Diabetes and the heart

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Diabetes mellitus adversely affects the pathology, presentation and outcome of patients with coronary artery disease. Knowledge of the risks and benefits of medical and mechanical therapies particular to diabetic patients is useful in the optimal management of diabetic heart disease.

Much of the excess cardiac morbidity and mortality among diabetic patients is attributable to accelerated atherogenesis. Young diabetics are at particular risk and, by the age of 50 years, 33% of those requiring insulin have died from coronary heart disease. Indeed, 75% of all deaths in patients with diabetes are from this cause (Bierman, 1992). While aggressive euglycaemic treatment diminishes the microvascular complications of diabetes, it has been more difficult to show any significant impact on macrovascular disease in general and coronary heart disease in particular.

MECHANISMS OF ACCELERATED ATHEROGENESIS

In diabetic individuals, conventional risk factors (e.g. smoking, hypertension and dyslipidaemia) increase the risk of coronary heart disease in much the same way as in non-diabetics. Thus, the fact that hypertension and dyslipidaemia are more prevalent in diabetes must itself contribute to the heightened risk of coronary heart disease in this group. The contribution is only partial, however, and it is estimated that these conventional risk factors account for less than 25% of the excess risk (Kannel and McGee, 1979).

In the Multiple Risk Factor Intervention Trial (MRFIT) study, for example, in which 361 662 men were followed up for 6 years, the mortality risk in both diabetic and non-diabetic individuals increased almost linearly with serum cholesterol (Stamler et al, 1993). However, at any given cholesterol level, diabetics had a 3–4-fold excess risk (*Figure 1*). It is now recognized that much of this excess risk is a consequence of accelerated atherogenesis, which in turn is attributable to multiple factors.

Dyslipidaemia

Oxidative modification of low density lipoprotein (LDL) is recognized as the central event that initiates and propagates atherosclerosis. Total cholesterol levels are not significantly higher in diabetic than non-diabetic individuals. However, it appears that the atherogenicity of LDL and very low density lipoprotein (VLDL) among diabetics is enhanced (Feher and Elkeles, 1999). Alterations in LDL include small dense particles, glycosylated particles, oxidised and desialiated particles, increasing the affinity of the endothelium towards the lipoprotein and increase its atherogenic potential in situ after uptake into the vessel wall (Taskinen, 1992).

Hypertriglyceridaemia is an important feature of diabetes and there is no longer any doubt that it represents an important risk factor for coronary artery disease (Hokanson and Austin, 1996). Patients with diabetes also have high lev-

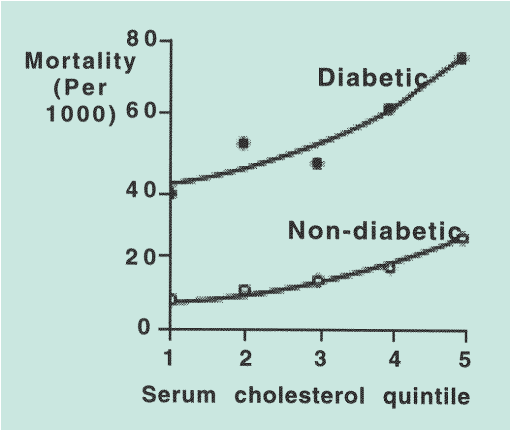

Figure 1. Coronary heart disease (CHD) mortality by cholesterol quintiles in the Multiple Risk Factor Intervention Trial (n=361 662) during 6 years follow-up. Data for diabetic and non-diabetic men are shown.

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els of VLDL cholesterol which is atherogenic, while levels of protective high density lipoprotein (HDL) tend to be lower.

Procoagulant factors

Acute coronary syndromes, including unstable angina and myocardial infarction, usually occur in response to rupture of an atheromatous plaque which provides the stimulus for intracoronary thrombosis (Davies and Thomas, 1983). In diabetes, platelet aggregability is increased as are the activities of multiple coagulation factors (Bierman, 1992). These abnormalities tend to exaggerate the thrombotic response to plaque rupture, increasing the plaque burden and the risk of myocardial infarction. Increased plasma concentrations of PAI-1 antagonizes endogenous lytic activity, further encouraging occlusive thrombus formation in coronary arteries.

Insulin resistance and hyperinsulinaemia

The syndrome of insulin resistance, particularly common in type 2 diabetes, is characterized by hyperinsulinaemia together with the dyslipidaemia described previously. Hyperinsulinaemia appears to be a risk factor for atherogenesis by promoting smooth muscle proliferation in the vessel wall (Bierman, 1992). There is a growing consensus that the susceptibility of South Asians to coronary artery disease is largely attributable to the insulin resistance syndrome (McKeigue et al, 1993).

