Second Edition

Heart Disease

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pocket tutor

JP

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chapter 3

Atherosclerosis

Atherosclerosis is a progressive process of atheroma formation – arterial wall lesions of white blood cells, lipid and cholesterol deposits and cell debris. These 'plaques' form in the intima of large and medium arteries, and can develop to include scar tissue, thrombosis and calcification.

All larger arteries develop atheroma as we age, but in excess it can cause hardening of the arterial wall (sclerosis) and narrowing of the lumen. The resulting obstruction restricts blood flow to cause ischaemia of downstream tissues. If the plaque becomes unstable and ruptures, thrombosis and thromboembolism can cause acute blockage and infarction of tissue.

Atherosclerosis is the underlying cause of most coronary and cerebral arterial disease; the two biggest killers in the western world. It is also accelerated by diabetes mellitus and underlies most peripheral vascular disease (PVD).

3.1 Clinical scenario

Painful and cold right foot

Presentation

Carol Newton is a 56-year-old store manager who presents to her local emergency department with a painful and cold right foot.

Diagnostic approach

Foot pain is common, and causes include PVD, gout, plantar fasciitis and ligament sprain. However, a cold foot suggests a problem with the blood supply. History should establish:

- Onset
- If it is worsening
- Associated symptoms, such as numbness and radiation of pain

Further history

The pain has been increasing for a couple of days, was not preceded by trauma, and has no focal tender point. It is worse when she lies in bed, causing her to hang her foot out of the bed. She is a lifelong smoker but has no other significant past medical history and takes no medications.

Clinical insight

The symptoms of acute limb ischaemia are the six *P's*.

1. *P*ain
2. *P*ulseless
3. *P*allor
4. *P*erishingly cold
5. *P*araesthesia
6. *P*aralysis

Examination

Other than having blood pressure of 155/95 mmHg, Carol's cardiovascular, respiratory and abdominal systems are all normal. She is afebrile, has normal oxygen saturation and blood glucose.

Her right foot is pale and pulseless, with a delayed capillary refill time of 6 seconds. The most distally palpable pulse is the femoral artery. Dorsiflexion and plantar flexion are difficult and painful when done passively.

Diagnostic approach

Lack of trauma or focal tenderness suggests the pain is unlikely to originate from the musculoskeletal system or a single structure. Night pain is common in lower limb ischaemia, because the raised limb decreases blood flow; lowering the foot increases flow and decreases the ischaemic pain.

Smoking and hypertension are major risk factors for atherosclerosis, increasing the likelihood of PVD. Accordingly, her delayed capillary refill time suggests impaired blood supply due to either the heart or the arteries.

The normal oxygen saturation, blood glucose and temperature rule out hypoxia, hyperglycaemia, hypothermia or overt sepsis as contributing factors, respectively. Cardiogenic or septic shock is unlikely as only one limb is affected, and she is not hypotensive.

A unilateral pulseless and cold foot confirms an arterial aetiology, likely distal to her palpable femoral artery.

Investigations

An electrocardiogram (ECG) and further blood tests (including full blood count and tests of renal and liver function) are done and are all normal.

The ankle-brachial pressure index (ABPI) is <0.5 (75 mmHg/155 mmHg).

Diagnosis

The diagnosis is acute lower limb ischaemia, as indicated by the unilateral painful, cold and pulseless foot and ABPI of <0.5, confirming a significantly lower blood pressure in her right foot than her arms. The foot pain at rest and delayed capillary refill indicate that tissue viability is threatened. Her difficulty in moving the foot means that urgent revascularisation is necessary.

Clinical insight

Patients with peripheral arterial disease are at higher risk of coronary heart disease (CHD) and cerebrovascular disease.

The blood tests are performed to obtain preoperative baseline values as blood loss and significant organ injury may follow any limb or life-saving operation.

Carol's condition is likely due to peripheral arterial atherosclerosis caused by cigarette smoking and worsened by uncontrolled hypertension.

3.2 Atherosclerosis

Atherosclerosis is the most common arterial pathology and underlies most diseases of ischaemia and infarction. Its features depend on the site affected, resulting from arterial constriction at the lesion and embolic disease. Treatment can be symptomatic relief of vasoconstriction, surgical removal of a thrombus, and stabilisation or bypass of the plaque. Primary and/or secondary prevention aims to treat symptoms and decrease risk factors.

