

Glycosylated Hemoglobin: Finally Ready for Prime Time as a Cardiovascular Risk Factor

More than 17 million people in the United States currently have diabetes, and this number is rapidly increasing (1). Affected individuals are at high risk for premature death as well as eye, kidney, nerve, cardiovascular, and other chronic diseases. Thus, the annual estimated costs of diabetes exceeded \$130 billion in 2002 (2)—an increase of greater than 30% since 1998 (3). This societal burden, and evidence that the diabetes epidemic is being fueled by our current lifestyle (4, 5), means that diabetes is now an urgent public health problem.

But diabetes is just the measured tip of a much larger “dysglycemic iceberg.” Diabetes is diagnosed when the fasting plasma glucose level is consistently 7 mmol/L or greater (≥ 126 mg/dL) or when the 2-hour plasma glucose level (after drinking a 75-g glucose load) is consistently 11.1 mmol/L or greater (≥ 200 mg/dL). These thresholds are much higher than the “normal” fasting and 2-hour mean glucose levels of 5.1 mmol/L (92 mg/dL) and 5.4 mmol/L (97 mg/dL), respectively (6). These levels were chosen because they effectively differentiated individuals at high risk for eye disease from individuals at low risk (7). They were not chosen on the basis of risk for cardiovascular disease; as such, there is no a priori reason to believe that they would differentiate people at high versus low risk for cardiovascular disease. Indeed, it is now clear that fasting or 2-hour glucose levels that are well below the diabetes cutoffs are cardiovascular risk factors (8, 9) and that a progressive relationship between glucose and cardiovascular risk extends from normal glucose levels right into the diabetes range with no clear lower threshold (9, 10).

Glycosylated hemoglobin is an easily measured biochemical marker that strongly correlates with the level of ambient glycemia during a 2- to 3-month period. As such, it (or hemoglobin A_{1c}, a specific type of glycosylated hemoglobin) reflects the usual daily fasting and postprandial glucose levels. Tests for glycosylated hemoglobin are also inexpensive and can be done at any time of day. The level of glycosylated hemoglobin is strongly linked to risk for incident eye, kidney, and nerve disease in people with type 1 and type 2 diabetes mellitus. Moreover, randomized trials have clearly shown that decreasing the glycosylated hemoglobin level reduces these risks (11, 12). It is therefore a valuable progressive and responsive risk factor for eye, kidney, and nerve disease in people with diabetes. Two studies reported in this issue carefully examine whether glycosylated hemoglobin is also a progressive risk factor for cardiovascular disease in people with diabetes, as well as in people without diabetes (that is, akin to the glucose level).

Selvin and colleagues (13) performed a careful meta-analysis of 10 cohort studies involving 7435 people with type 2 diabetes and 3 cohort studies involving 1688 people

with type 1 diabetes. For type 2 diabetes, a 1–percentage point absolute increase in glycosylated hemoglobin was associated with a significant 18% (95% CI, 10% to 26%) increase in the risk for coronary heart disease or stroke and a 28% increase in the risk for peripheral vascular disease. A similar but nonsignificant relationship was noted for type 1 diabetes. These data highlight the utility of the glycosylated hemoglobin level as a measure of risk for cardiovascular events in type 2 diabetes and suggest that it may also reflect cardiovascular risk in people with type 1 diabetes.

Khaw and colleagues (14) carefully analyzed the relationship of 1 hemoglobin A_{1c} measurement to incident cardiovascular events in a 6-year cohort study of 10 232 diabetic and nondiabetic men and women age 45 to 79 years. After adjustment for systolic blood pressure, cholesterol level, body mass index, waist-to-hip ratio, smoking, and previous myocardial infarction or stroke, there was a 21% increase in cardiovascular events for every 1–percentage point increase in hemoglobin A_{1c} level above 5% ($P < 0.001$). Similar relationships were observed for total mortality (22% for men [$P < 0.001$] and 28% for women [$P < 0.01$] per 1–percentage point increase in hemoglobin A_{1c} level). When both diabetes and the actual hemoglobin A_{1c} level were included in statistical models, only the hemoglobin A_{1c} level (and not diabetes) remained a significant predictor of incident cardiovascular events or death (implying that a hemoglobin A_{1c} level of 6.59% in a nondiabetic individual predicts a higher cardiovascular risk than a hemoglobin A_{1c} level of 5.5% in a well-controlled diabetic individual). Finally, even after individuals with a hemoglobin A_{1c} level of 7% or greater, diabetes, or heart disease were excluded, the increase in risk for coronary heart disease, cardiovascular disease, and total mortality for every 1–percentage point increase in hemoglobin A_{1c} was 40% ($P = 0.002$), 16% ($P = 0.08$), and 26% ($P = 0.02$), respectively.

What can we conclude from these 2 reports? First, they clearly prove that the glycosylated hemoglobin level is an independent progressive risk factor for incident cardiovascular events, regardless of diabetes status. They also provide a robust estimate of this relationship: Every 1–percentage point absolute increase above a clearly normoglycemic level predicts a 20% relative increase in the incidence of cardiovascular events. Second, these reports show that the glycosylated hemoglobin level can now be added to the list of other clearly established indicators of cardiovascular risk, such as blood pressure and cholesterol level. Thus, the presence or absence of diabetes is likely to become less important than the level of glycosylated hemoglobin in the assessment of cardiovascular risk (similar to the fact that a diagnosis of hyperlipidemia has become less important

than the level of low-density lipoprotein cholesterol). Third, these descriptive data highlight the relevance of several ongoing clinical trials that are directly testing the possibility that reducing glycosylated hemoglobin levels in both diabetic and nondiabetic persons may also reduce cardiovascular risk.

Finally, as noted by Khaw and colleagues (14), very small shifts in the general population's average hemoglobin A_{1c} level (for example, 0.1% to 0.2%) could dramatically affect the future incidence of cardiovascular disease. Unfortunately, these small population shifts are happening now. The increasing prevalence of diabetes means that the average hemoglobin A_{1c} level of the much larger nondiabetic population is probably increasing as well. This dysglycemia epidemic may therefore be the harbinger of a future epidemic of cardiovascular disease.

But this epidemic is not inevitable—it may be thwarted if we take action now. We know that lifestyle changes can dramatically reduce the incidence of diabetes and slow the hemoglobin A_{1c} increase in both nondiabetic and diabetic individuals (15–17). Broadly adopted lifestyle changes should therefore reduce diabetes-related eye, kidney, and nerve disease. Regardless of whether these lifestyle changes are ultimately proven to reduce cardiovascular disease in our society, public health approaches to facilitate them urgently need to be implemented. Structural changes to our society that reduce caloric intake and increase physical activity today will lower hemoglobin A_{1c} levels and reduce society's rates of diabetes, the consequences of diabetes, and possibly cardiovascular disease tomorrow. If we wait 5 years for the results of the ongoing cardiovascular trials before acting, and the results are positive, we may have to apply them far too late and in far too many individuals.

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