Advanced glycation of proteins in plasma and the arterial wall

Chronic hyperglycaemia leads to glycosylation of proteins by enzymatic and non-enzymatic pathways (*Figure 2*). Advanced glycation end products (AGEs) react with a specific receptor (RAGE) at the vascular endothelium, the expression of which is increased considerably in diabetes (Chappey et al, 1977). The AGE–RAGE interaction increases vascular endothelial production of superoxide anion and other oxidative products with important consequences. These include LDL oxidation, stimulation of monocyte adherence to the blood vessel (one of the earliest events in the atherogenic process), increased vascular permeability (allowing accelerated passage of macromolecules into the vessel wall), increased membrane expression of tissue factor (enhancing the procoagulant state), increased endothelin secretion and inactivation of nitric oxide (promoting vasoconstriction), and increased growth factor secretion (encouraging proliferation of vascular smooth muscle cells). Thus the AGE–RAGE interaction at the vascular endothelium is now regarded as a key factor in the accelerated atherogenesis of diabetes.

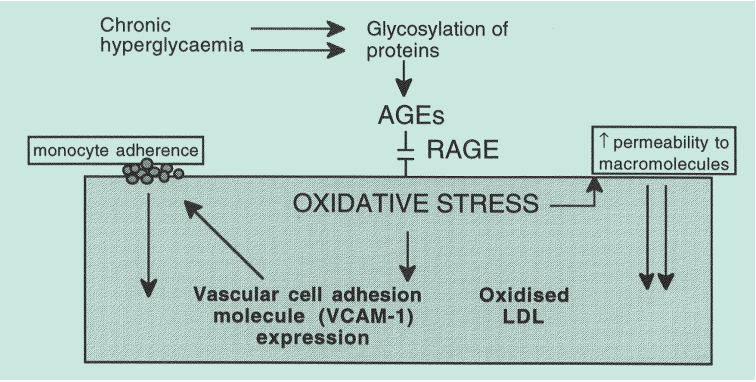

Figure 2. Advanced glycation end-products (AGE) and accelerated atherogenesis in diabetes. Reactions within the vascular endothelium (shaded box) are shown. Note that monocyte adherence is on the luminal surface of the endothelium. RAGE = receptor for AGE

Recent data indicate that reducing vascular exposure to AGEs by injection of soluble RAGE (which mops up circulating AGEs) suppresses accelerated atherosclerosis in diabetic mice, providing grounds for optimism about future clinical applications (Park et al, 1998).

ANGINA AND SILENT ISCHAEMIA

Accelerated atherogenesis inevitably predisposes diabetic individuals to angina and to acute coronary syndromes. However, the perception of angina in diabetes may be impaired as a result of autonomic neuropathy such that diabetic patients may take longer to experience symptoms after the onset of ischaemic electrocardiographic changes (prolonged anginal perceptual threshold; *Figure 3* (Ambepityia et al, 1990)) or may experience no symptoms at all (silent ischaemia (Nesto et al, 1988)).

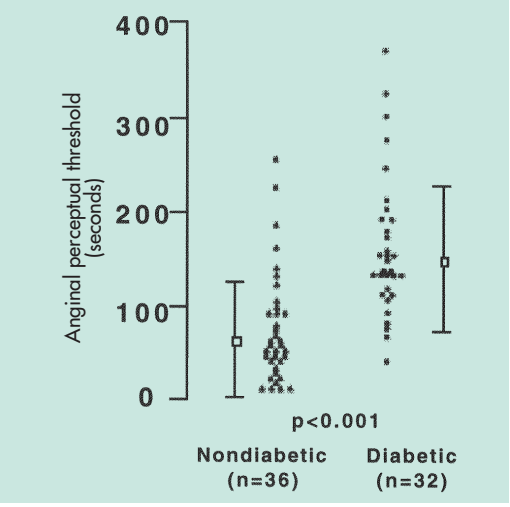

Figure 3. Anginal perceptual thresholds in diabetic and non-diabetic patients with coronary artery disease. Note that the thresholds are prolonged in diabetic patients.

In diabetics with silent exertional ischaemia, we have shown that autonomic function (whether measured by conventional bedside techniques or by heart rate variability) is consistently impaired compared with diabetics who experience angina (Marchant et al, 1993). Similarly, prolongation of the anginal perceptual threshold in diabetes correlates with autonomic function (Ambepityia et al, 1990), and as the heart rate response to the Valsalva manoeuvre deteriorates so the anginal perceptual threshold becomes more prolonged. Indeed anginal perceptual threshold is a major determinant of exercise capacity in diabetes, its prolongation depriving the patient of the signal to stop exercising as the heart becomes ischaemic (Ranjadayalan et al, 1990). This is potentially dangerous if it predisposes to ischaemic cardiac arrhythmias, and may account for the relationship between diabetic autonomic neuropathy and sudden death (Ewing et al, 1980).