Epidemiology

Atheroma begins to form as fatty streaks in late childhood and progresses with age. By the eighth or ninth decades, all medium and larger arteries have some degree of atheroma.

Atherosclerosis causes more deaths than any other pathophysiology.

Non-modifiable risk factors include age, sex and genetic predisposition (**Table 3.1**). Symptomatic disease is most common in males over 40 years of age.

Risk factor	Definition	Mechanism
Smoking	Tobacco smoke	Provokes endothelial damage and thrombosis
High blood cholesterol	• Age, sex, heredity, and diet affect cholesterol • High total cholesterol > 6.2 mmol/L (240 mg/dL) • High LDL cholesterol >3.4 mmol/L (130 mg/dL)	Increases cholesterol deposition in arterial wall
High triglycerides	>4.5 mmol/L (400 mg/dL)	Increases lipid deposition in arterial wall
Hypertension	>140/90 mmHg	Provokes endothelial damage
Physical inactivity	• >4 hours sitting a day • <30 minutes exercise four times a week	Increases thrombosis and exposure of vascular endothelium to glucose, lipids and toxins and decreases cardiovascular muscle fitness
Diabetes mellitus	Most diabetics die from myocardial infarction secondary to atherosclerosis	Hyperglycaemia promotes endothelial and vascular connective tissue damage
Stress	History	Increased heart rate, blood pressure and circulating leucocytes
Obesity	BMI > 30 kg/m^2	Increases vascular workload

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3.1 Risk factors for atherosclerosis and their contributory mechanism.

Aetiology

The lipid-rich, inflammatory cell and debris deposits of atheroma are a part of normal ageing (**Figure 3.1**). However, the process is accelerated in individuals with a family history of coronary artery disease or stroke, hyperlipidaemia, diabetes mellitus, smoking and hypertension.

Location

Haemodynamics – the physical forces of blood flow – affects where plaques tend to occur. Branched or curved sections of arteries, or areas where blood flow changes velocity or direction, are prone to atheroma. These areas have non-laminar flow with associated low shear stress, which promotes endothelial dysfunction and monocyte infiltration. Atheroma occurs most in the aorta, followed by the carotid, coronary, and iliofemoral arteries.

Guiding principle

'*Athere-*' is from a Greek word for 'gruel', a reference to the gross appearance of atheroma. '*Sclerosis*' is from the word 'skleros' meaning 'hard', describing the hardened fibrous cap of plaques.

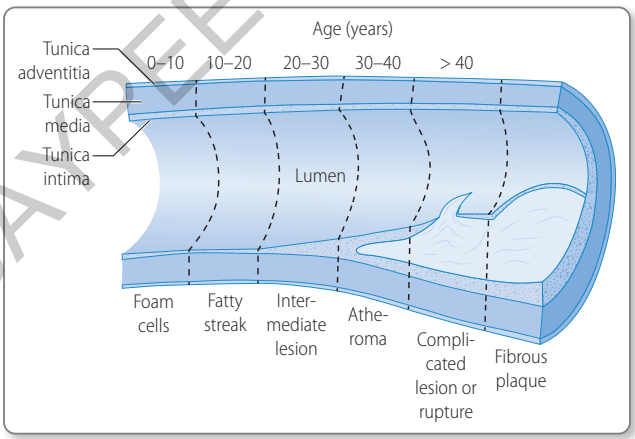

Figure 3.1 The progression of atherosclerosis.

Prevention

Prevention focusses on reducing modifiable risk factors with changes in lifestyle and medications (see Chapter 9). Lifestyle changes include cessation of smoking, regular exercise, weight loss if obese and control of diabetes and hypertension. A healthy diet is low in fat – especially saturated fat – salt, sugar, cholesterol, alcohol and high in fresh fruit and vegetables – and, therefore, antioxidants – and fibre.

Aggressive lowering of low-density lipoprotein (LDL) cholesterol can delay, stall and possibly even reverse atherogenesis.

Pathogenesis

Atherogenesis is generally considered a disordered response to endothelial injury, involving interactions between vascular endothelium, macrophages, smooth muscle cells, leucocytes and platelets (**Figures 3.1** and **3.2**).

