Cholesterol

Frequently asked questions

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The cholesterol was a bit high (7.1 mmol/L) but the patient wasn't fasting. Does this matter?

Not fasting has little effect on low density lipoprotein cholesterol (LDL-C) but can have some effect on high density lipoprotein cholesterol (HDL-C) and a dramatic effect on triglyceride (TG). Because of the effects on HDL-C and TG it is recommended that specimens be collected after at least 10 hours of consuming only water and preferably abstaining from smoking. Because prolonged fasting can decrease cholesterol and diurnal variation occurs, specimens should be collected early in the day and at the same time of day for an individual patient.[1]

Venostasis can increase all the lipid values as filtration of plasma will increase the concentrations of all proteins in the sample including lipoproteins. This can be important in patients where venesection is difficult and tourniquets may be left in place for a long time. In such patients, the laboratory should be requested to take a nonstasis specimen.

The stress associated with an acute illness can decrease cholesterol. For example, it is important to collect a specimen for cholesterol as close as possible to the onset of chest pain in someone suspected of having a myocardial infarction. Delaying for more than 2 days can result in misleadingly low values.

There are a range of secondary causes of hypercholesterolaemia (*Table 1*) and these should be excluded before treating a high cholesterol value which could be a sign of an underlying disease rather than the primary problem itself.

The total cholesterol was high (6.0 mmol/L) but the triglyceride was normal (1.0 mmol/L). Both the LDL-C and HDL-C were high (4.4 and 2.2). Should I start a statin?

First it would be important to confirm that the 'abnormalities' are real and not the result of some collection error (eg. venous stasis). Assuming the high values of both LDL and HDL-C are confirmed, the next step is to consider the person's absolute risk of a cardiovascular event. There is a range of tools available, some in general practice medical software. The New Zealand Guidelines Group[2] cardiovascular risk tables are commonly used and are promoted by the National Heart Foundation. High risk is defined as an absolute risk exceeding 15% of a cardiovascular event in the next 10 years.

Assuming the person is in the high risk category where hypolipidaemic therapy should be considered, the final step is to check for eligibility for a Pharmaceutical Benefits Schedule (PBS) subsidy (*Figure 1*). This depends on the absolute level of the three lipids. In this case the HDL cholesterol exceeds 1 mmol/L so, for the statin therapy to be subsidised, the total cholesterol must exceed 6.5 mmol/L unless the person has a history of ischaemic heart disease or peripheral vascular disease where the level is set at 4 mmol/L.

I started a statin and 3 months later the cholesterol had gone up! Why did this happen?

This problem may reflect an earlier omission. Neglecting to ensure appropriate collection at baseline or subsequently may result in comparing 'apples with pears' (eg. a nonstasis with a stasis specimen or a stress related specimen with a nonstress specimen). As noted it is important to ensure that the specimen has been collected

Table 1. Secondary causes of hypercholesterolaemia

- Pregnancy
- Endocrine disorders
  - hypothyroidism
  - uncontrolled diabetes
  - Cushing disease
- Renal disorders
  - nephrotic syndrome
  - uraemia
- Liver disease
  - obstructive jaundice
  - chronic liver disease
- Medications
  - oestrogens
  - progestogens
  - thiazides
  - protease inhibitors
- Rare
  - acute intermittent porphyria
  - anorexia nervosa
  - monoclonal gammopathy

