



How does diabetes damage the heart?

The clock starts ticking early

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Type 2 diabetes is a major cause of cardiovascular events and mortality. Despite this knowledge, optimal treatment of coronary risk factors for people with type 2 diabetes is not widespread.

Worldwide, 220 million people have type 2 diabetes and its prevalence is rising with the increasing obesity 'epidemic'. Cardiovascular disease is two to four times more common in people with type 2 diabetes than in those without diabetes. It is the cause of more than 70% of deaths in people with type 2 diabetes, driven predominantly by arterial atheroma. A diagnosis of type 2 diabetes itself carries an equivalent coronary risk as having had a previous infarct in a person without diabetes.¹ The relative risk for coronary heart disease is greater in women with diabetes than it is for men with diabetes, but cardiovascular risk factors are relatively undertreated in women with diabetes.² GPs can help improve management of cardiovascular risk factors in people with type 2 diabetes by a better understanding of the way the arterial disease develops.

A high percentage of people with type 2 diabetes die within a year of having a myocardial infarction,³ often outside the hospital. Understanding the evolution of coronary heart disease in people with diabetes should encourage earlier risk assessment with more effective management in the community. This article examines the mechanisms by which type 2 diabetes affects the heart.

Classic coronary risk factors in diabetes

The basic event in atherosclerosis is the accumulation of LDL cholesterol in the subendothelial matrix in both people with and without diabetes. Classic risk factors such as hypertension, smoking, obesity and hypercholesterolaemia play a major role. However, in people with type 2 diabetes plaque development is not only accelerated but also exhibits more lipid-rich atheroma, higher macrophage infiltration and a higher thrombogenic potential compared with people without diabetes (see Figure).⁴



Key points

- **Cardiovascular disease causes more than 70% of deaths in people with type 2 diabetes.**
- **Atheroma in patients with diabetes develops silently preceding hyperglycaemia, particularly when features of the metabolic syndrome are present.**
- **Classic coronary risk factors in people with diabetes (including hypercholesterolaemia and hypertension) contribute to the atheroma and should be actively treated, remembering that women in particular may be undertreated.**
- **Additional risk factors specific to diabetes (such as dyslipidaemia, central obesity, hyperglycaemia and autonomic neuropathy) accelerate atheroma in people with type 2 diabetes or can worsen the outcome.**

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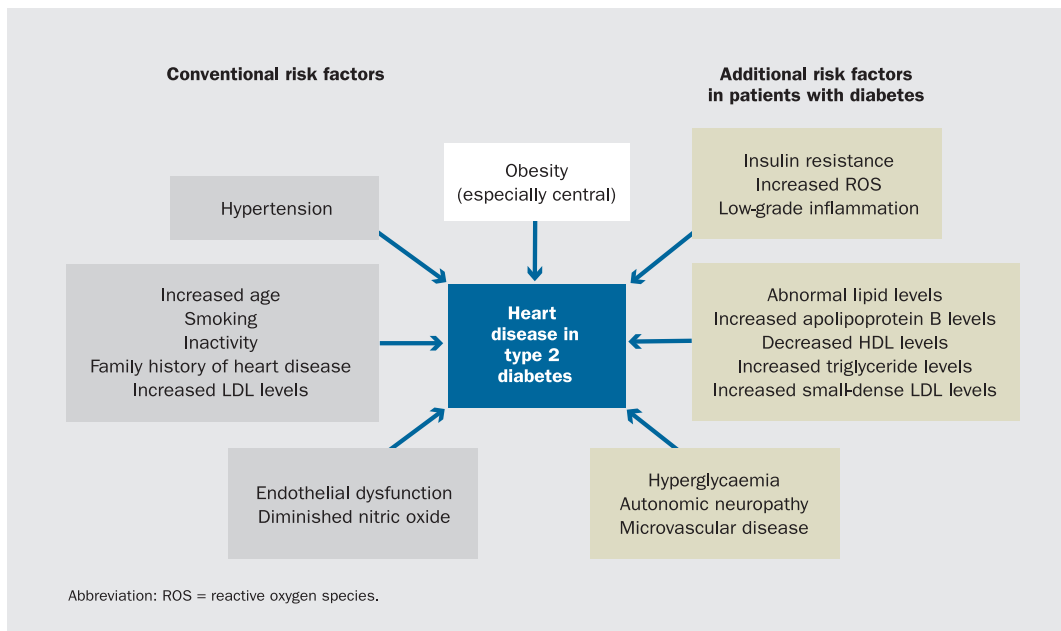


Figure. Risk factors causing heart disease in people with type 2 diabetes.

Dyslipidaemia

The classic diagnosis of dyslipidaemia in people with type 2 diabetes consists of higher triglyceride levels, higher apolipoprotein B levels and lower HDL cholesterol levels. This is associated with overproduction of large very LDL particles, resulting in the formation of small dense LDL cholesterol particles, the proatherogenic form. These particles enter the artery wall more rapidly, cause greater production of procoagulants and are more readily oxidised.⁵ Low HDL cholesterol levels and apolipoprotein A1 levels also contribute to impaired removal of excess cholesterol from atherosclerotic plaques. As plaques become more unstable they are predisposed to rupture, with thrombus formation and the occurrence of cardiovascular events.

Hyperglycaemia

Many people with type 2 diabetes already have vascular disease at the time of diagnosis. Several mechanisms are involved, including the production of excess reactive oxygen species, the triggering of low-grade inflammation, the formation of advanced glycation end products (AGEs) and inhibition of production of nitric oxide.⁶ Although the presence of microvascular disease such as retinopathy (which is strongly attributable to hyperglycaemia) is reported to predict coronary events, the relative risk of coronary disease from hyperglycaemia is much greater in people with type 1 diabetes than in those with type 2 diabetes.

