Macrovascular disease: pathogenesis and risk assessment

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Abstract

Type 2 diabetes mellitus is characterized by obesity and insulin resistance (IR). Macrovascular (cardiovascular) disease (CVD) encompasses myocardial infarction, stroke and peripheral artery disease. It is caused by atherosclerosis, a complex pathological process that is accelerated in people with diabetes and therefore accounts for a higher proportion of total mortality. Risk is modified by established factors including hypertension and dyslipidaemia (which are linked with underlying insulin resistance), and microalbuminuria/renal impairment. Hyperglycaemia is a relatively weak risk factor for CVD once diabetes is established. Potential 'novel' predictors include elevated B-type natriuretic peptide, hypoadiponectinaemia, vitamin D and testosterone deficiencies, as well as chronic periodontitis and collagen vascular disorders. Early identification of cases and prompt management of risk factors is important in improving long-term outcome. Smoking cessation is a neglected area that requires urgent attention. Relative cardiovascular risk also remains high in type 1 diabetes, particularly in younger patients, and is also an important area for future research.

Keywords atherosclerosis; cardiovascular risk; cerebrovascular disease; coronary artery disease; diabetes; dyslipidaemia; endothelial dysfunction; glycaemic memory; hypertension; peripheral arterial disease

What's new?

- Endothelial dysfunction and inflammation play key roles in the pathogenesis of atherosclerosis and are associated with underlying insulin resistance
- Arterial stiffness magnifies pulsatile shear, accelerating atherosclerosis
- Potential 'novel' risk factors for atherosclerosis include elevated B-type natriuretic peptide, hypoadiponectinaemia, and deficiencies of vitamin D and testosterone
- The cardiovascular burden in type 1 diabetes is disproportionately high despite an apparently favourable lipid profile. Hypertension and a family history of type 2 diabetes are the most important risk factors in patients with childhood-onset disease
- Smoking rates remain disturbingly high in most populations with diabetes

Diabetes mellitus is a complex, heterogeneous disorder characterized by an aggregation of established and 'novel' risk factors, which translates into a markedly increased risk of macrovascular and microvascular disease. The former is broadly defined by any of three 'large vessel' cardiovascular complications, namely coronary artery disease (CAD), cerebrovascular disease and peripheral arterial disease (PAD). These affect individuals with types 1 and 2 diabetes (T1DM/T2DM): in this review we highlight relevant pathophysiological processes in both conditions, with particular emphasis on T1DM in atherosclerosis in type 1 diabetes.

Epidemiology

Established (but not recently diagnosed) T2DM confers a long-term cardiovascular risk.[1] CAD remains the commonest cause of death in diabetes. Compared with normoglycaemic individuals, diabetic patients have higher rates of re-infarction and heart failure as well as poorer outcomes after sustaining an acute coronary syndrome.[2]

Diabetes is also associated with a two- to fourfold increased risk of PAD,[3] and affects particularly the distal lower extremity circulation increasing the risk of ulceration and the requirement for amputation. Large-vessel PAD carries a sixfold higher risk of death from cardiovascular causes.[4]

Even after adjusting for hypertension and dyslipidaemia, diabetes remains an independent predictor of ischaemic neurological events.[5] The spectrum of disease can range from large-vessel to small-vessel occlusive disease, and from symptomatic to clinically silent.

Endothelial dysfunction and atherosclerosis

Endothelial dysfunction is a key antecedent and modulator of atherosclerosis, and has been demonstrated in association with insulin resistance (IR) in pre-diabetes and T2DM,[6] as well as in first-degree relatives of T2DM patients. It results in disruption of the intricate physiological balance between vasoconstrictors (endothelin, angiotensin II) and vasodilators (nitric oxide, prostacyclin), growth promoting and inhibitory factors, pro-atherogenic and anti-atherogenic factors, and pro- and anti-coagulant factors (Figure 1).

Established and 'novel' risk factors for atherosclerosis

Established risk factors

Age and gender: the Framingham study was first to report that the prevalence of CVD increases with age, and that absolute risk is higher in men than in women.[7]

Family history: a family history of proven cardiovascular disease (CVD) in a first-degree relative before the age of 60 years approximately doubles the risk of a coronary event. In a large Finnish cohort, men with a family history of stroke had an 86% higher risk of ischaemic stroke.[8]

