DIABETES AND CORONARY HEART DISEASE

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EPIDEMIOLOGY

In the coming decades, the burden of cardiovascular diseases (CVDs) related to diabetes will increase substantially. Cardiovascular disease, which includes coronary heart disease (CHD), cerebrovascular disease, and peripheral vascular disease, is the leading cause of mortality in people with diabetes (1). Most diabetics die of CVD, and atherosclerosis accounts for some 80 percent of all diabetic mortality. Heart disease, particularly CHD, is a major cause of morbidity and mortality among patients with diabetes mellitus (2). CHD is much more common in diabetics than in the general population, affecting as many as 55 percent of these patients (3).

Results from the Framingham Study found that the presence of diabetes doubled the age-adjusted risk for CVD in men and tripled it in women (4). Similar data have been reported by the Multiple Risk Factor Intervention Trial (MRFIT) (5). A number of other observations have confirmed the increase in CHD in patients with diabetes mellitus.

The relative risk of myocardial infarction was by 50 percent greater in diabetic men and by 150 percent greater in diabetic women compared to age-matched nondiabetics (6).

Sudden cardiac death was by 50 percent more frequent in diabetic men and by 300 percent more frequent in diabetic women compared to age-matched nondiabetics (6).

Extent of coronary disease

The extent of the disease in coronary arteries is also greater among diabetic patients (7). Autopsy studies have reported that diabetic patients have a higher incidence of two- and three-vessel disease and a lower incidence of one-vessel disease compared to nondiabetics (8). Similar data have been reported from one large retrospective analysis of patients undergoing elective percutaneous transluminal coronary angioplasty (PTCA) (9). Multivessel disease was more common in diabetic patients.

Silent myocardial ischemia

In addition to the increased frequency of symptomatic CHD, another important clinical finding in diabetes is blunted appreciation of ischemic pain, often resulting in silent ischemia or even silent infarction (10). In one study that used ambulatory ST segment monitoring to examine diabetic patients with documented CHD, over 90 percent of ischemic episodes were asymptomatic (11). Silent ischemia in diabetes is thought to be caused by autonomic
denervation of the heart due to alteration in the normal link between the afferent and efferent limbs of the autonomic system (12).

Autonomic dysfunction can promote the development of ischemia and infarction by several mechanisms:
- increased heart rate at rest, thereby increasing myocardial oxygen demand,
- increased coronary vascular tone, thereby reducing myocardial flow, and
- reduced coronary perfusion pressure during hypotension.

Additionally, the disparity of sympathetic innervation between the proximal and distal portion of the left ventricle may contribute to a higher frequency of cardiac dysrhythmias and sudden death (13).

**Myocardial infarction**

Diabetes appears to be associated with an increased risk of myocardial infarction. Myocardial infarction may also be painless, or may present with non-specific symptoms. The loss of the normal circadian pattern of autonomic cardiovascular regulation may explain why cardiac events occur especially during the evening and at night, in contrast to the early morning peak in nondiabetic people. Myocardial infarction is two to three times more common among diabetic people than in the general population and carries a worse prognosis, particularly in women who have twice the expected mortality (14).

Another study compared the seven-year incidence of myocardial infarction in nodiabetics and patients with type 2 diabetes (15). The incidence rate of myocardial infarction was increased in diabetic patients, including those with and without prior myocardial infarction. Thus, type 2 diabetic patients without prior myocardial infarction were at the same risk of myocardial infarction and cardiac mortality as nondiabetic patients who had prior myocardial infarction. These data suggest that cardiovascular risk factors in diabetic patients should be treated as aggressively as in nondiabetic patients with previous myocardial infarction.

**ATHEROGENESIS AND THROMBOGENESIS IN DIABETES**

Numerous factors, including hyperglycemia, hyperlipidemia, hypertension, smoking, endothelial dysfunction, and platelet and coagulation abnormalities contribute to the process of accelerated atherosclerosis in diabetes (21).

**Dyslipidemia**

There are a number of differences in the lipid profile between diabetics and nodiabetics, which may contribute to the increase of atherosclerosis (16). Lipid abnormalities associated with type 1 diabetes are largely related to the level of glycemic control. The pattern of dyslipidemia in type 2 diabetes is that characteristically seen in the insulin-resistant states and metabolic syndrome (17). Low HDL and raised triglyceride concentrations are accompanied by normal LDL-cholesterol, although this is likely to be dominated by highly atherogenic LDL particles.

