Coronary heart disease in diabetes mellitus – antecedents and associations

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Introduction

Coronary heart disease and diabetes mellitus are closely linked.¹ In general, the risk of coronary heart disease is increased 2- to 6-fold in diabetic subjects.^{2–4} In countries such as the United Kingdom, where atherosclerotic vascular disease remains common, diabetes frequently accompanies coronary heart disease, and is often undiagnosed in its early stages.^{5,6} In addition, diabetic myocardial infarction is associated with a poorer prognosis and twice the mortality of non-diabetic cases.^{5,7} In countries such as Japan, where, in general, coronary heart disease is much less common, the presence of diabetes still confers at least double the risk of a subsequent myocardial infarction.⁸

It is important to recognize that additional causes of cardiac disease may be present in diabetes which compound the effects of coronary atheroma. Hypertension and cardiac microangiopathy are recognized complications of diabetes, and these in part explain why cardiac failure is observed with disproportionate frequency in diabetic patients.⁹ Autonomic cardiovascular dysfunction may compromise inotropic and chronotropic function and postural hypotension might 'tip the balance' in cases of critical coronary ischaemia. Indeed, the development of symptomatic autonomic neuropathy is associated with a grave prognosis, with cardiovascular causes of death frequently responsible for the 60% 5-year mortality rates.¹⁰ Less commonly, antecedents of both diabetes and cardiac disease, such as haemochromatosis and endocrine pathology (thyrotoxicosis, acromegaly and pheochromocytoma), or the coexistence of other conditions and their treatment (such as corticosteroids and steroid treatment), may complicate the issue.

In trying to elaborate mechanisms which might explain why coronary heart disease is so common in diabetes, it is worth bearing in mind the complex nature of atherosclerosis and its thrombotic

sequelae. Diabetes may be implicated at different stages of the process, from the initial intimal injury, to the point of smooth muscle proliferation, development of the mature atheromatous plaque, and, finally, vessel occlusion by thrombus.

At present, the prevention of cardiovascular disease has been the focus of much attention. The concept of 'risk factors' (or markers) has been applied to the general population to allow detection and treatment of individuals at 'high risk'. Tobacco consumption, and elevated levels of blood pressure and concentrations of serum cholesterol are the clearest modifiable risk factors, although in themselves they are relatively poor discriminators of individual risk.¹¹ In fact, the majority of cases of myocardial infarction have serum cholesterol concentrations less than 6.5 mmol/l,¹² although active lipid-lowering treatment is usually only advocated above this level.¹³ Initiatives to reduce the average serum cholesterol of the population would require major central government funding which does not appear forthcoming at present. We therefore need to identify those at highest risk with greater accuracy.

The presence of diabetes itself enhances the cardiovascular risk attributed to smoking, blood pressure or cholesterol 2-fold, for reasons that are not fully apparent.^{14,15} The prevalence of hypertension appears greater amongst the diabetic population.¹⁶ Previous epidemiological studies have shown that blood pressure and serum cholesterol, but not blood glucose, are predictors of vascular events in diabetes.^{17,18} There is also increasing recognition of the fact that serum triglyceride concentrations and proteinuria are independent risk markers of cardiovascular disease in glucose intolerant populations, in whom they may be better predictors than serum cholesterol.^{17,19–21}

Dyslipoproteinaemia in diabetes

Disturbed lipid metabolism in diabetes, therefore, appears of undoubted importance to coronary

heart disease, although, as yet, there are no prospective intervention studies which have examined the impact of correction of dyslipoproteinaemia on the incidence of diabetic macrovascular disease.

Lipid metabolism in diabetes is complex, although often over-simplified by reviewers. In comparison to matched non-diabetic populations, the dominant abnormality in both insulin dependent (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) is hypertriglyceridaemia.^{22,23} The prevalence of hypercholesterolaemia [predominantly increased low density lipoprotein (LDL) cholesterol] is no greater in IDDM and only marginally greater in NIDDM.²³ However, in the United Kingdom this will of course mean that the prevalence of hypercholesterolaemia (> 6.5 mmol/l) in diabetic clinics is considerable (27% in IDDM, and up to 50% in NIDDM).^{22,23} Levels of high density lipoprotein (HDL) cholesterol in NIDDM tend to be the same or lower than matched non-diabetic subjects, whereas in IDDM levels are, on average, equivalent or higher.²³ There is increasing evidence that altered lipoprotein composition is an intrinsic component of both IDDM and NIDDM.²⁴⁻²⁸

