Examining patients with dyslipidaemia may be useful in several ways. Some physical signs alert the examiner to the presence of a disturbance in lipoprotein metabolism and should prompt laboratory testing. In other patients dyslipidaemia may already have been documented in the laboratory and the physical examination is directed at finding physical signs that help clarify the nature and aetiology of the lipid disorder. A careful physical examination, especially of the cardiovascular system, may also reveal evidence of as yet unrecognised atherosclerotic complications and indicate the need for lipid-lowering treatment irrespective of the severity of dyslipidaemia.

This article describes physical signs that are directly attributable to dyslipidaemia. Most of these signs are easy to find and interpret, as they reflect the deposition of excess lipids in the skin, tendons or cornea. Plasma can be readily inspected after the blood sample has stood for a while (or has been centrifuged) and the ophthalmoscope allows the visualisation of the retinal vasculature.

Cutaneous signs
Triglyceride-rich lipoproteins have a particular predilection to deposit in the skin. Cutaneous stigmata of hyperlipidaemia are therefore most commonly seen in severe hypertriglyceridaemia but also occur in extreme hypercholesterolaemia.

Xanthelasma (Fig. 1) are the exception to the above rule. They do not always signify dyslipidaemia, but should prompt lipid screening. Xanthelasma do not aid classification of the dyslipidaemia.

Eruptive xanthomata (Fig. 2) occur with severe hypertriglyceridaemia of any cause. They are small yellow to flesh-coloured papules that may have an erythematous base. They are usually asymptomatic. They tend to occur in crops and then enlarge with time. Eruptive xanthomata may coalesce to form tuboeruptive
xanthomata (Fig. 3). Eruptive xanthomata are most commonly found around the elbows, knees and buttocks, but can occur anywhere on the body. Because severe hypertriglyceridaemia can cause acute pancreatitis patients with eruptive xanthomata must be investigated and treated with urgency.

Planar xanthomata are flat yellow to orange plaques. If found in the palmar creases they are called palmar crease xanthomata (Fig. 4) and are diagnostic of dysbetalipoproteinaemia. Interdigital xanthomata (Fig. 5) and planar xanthomata in other skin creases are seen in homozygous familial hypercholesterolaemia and occasionally in dysbetalipoproteinaemia.

Tuberous xanthomata (Fig. 6) are firm painless yellow-red nodules that may coalesce to form multilobulated lesions. They are most commonly found on the extensor surfaces of the elbows and knees. Tuberous xanthomata are most commonly seen in homozygous familial hypercholesterolaemia, but are also found in severe heterozygous familial hypercholesterolaemia.

Tendon xanthomata

Tendon xanthomata are most commonly found in the Achilles tendon (Fig. 7) or the extensor tendons of the hand (Fig. 8). On examination one feels for a nodularity of the tendon surface or thickening of the tendon. The nodule moves with the tendon. Routinely palpating the Achilles tendons ensures that xanthomata are not missed and also gives one a good appreciation of the range of normality. Tendon xanthomata are very important physical signs; their presence always indicates a serious problem. They are most commonly found in familial hypercholesterolaemia, but also occur in dysbetalipoproteinaemia and some rare disorders of sterol metabolism.

Ocular signs

Arcus cornealis (Fig. 9) reflects the deposition of lipids in the cornea. Its prevalence increases with age and is also higher in smokers and blacks. If found
in young (<40 years) patients it should prompt lipid screening. Arcus is associated with hypercholesterolaemia but its presence does not help to classify the lipid disorder. Lipaemia retinalis (Fig. 10) may be seen in severe hypertriglyceridaemia. Rare disorders of HDL metabolism may cause corneal clouding (‘fish eye disease’).

**Lipaemia**

White or milky serum or plasma (Fig. 11) indicates severe hypertriglyceridaemia and urgent action needs to be taken to avoid an episode of pancreatitis. Most commonly lipaemia will be observed in the laboratory and a comment of ‘lipaemic serum’ on the laboratory report should never be ignored.

**Screening**

International guidelines recommend 5-yearly screening intervals in low-risk patients. However, in the South African public sector, with its limited resources, one should aim to screen all adults at least once. A random total cholesterol level is sufficient for screening, but it should be followed up by a full lipid profile on a fasting sample if the total cholesterol is >5 mmol/l. Exceptions are patients with existing cardiovascular disease (CVD), a family history of premature CVD (men <55 years, women <65 years), or clinical signs of dyslipidaemia – in these patients a full fasting lipogram should be the initial investigation.