Atherogenic risk factors, i.e. hyperglycemia, hypertension, dyslipidemia and central obesity, cluster together with insulin resistance in the “metabolic” syndrome (syndrome X), which is strongly associated with accelerated atherosclerosis and CVD (18). These features are also associated with a cluster of thrombotic risk factors, notably elevated levels of plasminogen activator inhibitor-1 (PAI-1), and of factor VII, factor XII and fibrinogen (19,20).

**Table 1. Components of the metabolic syndrome**

- Insulin resistance
- Hyperglycemia
- Dyslipidemia
- Hypercoagulability
- Hypertension

However, at any lipoprotein level, diabetic patients have more significant CHD than nondiabetic persons. This may be due to qualitative differences in the lipoprotein fractions or the presence of other proatherosclerotic metabolic changes in diabetics. Two such changes are increased concentrations of LDL and perhaps lipoprotein (a) (16,21). In addition, the oxidation of lipoproteins, in particular LDL, seems to be enhanced in diabetics. Oxidation of LDL results in a
moiety that is cytotoxic to vascular endothelial and smooth muscle cells, probably contributing to atherogenesis.

It is also proposed that glycation of apoB is increased in diabetic individuals and may contribute to the development of atherosclerosis (22). According to this theory, glycation causes impaired recognition of LDL by its receptor on hepatocytes, thereby increasing its half-life. The glycated LDL is then taken up preferentially by macrophages via a separate receptor and degraded. Immunohistochemical analysis of coronary arteries in patients with type 2 diabetes showed high levels of advanced glycosylation end products (AGE) within atherosclerotic plaques (23).

**Endothelial dysfunction**

Endothelial dysfunction and impaired endothelial-dependent vasodilatation, perhaps representing early large vessel disease, have also been documented in diabetic patients who have normal coronary arteries and no other risk factors for coronary disease (24). The major functional defects in diabetes are summarized in Table 2.

**Table 2. Abnormalities of endothelial function in arteries and arterioles of diabetic patients**

<table>
<thead>
<tr>
<th>Increased endothelial adhesiveness</th>
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<tbody>
<tr>
<td>↑VCAM-1</td>
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<tr>
<td>↑E-selectin</td>
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<table>
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<tr>
<th>Impaired vasodilatation</th>
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<tbody>
<tr>
<td>↓NO production, -NO quenching</td>
</tr>
<tr>
<td>↓Prostacyclin (PGI2)</td>
</tr>
<tr>
<td>↑Endothelin-1</td>
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<table>
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<tr>
<th>Increased coagulation</th>
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</thead>
<tbody>
<tr>
<td>↓NO, PGI2</td>
</tr>
<tr>
<td>↑PAI-1 expression</td>
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<table>
<thead>
<tr>
<th>↑Tissue factor expression</th>
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<tr>
<td>Increased permeability</td>
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Increased endothelial adhesiveness and enhanced hemostasis are both thought to contribute to atheroma formation. Increased endothelial permeability may allow plasma lipoproteins and other proteins to enter the subendothelial space and muscular media, which may compromise arterial compliance and promote atherogenesis (25).

**Coagulation and fibrinolysis abnormalities**

Hypercoagulability may contribute to vascular risk in diabetes. Insulin resistance is associated with high levels of procoagulant proteins (e.g., fibrinogen, factor VII, von Willebrand factor) with suppressed fibrinolysis due to increased concentrations of PAI-1. Underlying mechanisms may include raised insulin, triglyceride and inflammatory cytokine levels (26).

**Plaque composition**

Plaque composition may differ in diabetics and affect coronary risk. Coronary tissue from diabetics contained a greater amount of lipid-rich atheroma and more macrophage infiltration, which are associated with a higher risk of plaque rupture and more frequent coronary thrombosis (27).

**DIAGNOSIS OF CORONARY HEART DISEASE IN DIABETES**

Thorough history and examination are essential but may fail to reveal significant disease. Appropriate investigations therefore need to be considered early and with a lower index of clinical suspicion than usual. Because diabetics have blunted anginal symptoms and poor outcome following coronary events, the issue of screening for CAD in patients with diabetes mellitus has particular importance. A recent American College of Cardiology/American Diabetes Association Consensus Development Conference has established guidelines for screening diabetic individuals for CHD (28). Table 3 summarizes indications for CAD testing.

