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Review Article

Coronary Heart Disease with Diabetes: A Review Article

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Abstract

There is a strong correlation between Coronary heart disease (CHD) and Diabetes mellitus (DM). There are complex relationships between insulin and glucose homeostasis and the development of atherothrombotic vascular disease, and involves clustering of metabolic and procoagulant cardiovascular risk factors which, in turn, are underpinned by genetic predisposition and genetic and environmental interactions. Diabetes is associated, not just with increased cardiovascular disease, but also with a worse outcome. One reason for this appears to be enhanced myocardial dysfunction leading to accelerated heart failure (diabetic cardiomyopathy) which predisposes patients to congestive heart failure. In fact, according to the American Heart Association, it may be appropriate to say, 'diabetes is a cardiovascular disease'. So, it is very important to assess the cardiovascular risk of diabetic patients and to provide appropriate levels of advice and medication to control blood glucose, blood pressure, lipids and other risk factors. Although tight glycemic control is essential, care should be taken to avoid treatments known to exacerbate cardiovascular risk factors. In addition to therapeutic intervention, lifestyle changes are certain to be the most important regulators of insulin resistance, glucose control, and overall cardiovascular risk.

Key words: Coronary Heart Disease, Diabetes, atherothrombotic vascular disease.

Introduction:

The prevalence of Diabetes mellitus (DM) is rapidly increasing in both developing and developed countries, and it is a worldwide epidemic. Coronary heart disease (CHD) is also highly prevalent and is the major cause of morbidity and mortality in diabetic patients. CHD accounts for up to 80% of mortality in patients with type 2 diabetes and the age-adjusted relative risk of cardiovascular death is three times greater in these patients than in the general population. Mortality from cardiovascular disease is 7.5 times greater in patients with type 2 diabetes without a previous myocardial infarction than in those without diabetes and three times greater in patients who have suffered a myocardial infarction and have type 2 diabetes than in non-diabetic individuals[1, 2]. Furthermore, diabetes increases the risk for cardiovascular death more in women than in men[3] and thus cancels out the usual sex differences in the prevalence of cardiovascular disease[4]. The article highlights cardiovascular risks, risks assessment as well as prevention of heart diseases among diabetic patients.

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Cardiovascular risk increases before the onset of diabetes:

In a 20-year study of the incidence of type 2 diabetes, heart disease and stroke among 117629 female nurses[5], 1508 women were diagnosed with type 2 diabetes at baseline. Over the next 20 years, 5894 developed type 2 diabetes during follow-up. 1556 new cases of myocardial infarction, 1405 strokes, 815 cases of fatal coronary heart disease and 300 fatal strokes were documented. Among those who developed type 2 diabetes, the age-adjusted relative risks of myocardial infarction were 3.75 for the period before diagnosis and 4.57 for the period after diagnosis. The risk of stroke was also significantly increased before diagnosis of diabetes (relative risk = 2.30). Further adjustment for history of hypertension or hypercholesterolemia did not appreciably alter the results. In a retrospective study with prospective follow-up of 197 consecutive non-diabetic patients with acute myocardial infarction followed for 1.5–2.5 years[6], the mean plasma glucose concentration at the time of the patient's admission to hospital was 8.15 ± 3.0 mmol/l. During follow-up, 60 patients (30%) died, 20 (10%) were re-admitted to hospital because of heart failure, 12 (6%) were re-admitted to hospital because of non-fatal reinfarction, and 79 (40%) had at least one of these events. Plasma glucose concentration at the time of the patient's admission to hospital was significantly greater in patients who suffered any of these events than in those who did not.

Role of insulin resistance syndrome as cardiovascular risk factor:

Insulin resistance is associated with metabolic and procoagulant cardiovascular risk factors, which may

account for the accelerated atherosclerosis and increased arterial thrombotic disease observed in these patients. The origins of insulin resistance and vascular risk clustering are poorly understood, but data from families, twins, and extended pedigrees suggest significant genetic and environmental contributions, with evidence of pleitropic influences that contribute to risk clustering. Important environmental determinants of insulin resistance may occur before birth and, in conjunction with adverse dietary and exercise habits that result in obesity, lead to increased insulin resistance and cardiovascular risk[7].

The insulin resistance syndrome:

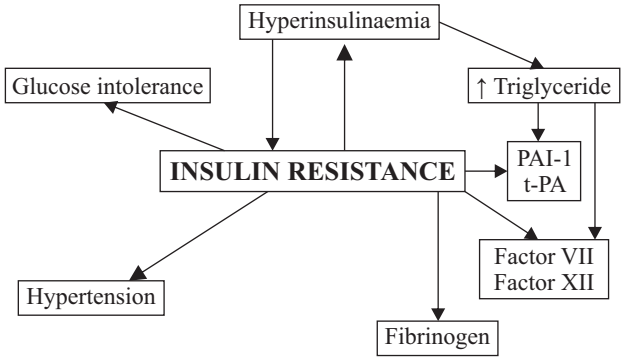

Figure 1: Atherothrombotic components of the insulin resistance syndrome.

PAI-1, Plasminogen Activator Inhibitor-1, t-PA, tissue-type Plasminogen Activator.[7]

Insulin resistance or β-cell dysfunction:

The majority of individuals with type 2 diabetes also have impaired β-cell function and deteriorating β-cell insulin secretion, which contribute to the progressive decline in glycaemic control that often occurs[8]. Therefore, β-cell dysfunction (rather than specific insulin resistance) has a potential role in the development of the atherothrombotic, pre-diabetic state.