In cases of abdominal obesity, high-density lipoprotein cholesterol (HDLc) and fasting triglyceride (TG) levels will contribute towards identifying patients with the metabolic syndrome. Decreased HDLC (<1.03 mmol/l in men and <1.29 mmol/l in women) and elevated TG (>1.7 mmol/l) levels are 2 of the 5 International Diabetes Federation (IDF) diagnostic criteria of the metabolic syndrome. This syndrome signals increased cardiovascular and diabetes risk.

**Basic tests**

Before a fasting lipogram is done, patients must receive clear instructions to ensure reliable results. They should not eat, drink (except water) or smoke for 12 hours before the blood test. Patients should maintain their usual diet, weight and activity level for at least 2 weeks before the test. Total cholesterol can be measured with good accuracy for opportunistic screening in patients who have not fasted. Diabetes may cause secondary hyperlipidaemia, and hyperglycaemia is an important contributor to cardiovascular risk. If the patient is fasting for a lipogram, glucose should also be measured.

Although laboratories often refer to ‘normal’ lipid ranges, it is important that the result be interpreted in the context of the individual patient. Many patients with ‘normal’ lipid values need lipid-lowering therapy, but there are also patients with ‘elevated’ levels who do not need treatment. When titrating therapy, a fasting lipid profile every 4 - 12 weeks is recommended. Thereafter, annual reassessment is probably sufficient.

In cases of hypercholesterolaemia, secondary causes should always be considered. Screening can be done for suspected alcohol abuse with gamma-glutamyl transferase, carbohydrate-
More about... genetic lipid disorder, genetic analysis may or physical signs suggestive of a severe cholesterol >8 mmol/l or LDLC >6 mmol/l also suggest small, dense LDL particles. A high LDLC level may for this purpose is still firmly entrenched. A very high apoB level that is disproportionally of CVD risk than total cholesterol or LDL hypertriglyceridaemia and carry a 2 - 3 times higher CVD risk. Assessment of dense LDL particles are associated with homocysteine concentration is an increased LDL particle size by electrophoresis is performed in lipid reference laboratories and may be done in patients with raised TG levels as part of optimal CVD risk assessment. Apolipoprotein B100 (apoB) is the structural protein of the atherogenic lipoproteins. Large epidemiological studies have shown that apoB is a better marker of CVD risk than total cholesterol or LDL cholesterol (LDLC), but use of a lipogram for this purpose is still firmly entrenched. An apoB level that is disproportionally high compared with the LDLC level may also suggest small, dense LDL particles.

In patients with very high lipid levels (total cholesterol >8 mmol/l or LDLC >6 mmol/l), a family history of severe dyslipidaemia or physical signs suggestive of a severe genetic lipid disorder, genetic analysis may be useful. A monogenic disorder affects treatment goals and genetic counselling may be offered. Non-lipid cardiovascular risk factors Non-traditional cardiovascular risk factors include high-sensitivity C-reactive protein (CRP) and homocysteine. Elevated CRP is strongly associated with CVD in epidemiological studies, but the benefit of routinely also measuring CRP in conventional risk assessment is controversial.† Moderate elevations of homocysteine may be caused by insufficient folate and vitamin B₁₂, a polymorphism in the methylenetetrahydrofolate reductase gene, renal failure or incorrect specimen handling. An increased homocysteine concentration is an independent epidemiological risk factor for CVD, but opinions differ with regard to the routine measurement of homocysteine. Intervention studies targeting homocysteine have generally disappointed.† Homocysteinuria is a rare genetic disorder that presents with arterial and venous thromboses in young patients – in such cases, with otherwise unexplained CVD or thromboses, homocysteine testing is important.

Conclusion
During cardiovascular risk assessment the laboratory tests performed will depend on the individual patient, the financial resources available and the complexity of the clinical scenario. Consultation with a medical pathologist should be considered, as the use and interpretation of laboratory tests are not always straightforward.

References

Atherosclerosis imaging – how and whom?
K H WOLMARANS, MB ChB
Medical Officer, Lipid Clinic, Groote Schuur Hospital and Lipid Laboratory, University of Cape Town Health Science Faculty

Coronary artery disease (CAD), cerebrovascular disease (CVD) and peripheral artery disease (PAD) cause significant mortality and morbidity. Clinical management in the symptomatic patient is aimed at treatment, while primary prevention requires early identification of asymptomatic individuals. The role of imaging is discussed.

