Glycaemia and heart failure in diabetes types 1 and 2

In recent years, major interest has developed in the prevention of heart failure as a new endpoint in cardiovascular management. In The Lancet, Marcus Lind and colleagues report a carefully done study of the benefits of optimum glycaemic control in type 1 diabetes. The data clearly show that the risk of heart failure could be lessened by tight control of glycated haemoglobin A1c (HbA1c). Thus, HbA1c has a curvilinear relation with the incidence of new heart failure during 9 years of follow-up. In an earlier study of intensive diabetes treatment, cardiovascular endpoints included death from cardiovascular disease, non-fatal myocardial infarction, stroke, confirmed angina, or the need for coronary revascularisation. However, at that time, heart failure was not often used as a major cardiovascular endpoint in type 1 diabetes.

Lind and colleagues’ study, which had a larger sample than that of Nathan and colleagues, has two key findings. First, of the 20 985 patients with type 1 diabetes who were followed up for 9 years, 635 (3%) needed to be admitted to hospital for heart failure, with an incidence of 3·38 events per 1000 patient-years. Second, patients with HbA1c of at least 10·5% had a four times greater risk of heart failure than did those with HbA1c of less than 6·5%. Even though the incidence of heart failure was low, it is clearly an important complication of type 1 diabetes. For optimum prevention of such heart failure, the mechanisms by which poor glycaemic control promotes heart failure need to be considered.

The metabolic background of heart failure in type 1 diabetes can be summarised as follows. Patients with type 1 diabetes and poor glycaemic control (mean HbA1c of 8·4%) have an abnormally high concentration of circulating free fatty acids, with increased myocardial uptake of free fatty acids and decreased myocardial uptake of glucose. The result is mitochondrial oxygen wasting and generation of excess reactive oxygen species. In a series of patients with poorly controlled type 1 diabetes who were followed up for about 2 years, Carugo and colleagues reported increasing signs of left ventricular failure with a falling ejection fraction and dilating heart. Thus, in patients with poorly controlled type 1 diabetes, as in those included in Lind and colleagues’ study, a small proportion have a high probability of diabatic cardiomyopathy.

Is there also a specific diabetic cardiomyopathy in type 2 diabetes? Yes, because data now strongly suggest the presence of a specific diabetic cardiomyopathy, with the emphasis on lipid loading and diastolic dysfunction. First, increased myocardial staining for triglycerides has been identified both in the explanted hearts of patients with type 2 diabetes who had cardiac transplantation for non-ischaemic cardiomyopathy and in the hearts of an animal model. Second, cardiac steatosis, imaged by localised ¹H magnetic resonance spectroscopy, has been seen in patients with abnormal glucose tolerance and impaired left ventricular function. In that study, lipid abnormalities were linked to impaired early left ventricular filling. Associations between increased myocardial triglyceride content and impaired left ventricular diastolic function are independent of age, body-mass index, heart rate, visceral fat, and diastolic blood pressure. Such findings lay the basis for the recognition of diabetic cardiomyopathy with impaired diastolic function in type 2 diabetes. However, in practice, coronary artery disease will provide a much stronger association between type 2 diabetes and heart failure.

How tightly should glycaemia be controlled in diabetes? The clear message from Lind and colleagues’ paper is that tight control of glycaemia in type 1 diabetes is essential (panel), especially now that they have shown that such control can prevent heart failure besides other aspects of cardiovascular disease. In the future, even...

Panel: Differing results of aggressive glucose lowering in diabetes

**Type 1 diabetes**
- Lowering glucose reduces cardiovascular complications, including heart failure
- Poor glycaemic control leads to increased circulating and myocardial uptake of free fatty acids, increased formation of toxic reactive oxygen species, and risk of cardiomyopathy

**Type 2 diabetes**
- Narrow window of optimum low concentrations of glucose
- Mechanisms of heart failure extend beyond glycaemia
- Increased myocardial triglyceride (steatosis)
- Overall, data support presence of a diabetic cardiomyopathy with diastolic dysfunction
- In practice, most heart failure is associated with coronary heart disease
- Needs multifactorial intervention
established type 1 diabetes cardiomyopathy might be rescued by gene-activated prosurvival paths, as shown in a mouse model. Only in developing countries, where tight control is often not feasible, could less strict control be acceptable for type 1 diabetes.

Does the need for tight glycaemic control also extend to type 2 diabetes? Here the problem is not insulin deficiency but insulin resistance, which needs multifactorial management (panel). Such management of patients with type 2 diabetes leads to a long-term reduction in mortality, even without tight glycaemic control.11 Truly whether a test for the control of diabetes, could also be used as a convenient laboratory test (eg, non-fasting), which reflects long-term hyperglycaemia over the preceding 2–3 months and is a proven measure of diabetes-related complications, should diagnose the disease more successfully than a single measurement of blood glucose.2 An international expert committee, after considering data on association of HbA1c and retinopathy, recommended that diabetes be diagnosed when HbA1c is more than 48 mmol/mol (>6.5%), provided this assay is done in a standard ised laboratory.3

HbA1c and blood glucose for the diagnosis of diabetes

Traditionally, blood glucose values (fasting, 2-h postprandial, or after a 75 g oral glucose load) have been used to diagnose diabetes, but the cutoff for diagnosis has been revised several times in the past few decades. For about a decade, it has been debated whether measures of glycated haemoglobin (HbA1c), a standard monitoring test for the control of diabetes, could also be used as diagnostic criteria.12 Those who support this idea argue that a convenient laboratory test (eg, non-fasting), which reflects long-term hyperglycaemia over the preceding 2–3 months and is a proven measure of diabetes-related complications, should diagnose the disease more successfully than a single measurement of blood glucose.2 An international expert committee, after considering data on association of HbA1c and retinopathy, recommended that diabetes be diagnosed when HbA1c is more than 48 mmol/mol (>6.5%), provided this assay is done in a standardised laboratory.3

Further, HbA1c of 39–46 mmol/mol (5.7–6.4%) was stated for the identification of prediabetes (an increased risk for diabetes).4 The recommendation made sense in many other aspects: measures of HbA1c might indicate prevalence of retinopathy better than fasting plasma glucose, and HbA1c has low pre-analytic instability and is relatively unaffected by acute situations. In particular, day-to-day and within-person variability of HbA1c.

I declare that I have no conflicts of interest.


Lionel H Opie
Hatter Cardiovascular Research Institute, Department of Medicine, University of Cape Town Faculty of Health Sciences and Groote Schuur Hospital, Observatory, Cape Town 7925, Western Cape, South Africa
lionel.opie@uct.ac.za