**Table 3. Indications for cardiac testing in diabetic patients (28)**

 Testing for CHD warranted in patients with:
1. Typical or atypical cardiac symptoms
2. Resting electrocardiograph suggestive of ischemia or infarction
3. Peripheral or carotid occlusive arterial disease
4. Sedentary lifestyle, age ≥35 years, and plans to begin a vigorous exercise program
5. Two or more of the risk factors listed below (a-e) in addition to diabetes
   a) total cholesterol ≥240 mg/dl (6.2 mmol/l), LDL cholesterol ≥160 mg/dl (4.2 mmol/l), or HDL cholesterol <35 mg/dl (0.9 mmol/l)
   b) blood pressure >140/90 mm Hg
   c) smoking
   d) family history of premature CHD
What are the most appropriate tests to detect the presence of CHD?

In general, the test chosen will depend on the purpose of the test. The reasons for choosing one test or another to detect coronary disease in patients with diabetes are similar to other nondiabetic populations with suspected coronary disease, except that, as a group, diabetic patients are less likely to be able to satisfactorily perform a standard treadmill test.

Exercise electrocardiography

In patients who can exercise on a treadmill and can be expected to have exercise-interpretable ECGs (i.e., resting ECG without LBBB, digitalis effect, WPW, or >1-mm ST segment depression), a simple exercise test will detect the great majority of patients with left main or significant multivessel CAD. These patients may also exhibit poor exercise capacity, marked ST segment changes, or a hypotensive response to exercise. On the other hand, a completely normal test is a marker for a good prognosis, despite its relatively low overall sensitivity for detecting single-vessel disease (29). It must be remembered that pharmacological therapy (e.g., β-adrenergic receptor blockade) can delay the time to onset of ischemia and attenuate the heart rate response to exercise, so that if detection of disease is the purpose of the test, consideration should be given to performing in the absence of cardiac medications likely to influence the results. An inadequate test (in which the patient fails to achieve approximately 85% of the maximal predicted heart rate response to stress) reduces the predictive value of the test: in such situations, additional testing should be considered (28).

Stress perfusion imaging

Stress perfusion imaging with thallium or technetium-labeled MIBI detects heterogeneous flow distribution due to decreased coronary flow reserve during exercise or pharmacological vasodilatation. This technique has a high success rate (<1% of images are not interpretable), and with MIBI it also provides a measurement of ejection fraction. A key clinical feature of perfusion imaging is that it allows for quantification of perfusion abnormalities, and this provides an important ability to prognostically stratify patients. In patients with single-vessel coronary disease, stress perfusion imaging may be superior to stress echocardiography, while the techniques are similar for detecting multivessel disease. Likewise, in a setting of prior infarction, perfusion imaging is superior to stress echo in detecting ischemia. Numerous studies have shown that perfusion imaging adds incremental information, which allows for prediction of longer-term outcome in both diabetic and nondiabetic subjects (28). In summary, perfusion imaging is useful in patients with diabetes since the technique provides quantifiable data and identifies low- and high-risk patients for future adverse cardiovascular events.

Stress echocardiography

Stress echocardiography depends on the detection of regional wall motion abnormalities induced by myocardial ischemia and the clear imaging of the endocardium. Approximately 5%-10% of patients have poor acoustic windows precluding echocardiography study. Treadmill exercise is generally preferred to pharmacological stress (e.g., with dobutamine). An experienced echocardiographer is required to obtain high-quality post-stress images within 60 s of termination of exercise and in order to avoid an incorrect interpretation of artifacts. Stress echocardiography is comparable to perfusion imaging for detection of multivessel CAD. However, currently there are insufficient outcome data in diabetic patients following stress echocardiography to define its role as a prognostic tool (28).

PRIMARY PREVENTION OF CORONARY HEART DISEASE AND RISK FACTOR MANAGEMENT

Lifestyle modification

Regular physical exercise and limitation of fat and total energy intake remain the cornerstones of the management of overweight diabetic patients. Diabetic patients should be encouraged to undertake moderate aerobic activity, such as walking, jogging, swimming and cycling. Current recommendations suggest brisk walking or its equivalent for 30-45 min on most days, and ideally every day. Patients with angina or breathlessness on exertion should exercise within their limitations, aiming gradually to increase their activity.
Before beginning a physical activity program, the patient with diabetes should have detailed medical evaluation with appropriate diagnostic studies. This examination should screen for the presence of macro- and microvascular complications that may worsen with the physical activity program.