It is important to recognize that this basic pattern is subject to a host of influences. Male gender, Caucasian ethnicity, increasing age and body mass, lack of exercise, diets with a high saturated fat content or tobacco consumption all tend to compound the 'atherogenic lipid profile' by leading to further increases in LDL cholesterol and/or reductions in HDL cholesterol.^{22,29,30}

Perhaps most specific is the effect of poor blood glucose control in either NIDDM or IDDM. Effective treatment by any means will lead to reductions in very low density lipoprotein (VLDL) and LDL and increases in HDL lipid content.^{23,26,31} Insulin therapy will almost always lower serum lipids in poorly controlled IDDM or NIDDM, provided the dosage is enough to enable a reduction in hyperglycaemia. Abnormal lipoprotein composition, however, may persist.^{32,33}

A genetic contribution to diabetic dyslipoproteinaemia may be apparent. For example the risk of both type III and type V hyperlipoproteinaemia is inherited, and diabetes mellitus is a frequent accompaniment of both conditions. The former condition is associated with alteration of the apoE phenotype which affects receptor affinity for apoE-containing lipoproteins. In diabetes allelic variation in apoE has been shown to affect levels of LDL cholesterol, as in the rest of the population, and the prevalence of the apoE₂ genotype may be over-represented.³⁴

Insulin resistance is a feature of both IDDM and NIDDM.^{35,36} It is now recognized that insulin insensitivity may be associated with a constellation of abnormalities, amongst which is obesity,

hypertension, hypertriglyceridaemia and reduced HDL cholesterol, thereby leading to further disturbances in the lipid profile.³⁵

Finally, and importantly, the role of diabetic nephropathy in modifying lipid metabolism, as well as increasing cardiovascular risk, is increasingly recognized.

Diabetic nephropathy

Diabetic nephropathy will ultimately develop in 41% of patients with IDDM of up to 40 years duration.³⁷ It has been shown that in comparison to those with normal albumin excretion, persistent proteinuria is associated with a relative 25-fold excess risk of cardiovascular mortality in young diabetic men.²¹ The relative risk is even greater in women, magnified 40-fold.²¹ In NIDDM, the incidence of nephropathy is much less certain, but may be as high as 50%.³⁸ Proteinuria in NIDDM is also associated with grave cardiovascular prognosis, and the excess risk is independent of associated hypertension, although the presence of both complications exerts an additive effect.³⁹ Part of the explanation for such a poor outcome is the clustering of several vascular risk factors in diabetic nephropathy.

Dyslipoproteinaemia in diabetic nephropathy

The effect of early nephropathy on lipoprotein metabolism in IDDM has been the subject of previous reports,⁴⁰⁻⁴⁶ some of which have suggested that alterations may be apparent at the stage of persistent microalbuminuria.^{41,42,44-46} The dominant abnormality whilst filtration function is maintained is reduced circulating HDL and HDL₂ cholesterol concentrations. The situation with regard to VLDL and LDL is much less clear. Recently we have found that cholesterol saturation of the atherogenic intermediate density lipoprotein (IDL₁) fraction (flotation density 20-60 Svedberg units) is increased in early diabetic nephropathy, but VLDL and 'true' LDL composition is unaltered.⁴⁷ Lipoprotein metabolism is further disturbed with advancing renal dysfunction. Nephrotic syndrome leads to increases in total and LDL cholesterol, and this is compounded by hypertriglyceridaemia and increased VLDL with the development of uraemia.⁴⁸ The effect of renal failure in NIDDM is similar. Reductions in HDL and HDL₂ cholesterol and increases in serum triglycerides were present 5 years after the development of microalbuminuria in NIDDM in one report.⁴⁹

Lipoprotein Lp (a) is a lipoprotein of hepatic origin which has been the focus of recent attention because it may be an independent predictor of coronary heart disease in the non-diabetic popula-

tion. It contains the apolipoproteins B and (a), the latter of which has structural homology with plasminogen, and the potential to interfere with fibrinolysis. The concentrations of apolipoprotein (a) are predominantly genetically determined, but recently we have demonstrated that the proportion of patients with increased levels predictive of coronary heart disease (CHD) is increased in *both* microalbuminuric and macroalbuminuric IDDM, perhaps as a consequence of altered elimination or by virtue of the fact that apo(a) might be nephrotoxic.⁵⁰

Other vascular risk factors in diabetic nephropathy

Hypertension itself is intimately linked with the development of diabetic nephropathy^{16,37} and is often present in proteinuric subjects.^{20,40} Its role in coronary disease is acknowledged, and its importance in diabetes is discussed elsewhere (see Feher, this issue, pp. 938–946).