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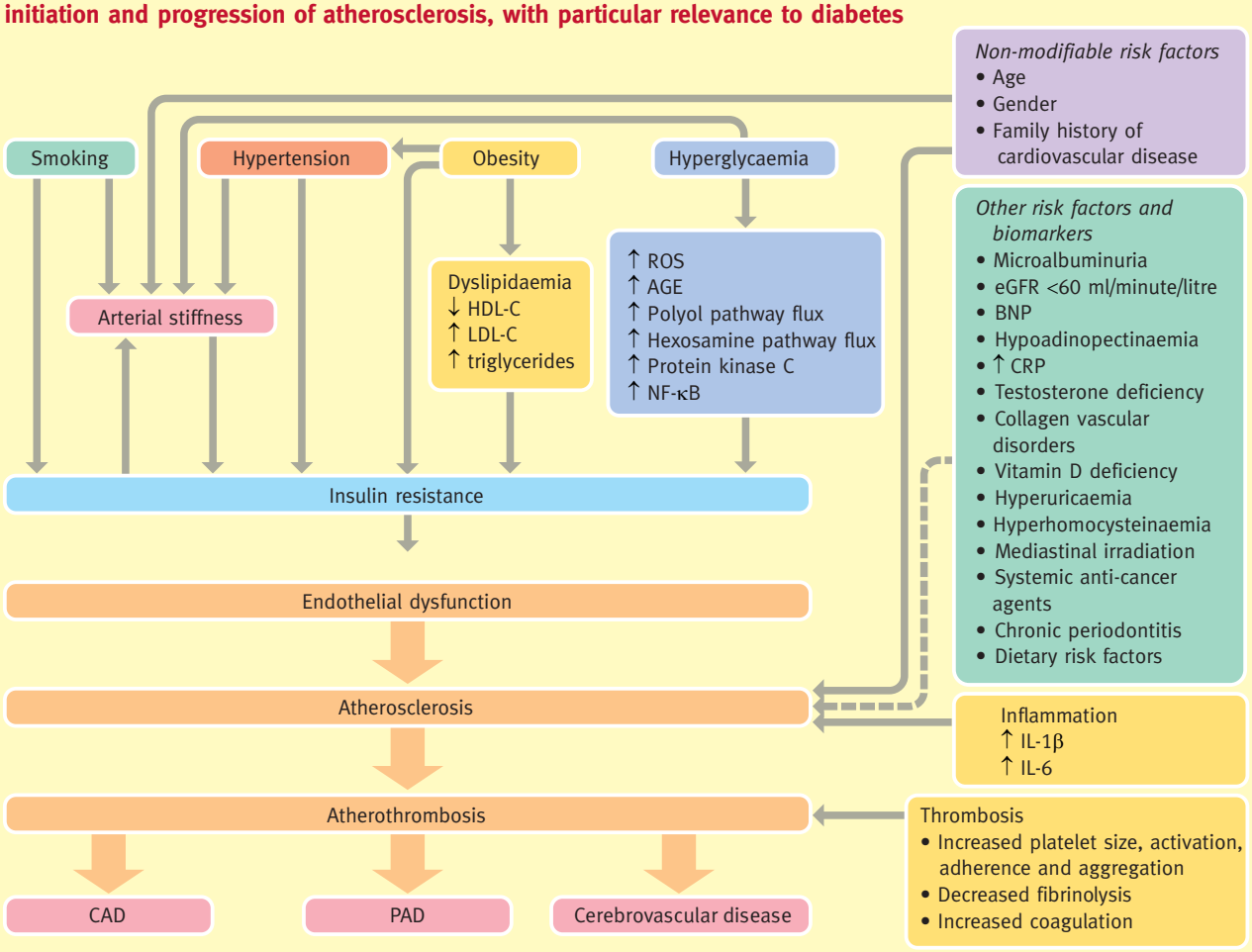
Schematic representation summarizing the current understanding of the interaction between risk factors and the initiation and progression of atherosclerosis, with particular relevance to diabetes



Causality and directionality of relationships are not firmly established for all pathways and intermediate mechanisms shown.
AGE, advanced glycation end-products; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IL-1β, interleukin-1β; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; NF-B, nuclear factor-κB; PAD, peripheral artery disease; ROS, reactive oxygen species.

Figure 1

Hypertension: the prevalence of hypertension among T2DM patients increases from 40% in individuals aged 18–44 years to 72% by the age of 64, affecting over 84% of patients thereafter.[9] The landmark United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the cardiovascular benefits of blood pressure (BP) control.[10]

Albuminuria and a reduced estimated glomerular filtration rate (eGFR): reflect generalized endothelial dysfunction, which results in atherosclerosis and CVD. Microalbuminuria is associated with a near doubling of major cardiovascular events in both diabetic and non-diabetic patients, with increased risk starting even below the diagnostic cut-off point.[11] Renal impairment with an eGFR below 60 ml/minute/l.73 m^2 is indicative of an even higher cardiovascular risk.[12]

Dyslipidaemia: T2DM is characterized by an atherogenic lipid profile, typically comprising elevated concentrations of small, dense low-density lipoprotein cholesterol (LDL-C), and high concentrations of triglycerides, triglyceride-rich remnants, very low-density lipoprotein cholesterol (VLDL-C) and apolipoprotein B, usually in combination with low concentrations of apolipoprotein A-1 and low high-density lipoprotein cholesterol (HDL-C). These abnormalities develop as a consequence of absolute or relative insulin deficiency. There is a strong relationship between total and LDL cholesterol and vascular events, such that a 1-mmol/litre reduction in LDL-C is associated with a 36% reduction in the risk of CVD.[13]

Glycaemic control and the glucose hypothesis: glucose control is crucial in reducing the risk of microvascular complications in people with diabetes. Epidemiological analysis of the UKPDS indicates that long-term hyperglycaemia is also associated with a higher incidence of macrovascular complications in T2DM.[14] Interestingly, this is also the case when glucose concentrations are high within the non-diabetic range.[15] Hyperglycaemia