**Smoking cessation**

Cigarette smoking is obviously an important but modifiable cardiovascular risk factor, yet about 25% of the diabetic population continue to smoke (30). Smoking cessation confers immediate and lasting benefits that are likely to be even greater in diabetic people whose vascular risk is additionally increased by smoking (31). Therapeutic options include nicotine replacement, bupropion, and cessation counseling programs.

**Intensive glycemic control**

Numerous studies have shown a positive correlation between CHD endpoints and increasing glucose levels in patients with diabetes. Neither the Diabetes Control and Complications Trial (DCCT) nor the United Kingdom Prospective Diabetes Study (UKPDS) has shown significant reductions in cardiovascular events with improved glycemic control, however, early and effective correction of hyperglycemia may reduce atherothrombotic risk (32,33). Metformin alone reduced the risk of myocardial infarction in the UKPDS, possibly because of its favorable effects on insulin resistance and associated risk factors (34). Accordingly, it has been suggested that metformin should be a first-line therapy in overweight type 2 patients (33).

**Treatment of dyslipidemia in diabetes**

Lipid abnormalities are common in patients with diabetes mellitus, and undoubtedly contribute to the increase in the risk of CVD. The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) made diabetes a “CHD equivalent” thereby elevating it to the highest risk category (35). Two major studies that included large numbers of diabetic patients (4S and CARE) both confirmed the benefits of lowering cholesterol (36,37).

A primary prevention study using statins showed a similar trend to reduce these events in a small number of patients with diabetes (38). In the Helsinki Heart Study, a primary prevention trial, a trend towards significant reduction in CHD events was observed in a small group of subjects with diabetes mellitus (39). The above findings provide clear support for the treatment of high serum cholesterol concentrations in all diabetic patients to reduce the risk of CHD. Target lipid levels are shown in Table 4.

**Table 4. Target lipid levels for adult patients with diabetes (40)**

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Goal</th>
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<tbody>
<tr>
<td>LDL-cholesterol</td>
<td>&lt;100 mg/dl (2.6 mmol/l)</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>Men: &gt;45 mg/dl (1.15 mmol/l) Women: &gt;55 mg/dl (1.40 mmol/l)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;=150 mg/dl (1.7 mmol/l)</td>
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</table>

**Target values**

Although diabetic patients may have a variety of lipoprotein abnormalities, the primary target of therapy in clinical trials has been LDL cholesterol. Since diabetes is treated as a CHD equivalent in ATP III, the serum LDL cholesterol goal has been set at <100 mg/dl (2.58 mmol/l) (35). Most patients with diabetes will require cholesterol lowering therapy in combination with therapeutic lifestyle changes if their serum LDL cholesterol concentration is >130 mg/dl (3.36 mmol/l) (35).

The American Diabetes Association (ADA) recommends the same targets for LDL cholesterol and beginning drug therapy at a serum LDL cholesterol concentration above 130 mg/dl (3.4 mmol/l). They recommended that the treatment of hypertriglyceridemia be left to physician discretion for patients with a serum triglyceride concentration between 200 (2.30 mmol/l) and 400 mg/dl (4.50 mmol/l). Above 400 mg/dl (4.50 mmol/l), strong consideration should be given to drug treatment of hypertriglyceridemia (40).

Pharmacological treatment is indicated if there is an inadequate response to lifestyle modifications and improved glucose control. The drug of choice is a statin in patients with hypercholesterolemia and mild hypertriglyceridemia, and fibric acid derivative (such as gemfibrozil) in patients with marked hypertri-
glyceridemia, or both (40). When prescribing fibrates in combination therapy with a statin, care is needed to minimize the risk of myositis.

Treatment of hypertension

Epidemiologic analyses show that blood pressures >120/80 mm Hg are associated with increased cardiovascular event rates and mortality in persons with diabetes (41). The endpoint blood pressure to protect against cardiovascular disease in patients with diabetes should be below 130/80 mm Hg (41,42).