ACUTE MYOCARDIAL INFARCTION

Epidemiology

Framingham data have shown that the risk of acute myocardial infarction is 50% greater in diabetic men and 150% greater in diabetic women than in non-diabetic individuals (Kannel and McGee, 1979). Indeed, acute myocardial infarction accounts for 30% of all diabetic deaths. It has long been recognized that diabetics are prone to 'silent' myocardial infarction and this presumably reflects impaired perception of ischaemic cardiac pain caused by autonomic neuropathy. Thus, in diabetes, acute myocardial infarction is silent or presents with atypical symptoms in 32–42% of cases compared with 6–15% of non-diabetic infarcts (Jacoby and Nesto, 1992).

Both the circadian and the seasonal rhythms of acute myocardial infarction are attenuated or absent in diabetic individuals in whom the incidence of infarction does not show a clear peak in the morning hours or the winter months (Sayer et al, 1997). The reasons for this are not clear but because these rhythms are largely driven by parallel rhythms of autonomic activity it is reasonable to assume that their absence is yet another reflection of diabetic autonomic neuropathy. The clinical significance of this is unclear but is likely to be unfavourable.

Complications

All the major complications of myocardial infarction occur more commonly in diabetes, particularly stroke and heart failure (*Figure 4*) (Jacoby and Nesto, 1992). Indeed, nearly 50% of diabetics with myocardial infarction develop heart failure compared with under 30% of non-diabetics. Coronary re-occlusion, re-infarction and decreased compensatory hyperkinesia of the non-infarct territory are more common in diabetics (Woodfield et al, 1996), contributing towards left ventricular dysfunction. Since heart failure is one of the major determinants of outcome, it is little surprise that both hospital and long-term mortality is increased in patients with diabetes.

Acute treatment

All diabetic patients with acute myocardial infarction should receive insulin and glucose infusions, based on the findings of the DIGAMI investigators who showed that this significantly increased survival in these high-risk patients (*Figure 5*) (Malmberg et al, 1995). In other respects the treatment of diabetic myocardial infarction should be the same as in non-diabetic patients. The Fibrinolytic Therapy Trialists' overview of thrombolytic therapy demonstrated a greater absolute mortality benefit in diabetics compared to non-diabetics (3.7% *vs* 2.1%; FTT, 1994). Beta-blockers have also been shown to provide quantitatively greater protection against recurrent infarction and death in diabetic than non-diabetic patients recovering from myocardial infarction (Malmberg et al, 1989).

Secondary prevention

Two recent trials comparing usual with optimal blood pressure control have demonstrated mortality benefits in diabetic patients. The hypertension optimal treatment study (HOT) (Hansson et al, 1998) demonstrated a 66% relative risk reduction on cardiovascular mortality in 1 500 diabetics, and this benefit was greater than in non-diabetics. Similarly the United Kingdom

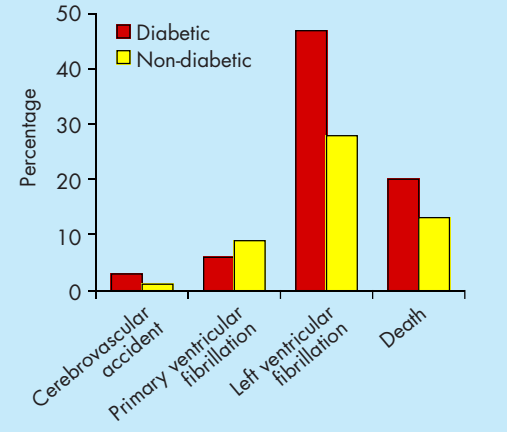

Figure 4. Complications of acute myocardial infarction in 1829 patients. These are unpublished data from the Newham coronary care unit database. *** P<0.001, ** P<0.01, * P<0.05.

prospective diabetes study (UKPDS) demonstrated benefits of tight glycaemic and optimal blood pressure control in type 2 diabetics (UKPDS, 1998a, 1998b). The target diastolic blood pressure for diabetics is ≤80 mmHg.

Angiotensin-converting enzyme (ACE) inhibitors have a special role in diabetic patients, not only because of the heightened risk of left ventricular failure but also because of renal glomerular disease, both of which are useful targets for ACE inhibition. Diabetic patients with average or above average cholesterol levels also obtain greater benefit from cholesterol reduction with statin therapy (Pyorala et al, 1997; Goldberg et al, 1998).

REVASCULARIZATION IN PATIENTS WITH DIABETES

Coronary bypass surgery

Diabetic coronary artery disease is typically more diffuse than in non-diabetics, involving not only the proximal coronary system but also more distal segments. When feasible, therefore, coronary bypass surgery is technically more challenging and the results tend to be less good. Indeed, diabetes has long been recognized as one of the major independent predictors of long-term mortality after surgery (Adler et al, 1986). Many surgeons avoid the use of bilateral internal mammary grafts in diabetic patients because of an increased risk of sternal wound dehiscence. The results of angioplasty also tend to be less good in diabetic compared with non-diabetic patients. Again, diffuse disease makes for technically more difficult angioplasty procedures and, in addition, restenosis rates are consistently higher (Carrozza et al, 1993).

