Cholesterol

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Cholesterol is a fatty substance circulating in the blood. It is essential for synthesising steroid hormones, vitamin D and bile acid, and it also forms part of cell membranes. Cholesterol is made in the liver, and it can also be ingested via certain foods.

As cholesterol is not water soluble, it is transported in blood in particles called lipoproteins. The alipoprotein B (apoB) containing molecules, such as low-density lipoprotein (LDL), are pro-atherogenic, and high circulating levels are associated with an increased risk of cardiovascular disease (CVD) and cardiovascular mortality.[1, 2]

High levels of serum cholesterol are linked to an increased risk of cardiovascular disease (CVD),[3-5] hence treating hypercholesterolemia is a key goal in the treatment and prevention of atherosclerotic CVD, one of the leading causes of death worldwide.[6]

Elevated levels of LDL cholesterol (LDL-C), in particular, are a well-recognised risk factor for atherosclerosis and CVD. These lipoproteins are more easily trapped in the arterial wall and more susceptible to oxidation. Oxidised LDL can be taken up by macrophages, forming a cholesterol-rich foamy cell, which accelerates the growth of plaque in the arteries. It has been recognised, however, that other pro-atherogenic lipoproteins are also crucial in the development of CVD, not just LDL-C. These include all types of cholesterol except high-density lipoprotein (HDL).[1]

These lipoproteins are grouped together, and referred to as non-HDL cholesterol, and have been shown to be a better predictor of CVD risk than LDL-C levels alone.[7] The National Institute for Health and Care Excellence (NICE) guidelines recommend that non-HDL cholesterol should be included in the assessment of CVD risk.[3]

HDL cholesterol (HDL-C), on the other hand, has an inverse association with CVD. It is involved in the reverse transport of cholesterol from peripheral tissues to the liver, and is known to have antioxidant, anti-inflammatory, anti-thrombotic and anti-apoptotic properties that can protect and help prevent atherosclerotic CVD.[1, 2]

Cholesterol targets for CVD prevention

Cholesterol targets depend on an individual's overall risk of CVD, which includes other comorbidities, such as diabetes (type 1 and 2), chronic kidney disease and the results from a QRISK^3 assessment (the QRISK^3 tool calculates the likelihood of having a stroke or heart attack in the next 10 years).[8] At LDL-C levels of around 1.8 mmol/L, the regression of atheroma can be observed,[9] hence guideline targets are based around this level. Another type of fat called triglycerides are also included in routine lipid profile tests, as high levels also correlate with increased risk of CVD (see **Table 1**).

Table 1: Lipid targets based on risk from leading guidelines on CVD prevention

		Total Cholesterol	Non-HDL	LDL	HDL	Triglycerides
Recommendation for healthy adults	NHS[10]	≤5 mmol/L	≤4 mmol/L		≥1 mmol for men ≥1.2 mmol for women	
People with established CVD, diabetes mellitus, and/or QRISK ≥10% over the next 10 years	JBS guidelines*[5]		≤2.5 mmol/L and ≥40% reduction from baseline	≤1.8 mmol/L	≥1 mmol for men ≥1.2 mmol for women	≤1.7 mmol/L (fasting)
	ESC Guidelines[4]			≤1.4 mmol/L and ≥40% reduction from baseline		≤1.7 mmol/L (fasting)

*NICE recommend a 40% reduction from baseline.[3] They have not published guideline figures, but the JBS targets are widely used in clinical practice.
Key: NHS = National Health Service; JBS = Joint British Societies'; ESC = European Society of Cardiology.

Cholesterol-lowering pharmaceutical agents

A range of medications are available for lowering cholesterol, the most widely used being statins. These act by blocking the enzyme HMG-CoA reductase which disrupts the synthesis of cholesterol in the liver.[11] Depending on the type and dose of the statin, they can reduce LDL-C levels by up to 55%.[8] They are highly effective and known to be safe to use.

Simvastatin interacts with grapefruit and grapefruit juice, as it inhibits a protein called CYP3A4,[12] which is involved in the degradation of the statins in the small intestine, hence increasing its potency and leading to an increased likelihood of side effects. However, NICE no longer recommends simvastatin, especially at higher doses, due to the increased risk of myopathy and muscle symptoms.[3] Atorvastatin also interacts with grapefruit but only if more than 1.2 litres of grapefruit juice is consumed daily. There is no interaction with other types of statins (e.g. fluvastatin, rosuvastatin).[3]

Several other medications are available for lipid lowering which can be used where statins are unsuitable (for example, due to side effects), but are more often used in conjunction with a statin to reach individual targets (see **Table 2**). Further specialist medication is usually only available via specialist lipid clinics.