- Endothelial injury occurs due to oxidised LDL, infections, toxins, free radical damage, hyperglycaemia or hyperhomocystinaemia, among others.

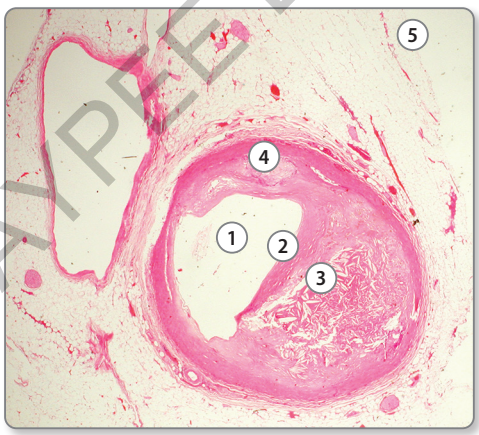

Figure 3.2 Haematoxylin and eosin staining of coronary artery (right) and vein (left). The artery shows a markedly diminished lumen (1) due to atherosclerotic plaque on the right side. There is a fibrous cap (2) overlying necrotic core matrix and cholesterol crystals (3). Some calcification is also present (4). Support fibrofatty tissue (5). Courtesy of Dr S.K. Suvarna.

- Vascular inflammation – monocytes in the blood adhere to and pass through the endothelium to infiltrate the arterial tunica intima and become macrophages, responsible for digesting debris and bacteria
- Foam cell formation and accumulation – macrophages consume oxidised LDL cholesterol to form foam cells, which promote inflammation (**Figure 3.3**)
- Foam cells proliferate to form the fatty streak – also known as intimal xanthoma – appearance of early atherosclerosis, along with T cells and smooth muscle cells
- Fibroproliferation occurs as activated smooth muscle cells and recruited fibroblasts produce extracellular matrix, i.e. scar tissue
- Scar tissue forms a fibrous plaque on the lumen side, covering the foam cells and deposits of lipid and necrotic cellular debris
- The plaque grows, stimulating neovascularisation of fragile vessels, and increasingly occluding the lumen.

Atherogenesis is generally progressive, but with periods of quiescence. Although it is a systemic disease, it manifests, usually at a late stage, with focal signs and symptoms. Symptoms develop as ischaemia progresses, or occurs acutely with plaque rupture or erosion, which can be catastrophic.

Plaque rupture Acute complications occur if the plaque ruptures or bleeds, promoting thrombosis and thromboembolism that can partially or completely block the artery (**Figure 3.4**). Rupture is predisposed by structurally unstable

Guiding principle

Vascular endothelial cells have important roles in atherogenesis, as key regulators of:

- Haemostasis, by secreting antithrombotic (e.g. heparin sulphate) and, under stress, prothrombotic molecules
- Blood flow, by secretion of vasodilators, e.g. prostacyclin and nitrous oxide, and when activated, vasoconstrictors (e.g. endothelin)
- The immune response – when stimulated by injury, they attract leucocytes with chemokines and express surface adhesion molecules to allow entry to the vascular wall.

