuated with additional adjustment for fasting glucose [3].

In this issue of *Diabetologia*, Gerstein and colleagues from the case-control INTERHEART Study add to the accumulating data on HbA_{1c} and cardiovascular disease [4]. They compared HbA_{1c} levels in 6,761 patients with recent myocardial infarction to 9,019 age- and sex-matched controls and were able to adjust for all established cardiovascular risk factors. Results are provided for the entire cohort and for those with no history of diabetes. In agreement with the studies quoted above, a 1% higher HbA_{1c} level was associated with a 19% higher odds ratio of having suffered a myocardial infarction in the fully adjusted model. The results for those with no history of diabetes were similar, namely a 29% higher risk (age-, sex- and region-adjusted analysis only). There are other interesting

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findings in the data presented. The association between HbA_{1c} and history of myocardial infarction was stronger in those with no history of diabetes than in those with diabetes ($p=0.009$ for heterogeneity), which probably reflects the effect of glucose-lowering therapies and possibly other mechanisms. Interestingly, there was an interaction by age, with stronger associations between HbA_{1c} and myocardial infarction noted in younger patients (defined as men <65 and women <55 years of age). As the authors recognise in the article, the case–control design of the study precludes any conclusions on causation—and indeed prediction of cardiovascular disease—by dysglycaemia being drawn, and the inevitable substantial differences between the cases and controls mean that residual confounding cannot be dismissed. Nonetheless, the large number of participants in the INTERHEART study and the broad agreement of the results with those in other recent publications provides further evidence of an independent relationship between HbA_{1c} and coronary events in those with and without a history of diabetes.

While it is useful to conclude that there is an independent relationship between HbA_{1c} and cardiovascular disease, the more important issue is the determination of its clinical utility. Important goals for the future will be to establish the role, if any, of HbA_{1c} in cardiovascular disease prediction and to fully evaluate its use as a macrovascular surrogate marker for glucose lowering in those with and without diabetes. What value does HbA_{1c} add for vascular prediction? The study conducted by Simmons and colleagues, using data on the European Prospective Investigation of Cancer–Norfolk cohort, is one of the few to have addressed this question [5]. Over 8.5 years in the 10,295 participants, the area under the receiver operator characteristic curve (AUROC) for the Framingham risk score was not improved by the addition of HbA_{1c} for women (0.80 for analyses with and without HbA_{1c}) and was only minimally improved for men (0.72 without HbA_{1c} and 0.73 with HbA_{1c}). Similarly, data from the ARIC study mentioned earlier showed a statistically significant but limited improvement in prediction of cardiovascular disease with the addition of HbA_{1c} to multivariable models [3]. Addition of HbA_{1c} led to a modest improvement in the net reclassification index for coronary heart disease prediction but not for either ischaemic stroke or all-cause death. Furthermore, it had little impact in models already containing conventional cardiovascular risk factors and fasting glucose [3]. Recent trials of intensive glucose lowering in patients with diabetes have produced variable results, including those for all-cause mortality. However, the consistent finding of a reduction in coronary events in the intensively treated arms in the relevant trials [6] supports the general concept that HbA_{1c} monitoring is valuable for both micro- and macrovascular risk in diabetes. There are fewer trials of glucose lowering in those at risk of diabetes. In the recently published placebo-controlled Nateglinide and

Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, the risk of cardiovascular events was not reduced in those patients randomised to nateglinide who had impaired glucose tolerance plus either cardiovascular disease or cardiovascular risk factors (HR 0.94, 95% CI 0.82–1.09) [7]. HbA_{1c} levels were not determined in this study and clearly the hypothesis that glucose lowering (or the manipulation of related pathways, i.e. insulin resistance) may reduce cardiovascular risk in those without diabetes remains to be proven.

Assessment of HbA_{1c} levels will inevitably remain a key test in patients with diabetes. In the wider context, this has recently been recommended as the primary tool for the diagnosis of diabetes in the USA [8], though not elsewhere as yet, and it provides the attractive possibility of dovetailing diabetes and cardiovascular risk screening using non-fasting samples for lipid and HbA_{1c} analyses [9]. The case for HbA_{1c} as a useful marker of cardiovascular risk in those without diabetes now requires further detailed study to fully elucidate its predictive capability.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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