Familial hypercholesterolemia (FH)

FH is an inherited condition which disrupts the regulation and the process of removing cholesterol from the blood, resulting in extremely high cholesterol levels. Left untreated, it can lead to the development of CVD, even at an early age. It is a common but underdiagnosed condition; only an estimated 10% of those who have FH worldwide are thought to have been diagnosed.[16] Treatment involves standard lipid lowering drugs such as statins, as well as other more specialist medication, in addition to diet and lifestyle modification advice.

Dietary effect on cholesterol

A large body of evidence has found that saturated fats have the most significant effect on cholesterol levels. Limiting their intake is, therefore, a key part of reducing LDL-C and overall CVD risk factors.[3-5, 17, 18] LDL-C can increase by 0.02-0.04 mmol/L for every additional 1% of energy coming from saturated fats.[19] NICE guidelines recommend a saturated fat intake of less than 7% of total energy,[3] whilst the Scientific Advisory Committee on Nutrition's (SACN) report on saturated fats recommends less than 10% of total energy.[17] This would equate to roughly 20 g per day for women and 30 g per day for men. The mean saturated fat intake for UK adults is above recommendations at 12.3%.[20] Common sources of saturated fats include fatty meat, butter, ghee, foods made with butter (e.g. pastries, cakes and biscuits), full fat dairy foods and coconut fat. They can be found in many pre-packed foods and appropriate label reading, such as checking the traffic light labelling, should be encouraged to help people make informed choices.

Research on what should replace saturated fats for improving lipid profiles has yielded mixed results. A recent Cochrane review concluded that there was no differential effect on LDL-C, HDL-C or triglycerides when replacing saturated fat with either poly or monounsaturated fats, carbohydrates or a mixture.[18]

Table 2: Common lipid lowering medication

Lipid-lowering drug	Mechanism of action	Approximate reduction in LDL-C	Indication & route of administration
Statin	HMG CoA reductase inhibitor – reduces the synthesis of cholesterol	20-60% (depending on dose and statin)[8]	• First line for those at risk of CVD • Taken orally
Ezetimibe	Decreases cholesterol absorption in the small intestine	15-22%[11]	• In combination with statin if target not reached, or as an alternative if patient cannot tolerate statins • Taken orally
PCSK9 monoclonal antibodies (mAbs)	PCSK9 inhibitor – increases hepatic LDL receptors, which leads to reduced LDL-C levels	60%[13] + may reduce atheroma[14]	• 'High risk' and LDL ≥4 mmol/L, or 'Very High Risk' and LDL ≥3.5 mmol/L • Injection every 2 weeks
Inclisiran	Small interfering RNA – reduces production of PCSK9 via gene slicing[15]	50%[11]	• Secondary prevention only and LDL-C level of ≥2.6 mmol/L despite treatment • Injection every 3-6 months
Bempedoic acid	ATP citrate lyase inhibitor – reduces the synthesis of cholesterol	17-28%[11]	• In combination with other lipid lowering therapies if target not reached, or as an alternative if patient cannot tolerate other therapies • Taken orally
Bile acid sequestrants	Reduces reabsorption of bile acids, increasing uptake of cholesterol from the blood for bile acid synthesis	18-25%[11]	• No longer widely prescribed • Taken orally with a meal
Fibrates	Peroxisome proliferator activated receptor agonists – involved in fat metabolism; main effect is reducing triglycerides	Triglycerides 50% LDL 20% Raised HDL 20%[11]	• Mainly taken alongside statins, more commonly to treat inherited cholesterol and triglyceride conditions. • Taken orally

National and international guidelines generally recommend that saturated fats should be replaced by sources of unsaturated fats, with replacement with polyunsaturated fats having the greatest effect on reducing LDL and CVD outcomes.[4, 17, 21] Sources of polyunsaturated fats include olive and rapeseed oil, oily fish, seeds, nuts and avocado. However, overall fat consumption should not exceed 35% of the daily intake of energy.[22]

There is no evidence to suggest that there is a significant correlation between dietary intake of cholesterol (for example, via the consumption of eggs) and serum cholesterol levels. In fact, consumption of eggs appeared to improve dyslipidaemia.[23] To reflect this, NICE recently removed its recommendation to limit dietary cholesterol, previously set at 300 mg per day.[3] Dietary cholesterol limits still apply to those living with familial hypercholesterolemia.[24]

Whilst there is evidence to suggest that dietary changes can alter LDL-C levels, HDL-C is not influenced significantly by diet. HDL cholesterol, like LDL-C, is also lifted by saturated fat intake.[19] However, whilst HDL-C is associated with a lower risk of CVD, no studies have shown raising HDL-C leads to an actual decrease in risk;[4] hence, saturated fat intake should be reduced even if, consequentially, it leads to lowering HDL-C.