Atherosclerosis
Atherosclerosis is a disease of the arterial wall. Arterial walls consist of three layers: intima, media and adventitia. When low-density lipoprotein (LDL) cholesterol infiltrates the subendothelial space and becomes oxidised, a complex inflammatory process is triggered. Plaques with large lipid cores and thin fibrous caps are vulnerable to rupture, resulting in thrombus formation and possible arterial occlusion. In early atherosclerosis there is thickening of the arterial wall. Narrowing of the lumen occurs late. There is a long subclinical period. Clinical presentation may be acute, with sudden death, myocardial infarct or stroke (occlusion) or chronic, with effort-induced stable angina pectoris or claudication (narrowing).

Risk factors
Large epidemiological studies have identified atherosclerosis risk factors including age, male gender, ↑LDLC, ↑ triglyceride, ↓ HDLC, hypertension, diabetes and smoking. Guidelines
stratify management according to CAD risk, calculated in primary prevention settings using the Framingham risk score (FRS) (USA) or Systemic Coronary Risk Evaluation (SCORE) (Europe).

Imaging modalities

Angiography

Conventional angiography (catherisation), CT angiography (CTA) and MR angiography (MRA) allow imaging of the lumen. Although conventional angiography is invasive, angioplasty and stent placement is possible. Both conventional and CT angiography expose the patient to ionising radiation and involve the use of contrast. CTA and MRA are non-invasive. However, CTA and MRA of the coronary arteries are technically difficult due to movement, small diameter (3 - 4 mm) and tortuosity of the arteries. The use of beta-blockers to slow the heart rate and ECG gating to allow imaging in mid-diastole may be needed to reduce motion artefacts. In selected patients with stable disease and normal cardiac rhythm multidetector CT (MDCT) has sensitivity of 96% and specificity of 74% for detection of significant coronary artery stenoses (>50% narrowing).²

It is not possible to identify early atherosclerosis or vulnerable plaque on an angiogram. Angiography is used in the evaluation of symptomatic patients and in clinical trials. It is not used in epidemiological studies or screening.

Ultrasound

Brightness mode (B-mode) ultrasound images the artery wall and is used to detect plaque in the carotid artery and peripheral arteries. Coronary arteries are too small and tortuous and are located deep within the chest cavity. Doppler studies are used to assess flow and quantify obstruction.³ Ultrasound is safe, non-invasive and without radiation exposure. Ultrasound is used in symptomatic patients and for evaluating the asymptomatic bruit. Doppler is not used in epidemiological studies as flow increases once disease is advanced.

Intima-media thickness (IMT)

B-mode images of the carotid and femoral arteries are analysed using computer software. The average distance between the lumen-intima and the media-adventitia interfaces is measured over a segment of arterial wall. Far wall IMT is more accurate and common carotid IMT more reproducible than bulb or internal carotid measurements. There is good agreement with histology.² In the Atherosclerosis Risk in Communities study (ARIC), the 75th percentile was 0.65 mm in men 35 - 45 years; 1.2 mm in men >65 years; 0.6 mm in women 35 - 45 years and 1.1 mm in women >65 years.² Common carotid IMT increases by approximately 0.010 - 0.012 mm/year. IMT is associated with risk for CAD and stroke.³ In a meta-analysis of eight studies relative risk of MI per 1 SD in common carotid IMT was 1.26 (95% CI 1.21 - 1.3) and per 0.1 mm difference 1.15 (95% CI 1.12 - 1.17). Relative risk of stroke per 1 SD in common carotid IMT was 1.32 (95% CI 1.27 - 1.38) and per 0.1 mm difference 1.18 (95% CI 1.16 - 1.21).⁷

Advantages of IMT are that it is a non-invasive, focused study with few incidental findings.² Potential problems are that it is difficult to establish age- and gender-adjusted norms, because laboratories use different protocols. Methods also need to be standardised.⁶ IMT is used in epidemiological studies, and as surrogate endpoint in statin and antihypertensive trials. It has a possible use in individual patients to help quantify risk.

Intravascular ultrasound (IVUS)

IVUS uses a miniature ultrasound probe inside a coronary artery catheter. Images of the arterial wall are acquired during cardiac catheterisation and allow measurement of plaque volume and characterisation of plaque. The disadvantage of IVUS is that it is invasive.