Angioplasty

In the Bypass Angioplasty Revascularisation Investigation (BARI) trial (1996), sub-group analysis showed that patients with diabetes randomized to angioplasty had a significantly worse 5-year survival than those randomized to bypass surgery. The investigators concluded that for most diabetics requiring revascularization coronary bypass surgery was preferable to angioplasty. Nevertheless, a recent presentation at the American Heart Association meeting (November 1998) reported a subgroup analysis from the EPISTENT trial (1998). The findings indicated that angioplasty and stenting combined with infusion of abciximab (an inhibitor of platelet aggregation through antagonism of the glycoprotein IIb/IIIa receptor on the platelet surface membrane) improves the long-term outcome in diabetic patients substantially, with a 6-month incidence of ischaemic endpoints comparable to that achieved in non-diabetic patients. The data suggest, therefore, that stenting and IIb/IIIa receptor blockade may have an important role in diabetic angioplasty.

HEART FAILURE: DIABETIC CARDIOMYOPATHY

Over 20 years ago, the Framingham investigators reported that the annual incidence of heart failure in diabetic men and women was substantially greater across all age groups than in non-diabetic individuals, even after controlling for underlying coronary and rheumatic heart disease (Kannel et al, 1974). They concluded that diabetes itself might predispose to heart failure independently of concurrent coronary or rheumatic heart disease. At about the same time post-mortem reports appeared in diabetics with heart failure describing completely normal coronary arteries and heart valves (Rubler et al, 1972). Histology, however, revealed major abnormalities including myocardial fibrosis, alterations in myocardial capillary basement membrane and microaneurysm formation.

In further studies, analysis of systolic time intervals provided evidence of both systolic and diastolic left ventricular dysfunction in diabetic individuals in whom there was no clinical evidence of coronary artery disease (Zarich and Nesto, 1989). Taken together these epidemiological, pathological and haemodynamic data have provided the basis for diabetic cardiomyopathy as a diagnostic entity. However, although the concept of diabetic cardiomyopathy is now well established it cannot be regarded as proven.

The epidemiological data summarized above may well have been distorted by co-existing but

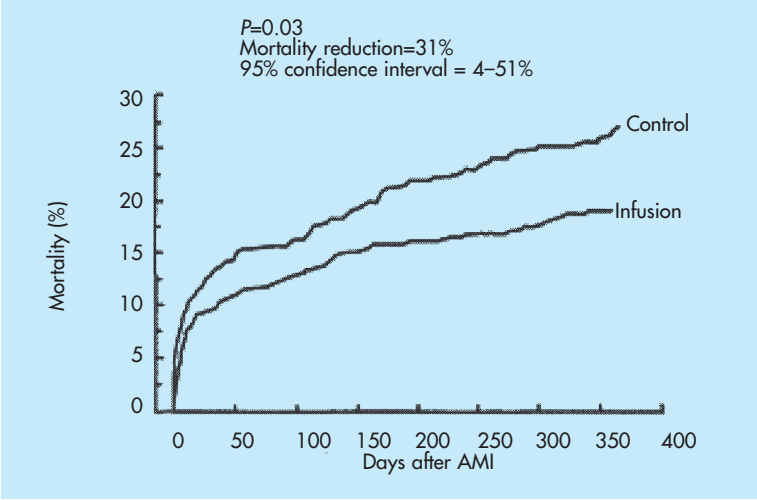

Figure 5. Mortality during first 12 months after acute myocardial infarction (AMI) in diabetic patients randomized to insulin and glucose infusion (n=306) or control (n=314).

asymptomatic coronary disease in many of the diabetic patients and the pathological data do not rule out the possibility of cardiomyopathy as a coincidental diagnosis. Nevertheless, there is no doubt that heart failure is particularly common among patients with diabetes and, notwithstanding the validity of diabetic cardiomyopathy, most cases are the result of coronary heart disease. HM

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KEY POINTS

- Coronary disease is more common in diabetic patients.
- Beware silent ischaemia: diabetic patients often present with left ventricular failure secondary to silent myocardial ischaemia or infarction.
- Diabetic patients with coronary disease benefit more from all medical treatments, especially beta-blockade.
- Diabetic patients presenting with acute myocardial infarction should receive intravenous insulin and glucose infusions, in addition to standard therapy.
- Diabetic patients have increased complications from revascularization.
- Diabetic patients with coronary disease warrant tight diabetic, blood pressure and lipid control.
- Patients with acute coronary syndromes with incidental raised glucose levels should be screened for diabetes.