Diabetes and the heart

Cardiovascular (CV) disease is the main cause of mortality and morbidity in patients with diabetes. In those with type 2 diabetes there is a 2–4-fold increased risk of CV events and mortality (Stamler et al, 1993). Modifiable factors associated with increased risk are well established: higher circulating levels of low density lipoprotein-cholesterol (LDL-C), low high density lipoprotein-cholesterol (HDL-C), smoking, obesity, hypertension and microalbuminuria. The incidence of coronary events increases with the degree of hyperglycaemia but the effect starts in the non-diabetic glucose range (Coutinho et al, 1999). Thus, patients with impaired glucose tolerance have high rates of coronary events similar to those seen in patients with type 2 diabetes. The early and late mortality of myocardial infarction (MI) in diabetes is double that of non-diabetic individuals.

CORONARY ARTERY DISEASE AND LIPIDS

Over the last 10–15 years much information has become available on the multiple mechanisms through which diabetes has its adverse effect on the heart. The development of atheromatous disease in large vessels is initiated by the overexpression of leucocyte adhesion molecules on the endothelial cell luminal surface. Production of chemokines and proinflammatory cytokines promotes migration of circulating monocytes into the arterial intima where they differentiate into a macrophage phenotype. These macrophages take up LDL-C.

Lipid-laden macrophages become foam cells which progress to form atheromatous plaques. The macrophages are involved in various aspects of atherosclerosis progression. They promote further leucocyte accumulation, smooth muscle proliferation and extracellular matrix remodelling. They release prothrombotic substances and inflammatory cytokines including proteases which weaken the fibrous plaque cap. Glycation and oxidation of LDL increase LDL uptake into these macrophages through a scavenger pathway. Oxidized LDL increases differentiation of monocytes into macrophages. Thus a number of biochemical and cellular changes resulting from glycation and oxidation of LDL contribute to the increased rate of macrovascular atheromatous disease in diabetes.

Other changes in circulating lipoproteins also contribute to cardiac disease in diabetes. HDL promotes reverse cholesterol transport: the carriage of cholesterol from the periphery back to the liver. This process is beneficial in that it stimulates hepatic metabolism and biliary excretion of cholesterol. HDL also prevents oxidation of LDL, and inhibits adhesion molecule expression and monocyte uptake. HDL levels tend to be low in patients with type 2 diabetes where the common lipid profile comprises low HDL-C, high triglyceride levels and highly atherogenic small dense LDL particles. This is the result of the increased very low density lipoprotein secretion from the liver and increased hepatic lipase activity that occurs in insulin resistant states. The same adverse lipid profile is found in subjects with impaired glucose tolerance indicating that obtaining good glycaemic control of diabetes to current targets (haemoglobin A_{1c} 7.0%) will not abolish the increased risk of coronary heart disease in diabetes.

MICROVASCULAR DISEASE

Small vessel disease in diabetes (diabetic microangiopathy) has its classical manifestations in retina, kidney and peripheral nerve. However, the microangiopathic process most probably occurs in all organ systems including the heart and is likely to contribute to worse cardiac outcomes in diabetic patients. Indirect evidence for an effect of small vessel disease comes from the finding that patients with retinopathy have worse cardiac outcome than those without. It is also argued that there is a specific diabetic cardiomyopathy which is a form of restrictive cardiomyopathy causing diastolic dysfunction and unlikely to be caused by microvascular disease. It is primarily metabolic rather than vascular in aetiology (Bell, 1995).

CARDIAC AUTONOMIC NEUROPATHY

Although often asymptomatic, cardiac autonomic neuropathy can be demonstrated in one sixth of patients with diabetes (O'Brien et al, 1986). A simple battery of tests that measure heart rate and blood pressure responses is available for this purpose. MI may occur without pain or with non-specific features of ill health in such patients. Up to 40% of diabetic patients at first presentation have evidence of a previous MI. Diabetic patients with autonomic neuropathy may die a sudden and unexpected death, often at night (hence the term 'dead in bed syndrome').

To try and identify those at risk, studies have investigated possible causes of cardiac arrhythmia. A long electrocardiographic QT interval predisposes to ventricular arrhythmia (torsade de pointes ventricular tachycardia). Diabetic cardiac autonomic neuropathy is associated with a long QT interval (Veglio et al, 1999). A long QT interval in diabetes is a predictor of mortality. The QTc dispersion (interlead variability) reflects regional differences in myocardial pathology and may be a better index of mortality risk.