It is used in research, but is not suitable for epidemiological studies or screening.⁸

Coronary artery calcium score (CACS)

The measurement of calcium in coronary arteries by rapid CT scan (CACS score) correlates well with histological findings and is predictive of CAD.³ Non-stenotic lesions may display calcification, resulting in high sensitivity but poor specificity for the detection of significant stenoses.⁹ Although CACS score has a poor positive predictive value for near-term events,³ patients with calcified plaques are more likely to have non-calcified plaques that may rupture. A meta-analysis of studies of CAD risk in 27 622 asymptomatic individuals and CACS found a summary relative risk ratio of 4.3 (95% CI 3.5 - 5.2) for any measurable coronary calcium compared with CACS score of 0 (p<0.0001).¹⁰

Advantages of CACS are good spatial resolution, fast image acquisition and sensitive calcium detection.¹¹ Dis-advantages include ionising radiation and incidental findings such as pulmonary nodules.

CAC is useful in asymptomatic individuals with intermediate FRS (10 - 20%) to discriminate higher risk, but not in patients with risk >20% or <10%. It is also not recommended in symptomatic patient (nonspecific for obstructive coronary disease)¹² or for routine screening.¹²

MRI

MRI using the ‘black-blood’ technique (wall shows up as white structure) allows non-invasive imaging of the arterial wall, characterisation of plaque and fibrous cap and can be used to study plaque progression and regression.¹³ Measurements of wall thickness, wall area and total plaque volume are highly reproducible, with little error in wall area measurement (aorta 2.6%; carotids 3.5%).¹¹

Advantages of MRI are that it is non-invasive, there is no radiation, and it does not require contrast. It also has good resolution. It is used to study carotid arteries in epidemiological studies and clinical trials, but is difficult to use in coronary arteries.

Conclusion

In conclusion, imaging techniques are becoming increasingly sophisticated. Atherosclerosis can be imagined using different modalities – some are used in clinical practice and others only for research purposes. Factors such as availability, cost, radiation dose, possible nephrotoxic effects of contrast and the specific vascular bed to be imaged, need to be considered.

References


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Getting the diet right

CECYL FULLER, RD (SA), BSc (Dietetics and Physiology), Dip Hosp Diet, BSc (Med) (Hons) Sport Science
Private Practising Dietitian, Cape Town

Getting the diet right is an initial, effective and low-cost approach to the management of patients with dyslipidaemia, but has become increasingly more difficult and challenging to promote with the widespread availability of lipid-lowering drugs. There is no doubt that dietary changes can significantly reduce total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides, often reducing the need for drug therapy.

However, dietary compliance requires highly motivated patients who are able to manage their diets despite our modern lifestyle. Although the food industry and fast-food chains do occasionally provide healthier alternatives, the less healthy options often are cheaper, more readily available and marketed aggressively.

Ideally all patients with dyslipidaemia should receive dietary counselling as it educates and teaches patients how to incorporate appropriate foods into their current eating patterns and how to make long-term dietary changes. Often patients have multiple medical conditions/risk factors (overweight, hypertension and diabetes) each with specific dietary recommendations and they therefore need to integrate information on food, nutrients and meal preparation with their cultural background and socio-economic status.

It has been recommended that patients receive at least three sessions of dietary counselling, as this would translate into a substantial annual cost saving on medications. Unfortunately not all patients have access to the services of a registered dietitian.

Hypercholesterolaemia
The primary focus of diet therapy for the prevention and treatment of hypercholesterolaemia is to progressively lower saturated fatty acid and cholesterol intake at an energy level that supports optimal weight management. Other dietary modifications may also be necessary for particular patient subgroups.

Dietary fats: amount and quality
Dietary intake of fats strongly influences the risk of coronary heart disease and stroke through effects on blood lipids, thrombosis, blood pressure, endothelial function and inflammation. Manipulating the qualitative composition of fats in the diet can modify this risk significantly (Table I).

The traditional target is to restrict the intake of saturated fatty acids to less than 10% of daily energy intake and less than 7% for high-risk groups. A very low intake of less than 1% of daily energy intake for trans fatty acids (hydrogenated oils and fats) is recommended.

Diet should provide an adequate intake of poly-unsaturated fatty acids (PUFAs) with an optimal balance between n-6 PUFAs and n-3 PUFAs. Mono-unsaturated fatty acids (MUFAs) should make up the rest of the daily triglyceride intake, so that the triglycerides provide 20 - 30% of daily calories.