Plasminogen activator inhibitor-1/tissue-type plasminogen activator:

Clinical studies have identified strong relationships between features of the insulin resistance syndrome and concentrations of PAI-1 and tPA[9,10]. In the recently reported Framingham Offspring Study, Meigs et. al.[11] examined the relationship between insulin concentrations and haemostatic factors in glucose-tolerant and intolerant individuals. Concentrations of PAI-1 and t-PA were greater in individuals with glucose intolerance, and increased significantly across insulin quintiles both in glucose tolerant and intolerant groups. Increased PAI-1 concentrations have also been found in the non-diabetic first-degree relatives of probands with type 2 diabetes[12] and in patients with established CVD[13,14].

Factor VII:

Increased FVII:c activity is associated with features of the insulin resistance syndrome in patients with type 2 diabetes[15] and has been reported in hyperinsulinaemic individuals with normal glucose tolerance[16]. The healthy, first degree relatives of diabetic probands show evidence of increased expression of insulin resistance and FVII:c activity was increased in the non-diabetic relatives of patients with type 2 diabetes[17].This difference was attenuated after adjustment for other features of the insulin resistance syndrome, and in separate regression models FVII:c was independently related to insulin concentrations. There is evidence of increased expression of factor VII in the presence of hypertriglyceridaemia[18] and genotype-specific interactions between triglyceride and factor VII gene polymorphisms[19].

Fibrinogen:

Fibrinogen may be of particular importance in the context of microalbuminuria, which predicts excess cardiovascular mortality in healthy individuals[20] and is associated with insulin resistance in non-diabetic individuals[21]. Several studies have demonstrated a consistent increase in plasma fibrinogen in patients both those with type 1 diabetes and those with type 2 diabetes who have microalbuminuria[22], and a recent study identified an independent association between fibrinogen and microalbuminuria in non-diabetic men[23]. The biological mechanism responsible for this association is unknown, but may involve protein glycosylation or the release of proinflammatory cytokines, or both, with resultant endothelial dysfunction[24].

Factor XII:

Factor XII a concentrations were strongly associated with the extent of coronary stenosis and past history of myocardial infarction, and were also found to correlate with many of the features of the insulin resistance syndrome, including triglyceride, BMI, PAI-1, factor VII, and insulin.

Risk Assessment:

Risk assessment must take into account the major risk factors viz. cigarette smoking, increased blood pressure, abnormal serum lipids and lipoproteins, and hyperglycemia. It must also consider predisposing risk factors viz. excess body weight and abdominal obesity, physical inactivity and family history of cardiovascular disease. Identification of risk factors is a major first step for developing a plan for risk reduction in persons with diabetes[7].

Detection of clinical and sub-clinical cardiovascular disease:

Because the typical cardiac symptoms are often masked in patients with diabetes, the diagnosis of myocardial infarction is commonly missed or delayed. Effective strategies for earlier detection of clinical cardiovascular disease viz. stress testing, Doppler Echo & radionuclide ventriculography and evaluation of autonomic dysfunction could reduce morbidity and mortality in patients with

diabetes. In addition, detection of sub-clinical atherosclerosis through history taking, physical examination, laboratory investigations- ECG, carotid ultrasound, electron beam CT and early clinical manifestation of cardiovascular disease could lead to more effective primary prevention in some patients with diabetes. Finally, the finding of sub-clinical cardiovascular disease signals the need for institution of more aggressive preventive measures[25].

Prevention of heart disease in diabetic patients:

The risk of cardiovascular disease begins to increase long before the appearance of overt diabetes. Thus early detection of the constituents of Syndrome X is needed in order to take appropriate primary prevention measures in patients at risk for diabetes. Signs of insulin resistance include abdominal obesity (or borderline abdominal obesity), high-normal blood pressure (or mild hypertension), high-normal triglycerides (150–250 mg/dl), reduced HDL cholesterol (<40 mg/dl in men; <50 mg/dl in women), borderline-high-risk LDL cholesterol (130–159 mg/dl) and, in some patients, impaired fasting glucose (110–126 mg/dl). The detection of impaired fasting glucose usually signifies long-standing insulin resistance and is therefore an important risk factor for type 2 diabetes[25].

Implications for treatment of patients with type 1 diabetes:

The most important risk factor for coronary heart disease in patients with type 1 (insulin-dependent) diabetes is duration of disease. Nonetheless, smoking, hypertension, renal disease and dyslipidaemias remain important. Effective glycaemic control reduces microvascular complications of type 1 diabetes and may also reduce risk for macrovascular disease[26]. Modification of other risk factors will almost certainly be beneficial. Measures include tobacco avoidance, blood pressure control, screening for microalbuminuria and reducing triglycerides to 200 mg/dl or even less. Although the optimal LDL cholesterol concentration in diabetes is ≤100 mg/dl, use of cholesterol decreasing drugs to achieve this in younger patients may not be appropriate. Aspirin is useful in patients who have long-standing type 1 diabetes and who have not achieved glycohaemoglobin targets.

Treatment choices in type 2 diabetes:

There are numerous effective pharmaceutical agents for the treatment of hyperglycemia, hypertension and dyslipidaemias, and clinicians have their own preferences for administration to patients with type 2 diabetes. However, because these patients are already at increased risk of cardiovascular disease, consideration should be given to avoiding treatments with known or suspected cardiotoxicity. For example, glitazones have been linked with a 50% increase in heart failure compared with controls[27]. Most sulphonylureas are associated with coronary artery spasms believed to be caused by interference with potassium channels[28], although this does not apply to gliclazide, a sulphonylurea with no cardiovascular ATP-sensitive potassium channel interaction[29].

Conclusions:

The incidence of diabetes (particularly type 2 diabetes) is increasing. Patients with diabetes are at greatly increased risk of cardiovascular morbidity and mortality. It is important to assess the cardiovascular risk of diabetic patients and to provide appropriate levels of advice and medication. Although tight glycemic control is essential, care should be taken to avoid treatments known to exacerbate cardiovascular risk factors.

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