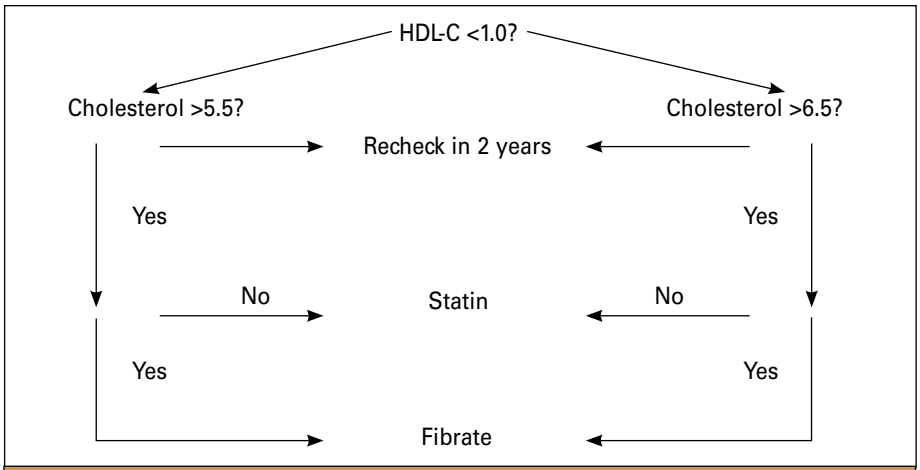

Figure 1. PBS guidelines – medications for diabetic dyslipidaemia[7]*

* In patients with ischaemic heart disease or peripheral vascular disease, a total cholesterol >4.0 mmol/L qualifies for PBS subsidy. Private prescriptions can be provided for patients who do not meet PBS guidelines

Targets recommended by the National Heart Foundation because those with diabetes are in a high cardiovascular risk group:

- Total cholesterol <4.0 mmol/L
- HDL-C >1.0 mmol/L
- Triglycerides <1.5 mmol/L
- LDL-C <2.5 mmol/L

appropriately and that secondary causes are excluded before starting therapy. Even then cholesterol values may vary overall by over 7%.[1,3]

The least significant change (LSC) is the change that is likely to be caused by a change in the clinical state as opposed to variability within the individual. To be 80% confident that the change is clinically significant, the LSC is an increase or decrease by more than 14%.

One way of improving the capacity to interpret changes is to establish a firmer baseline and follow up values. Appropriate collection of two specimens before starting therapy and repeating follow up checks if unexpected results occur, make it more likely that correct therapeutic decisions will be made.

The statin at 20 mg per day has only decreased cholesterol from 7.0 to 6.1 mmol/L and I would like to increase the dose. Should I worry about muscle, liver or other problems?

Statins are highly effective but they have three major limitations:

- the rule of sixes
- doubling dose more than doubles side effects, and
- statin run out.[4]

Lifestyle change can result in a 10% change in cholesterol. Adding a low dose statin (10 mg/day) might reduce it a further 20%, but further doubling adds only 6% to the effect with each doubling.

Unfortunately the decreasing statin effect on cholesterol is not associated with a decrease in the risk of side effects. In fact, the risk of muscle and liver side effects more than doubles with doubling of the dose.[5] Moreover the effectiveness of a statin decreases with time with the LDL increasing by some 10% over 6 months. This occurs even in clinical trials where dosage adherence is required to be at least 80%. In the real world, where adherence is likely to be much less, the effect of prescribed statin is accordingly reduced.

These limitations are especially important where there are special risks associated with statin therapy. For example, older age, female gender, and certain conditions and medications increase the risk of side effects (*Table 2*).[6] In these groups often only lower dose statin therapy is safe (eg. 5–10 mg per day).

Ezetimibe offers an alternative to increasing statin dose as it decreases gastrointestinal cholesterol absorption as opposed to decreasing hepatic cholesterol synthesis as the statins do. Ezetimibe adds a further 15% to the reduction in cholesterol. Unfortunately it also adds to the risk of side effects. However the benefit/risk ratio is better than doubling the statin dose because of a 15 versus 6% decrease in cholesterol and a 30 versus >100% increased risk of muscle problems with ezetimibe versus statin doubling.[4]

Conflict of interest: none.

Table 2. Factors increasing statin myotoxicity

- Major illness
  - severe infection
  - surgery
  - trauma
  - hypoxia
  - hypothermia
  - uncontrolled seizures
- Chronic illness
  - debilitation
  - chronic renal or liver failure
- Endocrine and metabolic disorders
  - hypothyroidism
  - hyponatraemia
  - metabolic acidosis
- Medications (inhibit CYP3A4*)
  - fibrates (gemfibrozil more than phenofibrate)
  - macrolide antibiotics
  - azole antifungals
  - calcium channel blockers (verapamil, diltiazem)
  - antidepressants (fluoxetine, fluvoxamine)
- Other
  - warfarin
  - cyclosporin
- Viral infection
  - concomitant use of recreational drugs

* Atorvastatin and simvastatin more than pravastatin; grapefruit juice also inhibits this enzyme

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