Dietary cholesterol
Cholesterol in the blood and tissues is derived from two sources: diet and endogenous synthesis. Animal products (especially dairy fat and meat) are the only dietary source of cholesterol. There is no requirement for dietary cholesterol and it is advisable to keep the intake as low as possible, i.e. <300 mg/day and lower (100 - 200 mg/day) for individuals at high risk.

Dietary plant sterol supplements have been shown to reduce LDL-C by 10 - 20% by inhibiting cholesterol absorption. Patients can include commercial products (margarine, yoghurt) which contain plant sterols and stanols into their daily diet provided they are substituted for foods of a similar fat content.

Hypertriglyceridaemia
Lifestyle and dietary changes are critical for individuals with hypertriglyceridaemia and depending on the severity of the hypertriglyceridaemia, a dramatic restriction of total triglyceride intake (<30 g fat/day) may be sufficient to lower and maintain triglycerides at a desirable level without the need for medication.

Apart from the benefits derived from a very low-fat diet, patients with hypertriglyceridaemia also need to avoid alcohol or reduce their consumption to minimal levels. Fish oil supplements have been shown to lower triglycerides and patients with moderate hypertriglyceridaemia can be treated with fish oil supplements that provide 2 - 4 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day. A practitioner with experience in the management of hypertriglyceridaemia should monitor the patient.

Table I. Fat intake goals: amount and quality

<table>
<thead>
<tr>
<th>Dietary fat</th>
<th>Goal (% of total energy)</th>
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<tbody>
<tr>
<td>Total fat</td>
<td>15 - 30%</td>
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<tr>
<td>Saturated fatty acids</td>
<td>&lt;10%</td>
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<tr>
<td>Polyunsaturated fatty acids (PUFAs)</td>
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<td>n-6 PUFAs</td>
<td>5 - 8%</td>
</tr>
<tr>
<td>n-3 PUFAs</td>
<td>1 - 2%</td>
</tr>
<tr>
<td>Trans-fatty acids</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Monounsaturated fatty acids (MUFAs)</td>
<td>By difference</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;300 mg</td>
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</table>
Summary
Although these dietary goals and recommendations are commonly used as initial interventions, dietary advice needs to be individualised based on nutritional assessment, body mass index (BMI), co-existing risk factors, lifestyle and lipid-lowering goals. Patients eat foods, not nutrients, and the following goals need to be quantified and translated into foods to be meaningful for patients:

- Limit the intake of fat from meat and dairy sources.
- Avoid the use of hydrogenated oils and fats in cooking or foods that contain these.
- Use vegetable oil in small amounts.
- Eat oily fish (salmon, sardines, pilchards and mackerel) regularly (i.e. twice a week).
- Use non-frying methods to prepare food.

In addition to focusing on the type and amount of fat in the diet, the balance of energy intake and physical activity should be tilted towards achieving or maintaining ideal body weight. Consuming wholegrain high-fibre foods, plenty of fruit and vegetables and reducing alcohol and salt intake also optimise the dietary response.

Further reading

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Single Sutures

Men better at curbing hunger pangs than women
A study published in the Proceedings of the National Academy of Sciences suggests that men are better than women at avoiding temptation when they are hungry. After fasting, 23 non-obese adults were offered their favourite foods. Some of the group were told to suppress their thoughts about eating, while the rest of the group were allowed to behave as they pleased.

Self-reported desire to eat and hunger increased to a similar extent in both sexes, as did whole-brain metabolism as shown by positron emission tomography. Deliberate cognitive inhibition of the desire for food reduced reports of hunger in both sexes, but only the men showed decreased activity in regions of the brain activated by food stimuli.


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Speed of thought important in the elderly’s ability to drive
Elderly drivers are usually thought to be limited by eyesight, general health and their physical functioning. However, a recent study in the Gerontologist suggests that cognitive processing ability is the best predictor of whether or not an elderly person should still be driving.

The study was carried out on 1 838 people participating in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study who were drivers at baseline and completed the 3rd-year assessment. None suffered from dementia. All participants were tested at baseline for health, sensory function, physical function, cognitive abilities, instrumental functional performance and depressive symptoms. They were followed up for 3 years, when their driving status was again assessed.

There were 4 significant risk factors for stopping driving – older age, poor balance, slower cognitive speed of processing, and poorer instrumental functional performance. These latter 2 risk factors appeared to be the most important.