Table 5. Indications for initial treatment and goals for adult hypertensive diabetic patients (43)

<table>
<thead>
<tr>
<th>Goal (mm Hg)</th>
<th>Systolic</th>
<th>Diastolic</th>
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<tr>
<td>Behavioral therapy alone (max 3 months) then add pharmacological treatment</td>
<td>130 - 139</td>
<td>80 - 90</td>
</tr>
<tr>
<td>Behavioral therapy + pharmacological treatment</td>
<td>≥140</td>
<td>≥90</td>
</tr>
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</table>

The optimal initial antihypertensive agent for hypertensive type 1 diabetic patients is usually an ACE inhibitor because of its lack of metabolic complications, and its renal-sparing effects (44). The best choice for the treatment of hypertension in those with type 2 diabetes is less certain. For patients without nephropathy, an ACE inhibitor is the optimal first choice. However, in terms of renoprotection among those with renal disease, the benefit of an angiotensin receptor blocker (ARB) is clear, as shown in the Ibersatan Diabetic Nephropathy and RENAAL trials (45,46). However, an ARB is not necessarily the best choice for hypertensive patients with diabetic nephropathy due to type 2 diabetes. The mortality benefit seen with ramipril in the HOPE trial was not found in the major ARB trials (45-47). When an ACE inhibitor or ARB does not produce the desired level of blood pressure control, the addition of a low-dose long-acting diuretic or perhaps combination therapy with an ACE inhibitor and ARB can be considered (48).

The place of calcium-channel antagonists was questioned by results of the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial, which reported on a fivefold increase in myocardial infarction with nisoldipine as compared with enalapril (49). On the other hand, two large studies in diabetic populations have demonstrated significant reductions in infarction risk with nifedipine and fenoldipine (41,50).

In patients over age 55 with hypertension or without hypertension but with another cardiovascular risk factor (history of CVD, dyslipidemia, microalbuminuria, smoking), an ACE inhibitor (if not contraindicated) should be considered to reduce the risk of cardiovascular events. In patients with a recent myocardial infarction, β-blockers, in addition, should be considered to reduce mortality (43).

Treatment of coagulation disorders

At present, the role of antiplatelet therapy in primary prevention of heart disease in diabetic subjects is unproven. However, the Antiplatelet Trialists’ Collaboration have reported on a 17% reduction in the risk in diabetic subjects who had already had cardiovascular disease, a result that has been supported by the US Physicians and Early Treatment Diabetic Retinopathy Study (ETDRS) reports (51,52). As diabetic subjects without a prior vascular event have a similar risk as a nondiabetic with vascular disease, it seems logical to suggest the use of aspirin (75-325 mg/day) in all diabetic patients as long as there are no contraindications (15).

MEDICAL MANAGEMENT OF CORONARY HEART DISEASE IN DIABETES

Angina

Angina is managed conventionally, with β-blockers, nitrate and aspirin. Cardioselective β-blockers do not interfere significantly with catecholamine-driven responses and symptoms in hypoglycemia. Early consideration should be given to coronary angiography and revascularization, if the symptoms worsen.

Unstable angina

Acute coronary syndrome without definite evidence for myocardial infarction must be treated as high-risk events. Diabetic patients should be treated with low
molecular-weight heparin, a β-blocker and the platelet inhibitor clopidogrel. An alternative to clopidogrel is to treat high-risk patients, particularly those with elevated plasma troponin concentrations, with an inhibitor of platelet glycoprotein IIb/IIIa such as tirofiban or eptifibatide.

Acute myocardial infarction

Similar to nondiabetic patients, diabetics with an acute myocardial infarction are treated with aspirin and thrombolytic therapy or primary angioplasty. Aspirin administration decreases the risk of reinfarction in 38 per 1000 treated patients, as compared with a reduction in 36 per 1000 nondiabetic subjects (51). Thrombolysis reduces mortality at 35 days by 21.7% in diabetic patients and by 14.3% in normoglycemic subjects (53). Pain should be treated with nitrates and opiate analgetics if necessary.

Beta-blocker therapy after myocardial infarction reduces infarct size, the incidence of infarct extension, recurrent ischemia, reinfarction, and cardiac and sudden death mortality (54). Treatment should therefore be carefully monitored, as diabetic patients are at a greater risk of heart failure following myocardial infarction, and this may be precipitated by β-blockers.

When given after an acute myocardial infarction, ACE-inhibitors reduce infarct size, limit ventricular remodeling, and reduce mortality. ACE-inhibitors may be of particular benefit in diabetic patients, as illustrated by data from GISSI–3 and TRACE (55,56).

There is now solid evidence that imposing good glycemic control soon after an acute infarction and maintaining it for some months thereafter can reduce both immediate and late mortality in diabetic people. In the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, patients with diabetes were treated with intensive insulin therapy from soon after infarction for 3 months; compared with conventionally managed controls, the 12-month mortality was reduced by 30% (57). It is not clear whether the benefits were related to the acute effects of insulin soon after infarction, or to longterm influences.

REFERENCES