People with impaired glucose tolerance or impaired fasting glucose often have significant cardiovascular disease, again suggesting that although hyperglycaemia contributes to vascular damage, it is not the major cause. Although AGEs formed by glycation or glycoxidation of proteins and lipids during hyperglycaemia are linked to premature atherosclerosis in diabetes, in a prospective study of 874 Finnish

people with diabetes followed for 18 years, increased levels of serum AGEs predicted total and cardiovascular mortality only in women.⁷

Insulin resistance

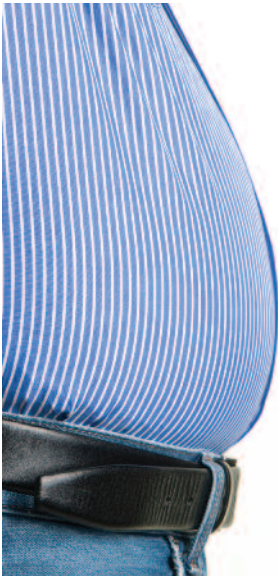
Insulin resistance precedes frank type 2 diabetes and clusters with hypertension, central obesity and the typical dyslipidaemia already described. This atherogenic cluster, including impaired glucose tolerance, is called the metabolic syndrome. The metabolic syndrome concept (by any classification) is useful to alert clinicians (before diabetes or a diagnosis of cardiovascular disease) to the presence of potentially treatable risk factors for coronary disease and for diabetes itself. Increased adiposity, in particular visceral obesity, is closely coupled with insulin resistance in predicting coronary heart disease.⁸

'The perfect storm'

The higher free fatty acid levels, related to central obesity, insulin resistance and increased lipolysis, induce low-grade inflammation, worsen insulin resistance and impair endothelial-dependent vasodilatation. Insulin resistance is associated with impaired vasodilatation, increased oxidative stress, raised plasminogen activator inhibitor-1 levels, and increased circulating cytokine levels and cellular adhesion molecules.⁹ The associated increased oxidative stress and low-grade systemic inflammation that accompany insulin resistance contribute to atheroma formation with a higher level of C-reactive protein reported to be an independent predictor of deaths from coronary heart disease.

Hypertension

Hypertension is more common in people with type 2 diabetes, being part of the insulin resistance cluster already mentioned.



Awareness of the effects of insulin resistance in the metabolic syndrome can lead GPs to carry out an early cardiovascular risk assessment and to start treatment.

Hypertension is more common and more severe in people with diabetic renal damage or renal arterial stenosis. A failure of reduction in blood pressure overnight, probably due to sympathetic overactivity, is associated with left ventricular hypertrophy and predicts coronary events.

Annual screening for diabetes complications by measuring microalbumin levels detects early renal involvement, which is in itself a risk factor for vascular disease. Good control of hypertension in people with type 2 diabetes was shown to reduce coronary events in the UK Prospective Diabetes Study (UKPDS).¹⁰

Cardiac effects of diabetes

Cardiac autonomic neuropathy

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study of 1123 people with type 2 diabetes and no known or suspected coronary artery disease found cardiac autonomic neuropathy to be a strong predictor of silent ischaemia and subsequent cardiovascular events.¹¹ The vagus nerve (the longest in the body) is damaged first and the related cardiac sympathetic overactivity may increase noradrenergic activity and mitochondrial oxidative stress, contributing to myocardial injury. The increased noradrenergic activity and myocardial injury probably contribute to the high risk of sudden death reported in patients with autonomic neuropathy. Elevated resting heart rate (reflecting increased sympathetic tone secondary to vagal impairment) and orthostatic hypotension (from sympathetic denervation) are clinical signs of autonomic neuropathy.

Diabetic cardiomyopathy

There is strong evidence that diabetes increases the risk of cardiac dysfunction and heart failure independent of coronary artery disease and traditional risk factors. Although the pathophysiology is not fully understood, cardiomyopathy is diagnosed by the presence of

myocardial dysfunction in the absence of both coronary artery disease and hypertension.

Diastolic dysfunction is the earliest finding of diabetic cardiomyopathy, characterised by impaired relaxation and filling of the left ventricle.⁹ If a reduced left ventricular ejection fraction accompanies the cardiomyopathy, the primary process is thought to be deposition of myocardial collagen and AGEs, resulting in initial diastolic dysfunction with systolic dysfunction later. The generation of reactive oxygen species appears to be involved at all stages, with increased fatty acid uptake and use by the diabetic cardiac muscle, and less glucose oxidation, leading to lipotoxicity, muscle cell apoptosis and fibrosis.

Summary

Overall, type 2 diabetes is a major cause of cardiovascular events and mortality. Despite this knowledge, optimal treatment of risk factors in people with type 2 diabetes is not widespread.¹² The cardiac 'clock starts ticking' before a diagnosis of hyperglycaemia is made because prior insulin resistance, obesity, dyslipidaemia and hypertension substantially increase atherogenic risk. When hyperglycaemia eventuates the damage is compounded.

Awareness of the covert adverse effects of insulin resistance in the metabolic syndrome can lead GPs to carry out an early cardiovascular risk assessment and to start treatment. This awareness should also encourage GPs to treat the classic risk factors early and to target both men and women with known type 2 diabetes to prevent potentially fatal cardiovascular complications. **CT**

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