Moderate alcohol intake may increase HDL-C, although due to the overall detrimental effects of high alcohol consumption on health, increasing alcohol consumption for the purpose of increasing HDL-C should be discouraged.[19] Other lifestyle factors, like weight loss and exercise, may be more effective. For example, aerobic activity such as 25-30 km of brisk walking per week may increase HDL-C by 0.08-0.15 mmol/L,[19] whilst a modest increase of 0.01 mmol/L in HDL-C may be achieved for every kilogram of body weight lost (if the weight loss is maintained). One evidence review suggests smoking cessation may increase HDL-C levels by up to 30%.[25]

Dietary fibre

Dietary fibre appears to have a role in effecting serum LDL-C levels.[26] The evidence is strongest for soluble fibre and, in particular, beta-glucans, found in grains such as oat, barley and rye, shiitake mushrooms and some varieties of seaweed, which has been shown to be effective in lowering serum LDL-C levels.[27, 28]

The proposed mechanism for the cholesterol-lowering effect of beta-glucans is that they increase the viscosity in the gastrointestinal tract, trapping and promoting the excretion of bile acid via faeces and preventing reabsorption. The liver then steps-up production to replace lost bile acids and uses cholesterol to do so, thus lowering serum cholesterol levels.[26] Beta-glucans can also decrease the absorption of dietary cholesterol. Furthermore, as it is easily digestible for gut microbes, it acts as an effective prebiotic. An abundance of gut microbes can lead to increased production of short-chain fatty acids (e.g. propionate and butyrate) which, through mechanisms that have not yet been clearly established, influence cholesterol metabolism; including decreasing the synthesis of cholesterol in the liver, helping to lower serum cholesterol.[26]

Functional foods for cholesterol lowering

Plant stanols and sterols (PSS)

These are natural compounds found in beans and pulses, vegetable oils and some seeds and nuts. Food products and supplements containing high doses of PSS have shown to decrease serum cholesterol levels. Specifically, 2 g of PSS with a meal can lower total cholesterol and LDL-C by 7-10%,[29] which is similar in effect to doubling the dose of a statin.

Due to its structure being similar to cholesterol, PSS can help inhibit the absorption of cholesterol from the diet and bile derived cholesterol in the gut. Although evidence for its cholesterol lowering potential is relatively strong, NICE do not recommend it as the link between the use of PSS and an improvement in actual CVD outcomes is not as robust.[3] It is important to note that it is only effective whilst the correct dose is taken daily, and it would be an additional cost to the patient as PSS products are not available on prescription. They are also unsuitable for those living with sitosterolaemia, a rare genetic condition involving excess absorption of PSS.[30] However, they may be worth considering if other lipid lowering therapies are not appropriate, and dietary changes have not yielded the desired lipid lowering results.

Red yeast rice

Recent enthusiasm for red yeast rice as a functional food in driving down cholesterol stems from it consisting partly of monacolin K, an active ingredient in some statins. Yet, until more is known about its effectiveness, safety and dosage, it's use to lower cholesterol is not recommended.[2, 19]

Soy protein

A component of soy protein has also been proposed to help combat high cholesterol by inhibiting hepatic apo-B synthesis, as well as soy isoflavones contributing antioxidant effects. A meta-analysis found that 25 g of soy protein per day may reduce LDL-C by 3-5%.[31] Whilst this is promising, confounding factors have not been ruled out and the current evidence is not strong enough to routinely recommend a daily intake of soy. Moreover, 25 g of soy protein is the equivalent of 150 g soya mince, 200 g of tofu or 750 ml of soya milk,[32] which may not be a realistic amount to introduce into the diet daily.

Conclusion

Serum cholesterol levels are important risk factors to consider when managing CVD risk. Effective pharmaceutical treatment is available to lower cholesterol, and diet changes can significantly affect lipid profiles, while providing other protective effects to health. Evidence linking certain foods to cholesterol lowering effects is strong, but extrapolating this evidence to determine whether these foods effect CVD outcomes is not as definitive. As the goal for cholesterol management is to achieve reduced CVD risk, advice around diet should focus on a balanced cardio protective diet with lipid-lowering elements.

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