Tattersall and Gill (1991) described 22 cases of unexplained sudden death in diabetic patients which occurred at night or early morning. Hypoglycaemia seemed to be a major factor since few had documented microvascular complications or neuropathy. Hypoglycaemia is arrhythmogenic and has been shown to prolong the QTc interval (Marques et al, 1997). Thus, hypoglycaemia may contribute to cardiac arrest in an uncertain proportion of cases.

As regards management of patients with autonomic neuropathy and long QT interval, there is some evidence

that they may benefit specifically from angiotensin converting enzyme inhibitor or beta-blocker therapy.

ENDOTHELIAL DYSFUNCTION

The vascular endothelium is an important source of a number of locally active substances, including nitric oxide, which influence vascular smooth muscle tone and control perfusion. Endothelial dysfunction is often present in type 2 diabetes. This is likely to adversely affect organ perfusion and contribute to impaired outcomes.

Endothelial dysfunction occurs early in atherosclerotic disease in both diabetic and non-diabetic individuals. Both hyperglycaemia and insulin resistance have been implicated in the genesis of endothelial dysfunction. The vasodilator action of insulin is mediated by nitric oxide through stimulation of endothelial nitric oxide synthase. A defect in post-receptor insulin signalling (activation of PI-3 kinase) could be responsible for both insulin resistance and endothelial dysfunction, although this remains to be confirmed.

Hyperglycaemia alone cannot be responsible for endothelial dysfunction because endothelial dysfunction has been demonstrated in normoglycaemic states. Hyperglycaemia has a toxic effect on the endothelium and vascular cells through overproduction of superoxide by the mitochondrial electron transport chain. This important biochemical abnormality is common to each of the four widely studied mechanisms of hyperglycaemic microvascular injury: sorbitol generation, increased hexosamine pathway flux, activation of protein kinase C isoforms and formation of advanced glycation end-products (Brownlee, 2001). Hyperglycaemia generates oxidative species. Cytosolic NADPH (nicotinamide adenine dinucleotide phosphate hydrogen), which would quench these molecules and reduce their toxicity either directly or via generation of reduced glutathione (the main intracellular antioxidant), is depleted, allowing oxidative stress to cause tissue damage.

The atherogenic lipid profile of type 2 diabetes (see above) may have a toxic effect on the endothelium since LDL size correlates with degree of endothelial dysfunction. Insulin resistance has also been linked with other mechanisms contributing to atherothrombotic coronary disease. Insulin is an acute vasodilator but may raise blood pressure by promoting renal tubular sodium retention and stimulating the sympathetic nervous system. Insulin resistance is associated with hypertension, increased levels of plasminogen activator inhibitor 1, raised levels of von Willebrand factor (a marker of endothelial dysfunction) and elevated fibrinogen. All of these changes are prothrombotic.

INTERVENTION

Much can be done to prevent coronary events in diabetic patients. Major randomized studies confirm the benefits of lowering LDL-C through inhibition of HMG-CoA (hydroxy-methyl-glutaryl Co A) reductase with statin therapy. Initial studies included limited numbers of diabetic patients but recent work indicates that the benefits in diabetes may exceed those in the non-diabetic population. The Multiple Risk Factor Intervention Trial (MRFIT) study (Stamler et al, 1993) and data from Framingham indicate that low HDL-C is an independent risk factor for CV events.

Increases of around 10% in HDL-C levels can be achieved with fibrate therapy or the more potent statins (atorvastatin, rosuvastatin). Niacin has a greater effect on HDL-C although facial flushing is a problem. Drugs are now in development which will provide substantially greater increases in HDL-C by inhibiting the action of cholesteryl ester transfer protein (Brousseau et al, 2004). Physical exercise improves CV function and increases HDL-C. The antiplatelet action of aspirin reduces coronary events in diabetes by 25%. Thrombolytic therapy in acute MI is equally effective in patients with diabetes but saves more lives because of the greater absolute mortality in diabetes. The benefits of stopping smoking are substantial even after many years. Last but not least, reducing hyperglycaemia is beneficial but the UK Prospective Diabetes Study clearly showed that this has more effect on the microvascular complications of diabetes than the macrovascular endpoints. HM

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KEY POINTS

- Ischaemic heart disease is the leading cause of mortality and morbidity in patients with diabetes.
- The mechanisms underlying coronary atherosclerosis and the other factors which are responsible for poor outcomes in diabetes are being elucidated.
- An increasing range of interventions based on knowledge of the underlying pathophysiology will be coming into clinical practice.