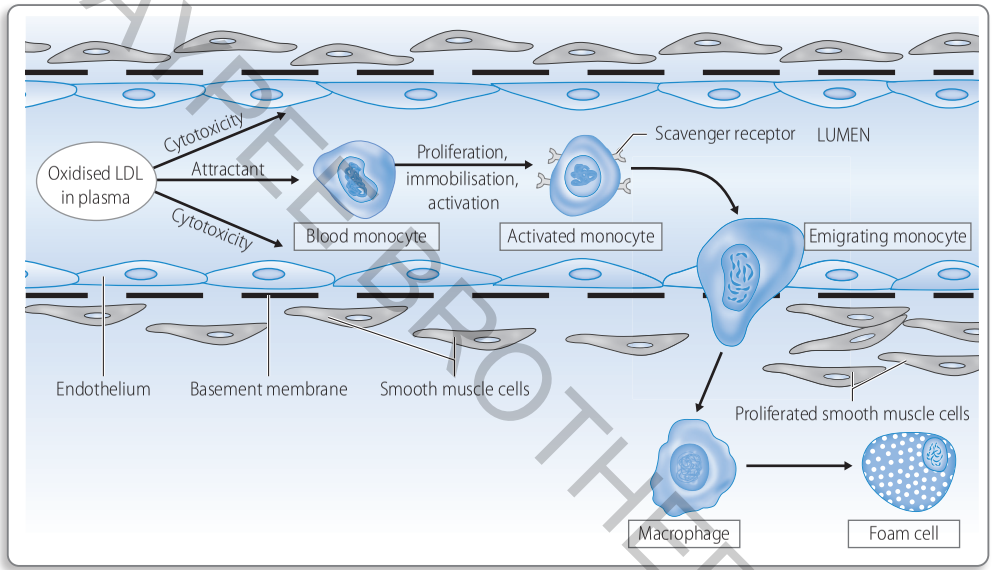

Figure 3.3 The formation of foam cells – the initiation of atherogenesis. LDL, low-density lipoprotein.

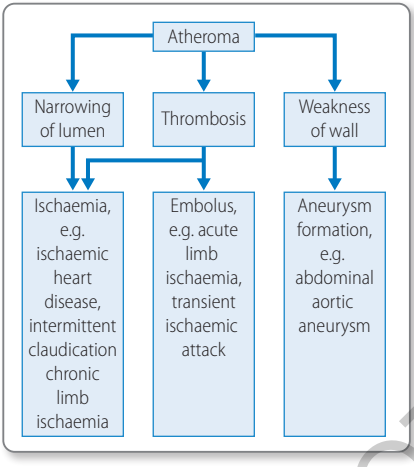

Figure 3.4
Complications of atherosclerosis.

fibrous caps and increasing size of the necrotic core. It is also associated with:

- Neovascularisation
- Intra-plaque haemorrhage/iron deposition in the lesion
- The presence of inflammatory enzymes
- Non-laminar blood flow
- Macrophage calcification

Atherosclerosis also weakens vascular connective tissue, increasing the risk of aneurysm formation and associated wall rupture.

Plaque erosion: Acute arterial occlusion can also occur when endothelium covering or near the plaque erodes to expose smooth muscle cells and extra cellular matrix. This initiates the clotting cascade and thrombosis, which can block the vessel at the lesion site or distally by thromboembolism.

Immune dysregulation: Vascular injury activates smooth muscle cells and endothelial cells to express inflammatory mediators, vasoactive compounds and surface adhesion molecules to recruit immune cells, i.e. monocytes/macrophages

lymphocytes, dendritic antigen-presenting cells and fibroblasts. This immune response is dysregulated in atherosclerosis.

The involvement of immune cells means there is some overlap with diseases of immune dysregulation, such as autoimmune disease. For example, continually raised levels of C-reactive protein are predictive of symptomatic PVD in later life.

Calcification: As plaque cells die, calcium deposits crystallise and collect at the border between the plaque and vascular smooth muscle. This intramural calcification occurs as plaques age, decreasing elasticity of the wall. In late stages, calcifications are seen on CT images as halos of increased radiodensity around atheromatous plaques.

Clinical features

Atherosclerosis can occur in any medium or large artery and is mostly asymptomatic. It causes signs and symptoms by obstruction of blood flow at the site of atheroma or acute thromboembolic occlusion downstream (**Table 3.2**). Lesions

Site	Ischaemic pathology	Infarcted pathology
Coronary arteries	Angina	
Carotid arteries	Transient ischaemic attack	Haemorrhagic or ischaemic cerebrovascular accident
Cerebral arteries		
Iliofemoral arteries	Intermittent claudication	Impotence, persistent ulceration and infection of peripheries, necrosis, and gangrene
Mesenteric arteries	Mesenteric angina – epigastric postprandial pain	Haematemesis, haematochezia, diarrhoea, melena, nutritional deficiencies, and weight loss
Renal arteries	Renal artery stenosis; resistant hypertension	Kidney atrophy, necrosis, and renal failure

Table 3.2 The site of atherosclerosis and associated features of ischemic and infarcted pathology.

increase the risk of aneurysm or dissection of an artery. For example, an abdominal aortic aneurysm presents as an asymptomatic pulsatile abdominal mass but is at increasing risk of rupture and massive haemorrhage as it increases in size.

Ischaemic pain, such as leg claudication or angina, increases proportional to exertion, as the metabolic needs of tissues are not met by the limited blood supply. Conversely, it improves on rest.