Proteinuria is associated with increased transcapillary escape rates of albumin,⁵¹ and it has been suggested that increased glomerular porosity may reflect a state of generalized vascular permeability and endothelial damage,⁵² which might facilitate the passage of lipoproteins and other atherogenic molecules into the arterial wall, and thus the progression of atherosclerosis.

Case-control studies have demonstrated that smoking is commoner amongst proteinuric IDDM patients, raising the possibility that smoking might be a permissive factor in the progression of diabetic renal disease.⁵³ If this is true, then at least some proteinuric diabetic patients would be at risk of CHD simply as a result of smoking.

The role of platelet dysfunction and coagulopathy in diabetic microvascular and macrovascular disease remains incompletely understood.⁵⁴ Nonetheless several reports have demonstrated that platelet hyperaggregability and increased circulating fibrinogen and clotting factors may be a feature of diabetic nephropathy^{41,46,55} and in the non-diabetic population, at least, there is evidence that fibrinogen and factor VII might operate as independent predictors of CHD.^{56,57}

The potential of cardiovascular autonomic neuropathy to accelerate established CHD has been alluded to earlier, but it is important to recognize the fact that albuminuria and autonomic neuropathy frequently coexist in diabetes.⁵⁸ In addition, diabetic microvascular disease frequently affects several organ systems, and cardiac microangiopathy may accompany diabetic nephropathy, thereby further compromising cardiac function.⁵⁹

Free radicals are highly unstable molecules with unpaired electrons in their structure leading to lipid peroxidation, which may initiate endothelial

injury, and alter lipoprotein and cell membrane fatty acid structure. Oxidized lipoproteins may be particularly atherogenic,⁶⁰ and could be a feature of poorly controlled or complicated diabetes,^{61–63} although it is not clear whether lipid peroxides contribute to, or are simply the consequence of diabetic CHD.⁶⁴

Insulin and diabetic coronary heart disease

The question of whether or not insulin is an independent causal risk factor for CHD remains controversial.⁶⁵ Epidemiological studies in non-diabetic populations have produced conflicting results^{65–68} and insulin could simply be acting as a marker for dyslipoproteinaemia and/or hypertension and/or coagulopathy.^{69–72} This is suggested by increasing recognition of the syndrome of obesity, hypertension glucose intolerance and dyslipoproteinaemia in hyperinsulinaemic/insulin resistant individuals (syndrome X),³⁵ with a suggestion that heredity may play a role in its development⁷³ (see Bain and Dodson, this issue, pp. 922–927).

Peripheral hyperinsulinaemia is a feature of insulin-treated IDDM and NIDDM, and possibly also early NIDDM. Cross-sectional studies have demonstrated increased endogenous insulin reserve (assessed by C-peptide) in addition to increased insulin requirements in insulin-treated NIDDM with CHD in comparison to those without CHD.^{74,75} Although these findings were independent of body mass and age, multivariate analysis taking account of HDL and triglycerides was not carried out, so the role of insulin remains uncertain. It is also extremely difficult to separate the effect of hyperinsulinaemia from insulin resistance (better termed insensitivity) in these studies. Insulin insensitivity has, in fact, been estimated in a prospective study in IDDM and shown to predict CHD,⁷⁶ although again this is not necessarily directly attributable to insulin, and might mark out those individuals with a tendency to dyslipoproteinaemia and/or hypertension.

Conclusion

Diabetes mellitus is associated with multiple metabolic, haemorrhological and haemodynamic abnormalities which may together conspire to make the hyperglycaemic individual especially vulnerable to atherosclerotic coronary heart disease. Efforts to reduce the excessive mortality from CHD should concentrate on those in whom 'risk markers' cluster, particularly those with albuminuria or 'syndrome X'.

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