Lesions may be evident on palpation as pulsatile, hardened masses, and bruits heard on auscultation due to turbulent blood flow.

All patients should be assessed for features of atherosclerotic risk factors, as most diseases are asymptomatic, and prevention is based on control of modifiable risk factors (**Table 3.3**).

Clinical insight

Atherosclerosis is a systemic disease; evidence of it in one artery usually indicates its presence in other arteries. For example, peripheral vascular disease (PVD) strongly suggests that there are similar lesions in the coronary arteries.

Diagnostic approach

Diagnosis involves assessing for atherosclerotic risk factors, imaging of arteries to visualise lesions and loss of lumen patency, stress testing to indicate loss of blood flow as well as assessment of end-organ damage due to ischaemia or infarction.

Risk factor	Clinical features
Smoking	History; tar-stained fingers or hair
High blood cholesterol/triglycerides	Xanthelasma and tendon xanthoma
Hypertension	BP > 140/90 mmHg
Sedentary lifestyle	History, overweight or obese
Diabetes mellitus	History, raised blood glucose, or
Obesity	HbA1c

HbA1c, glycated haemoglobin.

Table 3.3 The main clinical features of risk factors for atherosclerosis.

Investigations

Atherosclerotic disease is investigated with blood tests to assess for risk factors or signs of end-organ damage, imaging to visualise the lesion and functional tests that gauge the ischaemic effect of the lesion.

Laboratory tests: A lipid profile assesses for hyperlipidaemia; high levels of LDL cholesterol are associated with increased atherosclerosis. Blood glucose and glycated haemoglobin (HbA1c) are measured to monitor for diabetes mellitus.

Some blood tests, such as cardiac enzymes, can indicate the timing and extent of tissue ischaemia or infarct. A raised white blood cell count is often found post-myocardial infarction.

Imaging: Doppler ultrasound is used to quantify the extent of atherosclerotic stenosis in the carotid arteries. Angiography can be performed in cerebral, coronary, peripheral, mesenteric or renal arteries to visualise the extent of narrowing. As contrast is injected into the circulation, the lumen is visible on X-ray, CT or MRI. CT is usually best as it is high resolution and quicker to perform than MRI.

CT calcium scoring quantifies the amount of calcification present within the coronary circulation, which correlates with plaque size. It does not show areas of soft plaque or thrombus.

Imaging can be essential for diagnosing and assessing end-organ damage from infarction. For example, a CT of the head is essential to investigate a suspected cerebrovascular accident.

Functional testing: Stress testing, such as the cardiac stress test, is used to assess the significance of a coronary stenosis and can indicate loss of function due to ischaemia.

Management

Primary and secondary prevention focusses on control of risk factors, including lifestyle changes and medication.

Symptomatic treatment, such as glyceryl trinitrate, relieves ischaemic pain. Revascularisation of the circulation is either by percutaneous intervention using stents or bypass surgery.

Lifestyle: Lifestyle changes reduce or control modifiable risk factors and are central to primary and secondary prevention:

- Smoking cessation
- Strict control of hypertension and diabetes
- Regular aerobic exercise, i.e. >30 min/day most days of the week
- A Mediterranean-style diet, rich in fresh fruit and vegetables.

The widespread incidence means all patients should be encouraged to meet these targets, which also benefit general health and well-being.

As disease remains asymptomatic until a late stage, patients can be motivated by discussion of cardiovascular or cerebrovascular risk scores, and referral to fitness training, dietitians or other specialists.

Medication: Common medications include those to manage hyperlipidaemia, hypertension, diabetes mellitus and smoking cessation.

Surgery: Surgical treatments are indicated for patients with ongoing symptoms despite optimal medical management.

Clinical insight

Venous grafts used in heart bypass surgery also develop atherosclerosis.

Prognosis

Atherosclerosis is a multifactorial disease with a genetic predisposition, but lifestyle plays an equally important role. Patients present in many ways and symptoms do not clearly correlate with the level of atherosclerosis. Some patients remain asymptomatic throughout life, while for others the first sign may be sudden cardiac death.

Although primary prevention and medical and surgical symptomatic treatments are improving, there is no direct treatment of the underlying disease.

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