

Cholesterol (blood, plasma, serum)

1 Name and description of analyte

- 1.1 Name of analyte
Cholesterol (plasma; also blood, serum)
- 1.2 Alternative names
2,15-dimethyl-14-(1,5-dimethylhexyl)tetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptacos-7-en-5-ol (systematic); 3 β -cholesten-5-en-3-ol (IUPAC); also frequently included in the collective term 'lipids', which includes total triglycerides (triacylglycerols) and sometimes other lipoproteins.
- 1.3 NLMC code
To follow
- 1.4. Function(s) of analyte
Cholesterol is the principal sterol synthesised by animals, an essential component of cell membranes, and precursor of steroid hormones, vitamin D and bile acids. It is also a component of lipoproteins, which are required for transport of triglycerides. Although most cells in humans are able to synthesize cholesterol, the majority is synthesized in the liver; dietary intake contributes less, although diet does influence plasma [cholesterol] through variation of lipoprotein production in response to the overall energy intake. Cholesterol is transported in plasma primarily (but not exclusively) in the form of low density lipoproteins (LDL); the principal route for its removal from tissues to the liver is in high density lipoproteins (HDL), followed by excretion in the bile.
- Plasma [cholesterol] has long been known to be associated with cardiovascular risk; this is because the total plasma [cholesterol] correlates with the presence of lipoproteins (LDL and -small, dense, LDL in particular) that may become trapped in the intima of coronary (and other) arteries to form atherosclerotic plaque. Many therapies have therefore been aimed at reducing this process, the principal at present being statins, drugs which inhibit the rate-limiting step of cholesterol synthesis catalysed by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. They also suppress inflammation that is thought to induce plaque instability. Cholesterol metabolism is, however, also linked with inflammation: reducing plasma [cholesterol] reduces low-grade inflammation whereas ongoing inflammation decreases plasma [cholesterol].

2 Sample requirements and precautions

- 2.1 Medium in which measured
Cholesterol can be measured in serum or plasma: this article refers only to measurements in these fluids made in laboratories. Point-of-care testing (using capillary blood) is, however, also well established.
- 2.2 Precautions re sampling, handling etc.
Cholesterol is stable in blood and requires no specific handling precautions, however given the influence of inflammation on plasma

[cholesterol], it is better to avoid sampling when the presence of an acute phase response is likely to give misleading results. For example, cholesterol should be measured at the time of admission with chest pain rather than the following day, by which time the concentration may have dropped significantly. It is important to note that this suppression may last several months.

Samples for lipids other than cholesterol are best taken after fasting to reduce the influence of recent dietary intake.

It is often recommended that diagnosis and treatment should not be based on individual measurements because of the relatively high biological variation.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

Cholesterol measurements are used to diagnose and monitor hypercholesterolaemia (monogenic, polygenic and secondary), and to assess cardiovascular risk.

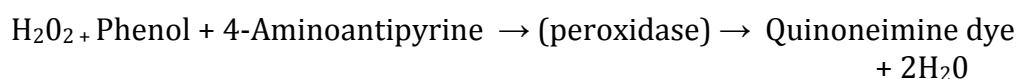
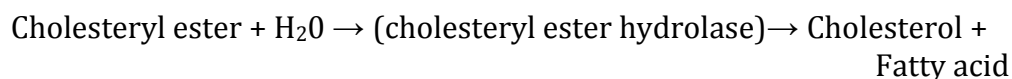
3.2 Limitations

Cholesterol measurements cannot provide information as to the cause of hypercholesterolaemia, and will not provide accurate assessment of hypercholesterolaemia or cardiovascular risk in the presence of an acute phase response. In risk assessment, cholesterol measurements should be considered in relation to other risk factors (e.g. cigarette smoking, hypertension, diabetes mellitus, a personal history of cardiovascular disease etc.)

4 Analytical considerations

4.1 Analytical methods

Total cholesterol is measured using an enzymatic colorimetric method, typically using cholesteryl ester hydrolase (EC 3.1.1.13) to hydrolyze cholesteryl esters, cholesterol oxidase (EC 1.1.3.6) to produce hydrogen peroxide and peroxidase (EC 1.11.1.7) plus a dye to form a coloured product; the absorbance of the complex is measured as an endpoint reaction:



4.2 Reference method

(Center for Disease Control (USA): modified Abell-Kendall method). The cholesterol in ester form is released by saponification of a serum sample with alcoholic potassium hydroxide. This is followed by extraction with hexane, evaporation of an aliquot of the extract, and development of a

chromophore at 620 nm with Liebermann-Burchard reagent (acetic anhydride, glacial acetic, and concentrated sulfuric acid).

- 4.3 Reference materials
Cholesterol (The National Institute of Standards and Technology, Standard Reference Material (NIST SRM) 911c (Washington DC, USA)).
- 4.4 Interfering substances
The standard laboratory methods are not specific for cholesterol: other β -hydroxy steroids and plant sterols such as β -sitosterol also react. There is no significant interference from haemolysis, icterus or lipaemia, but note that, where lipaemic samples require pre-treatment with a clearing agent, cholesterol should be assayed prior to the treatment.
- 4.5 Sources of error
None of significance

5 Reference intervals and variance

- 5.1.1 Reference interval (adults)
Because the association between increased cardiovascular risk and plasma [cholesterol] extends to values typically seen in healthy individuals, measurements are usually compared to recommended action limits rather than reference intervals (see section 9). Concentrations typically rise throughout childhood and after infancy are slightly higher in females than males, e.g. late teenage female 3.08–5.18 mmol/l, male 2.93–5.10 mmol/l; older adult female 4.43–7.85 mmol/l, male 4.09–7.10 mmol/l.
- 5.1.2 Reference intervals (others)
Concentrations typically rise throughout childhood and are higher in females than in males e.g. infant female 2.90–5.18 mmol/l, male 2.95–5.25 mmol/l; early teenage female 3.21–5.20 mmol/l, male 3.08–5.23 mmol/l.
- 5.1.3 Extent of variation
- 5.1.3.1 Interindividual CV: 22.3% (tends to be higher in older females)
 - 5.1.3.2 Intraindividual CV: 8.2%
 - 5.1.3.3 Index of individuality 0.37
 - 5.1.3.4 CV of method approx. 4.5%
 - 5.1.3.5 Critical difference approx. 22%
- 5.1.4 Sources of variation
[Cholesterol] is reduced in acute and chronic disease, especially in the presence of inflammation. It is also decreased during periods of reduced calorie intake.

6 Clinical uses of measurement and interpretation of results

- 6.1 Indications and interpretation
1. Screening for hypercholesterolaemia/dyslipidaemia. Concentrations should be interpreted as part of a global cardiovascular risk assessment (e.g. according to algorithms developed by the Framingham Study, Prospective Cardiovascular Munster Study (PROCAM), QRISK2, ASSIGN (ASSessing cardiovascular risk using Scottish Intercollegiate Guidelines Network guidelines), unless particularly high, in which case other reasons

of hypercholesterolaemia should be considered. The Simon Broome criteria are used when familial hypercholesterolaemia (FH) is being considered. Risk can be further refined by measurement of plasma triglycerides, HDL -cholesterol and LDL -cholesterol.

2. Monitoring of treatment – most recommendations suggest treating to a target [cholesterol], particularly for patients with FH or existing cardiovascular disease; measurements are also used for assessing adherence to treatment.

6.2 Confounding factors

None, but the relatively high biological variation should be born in mind when considering serial measurements.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

- familial (monogenic) hypercholesterolaemia and variants
- polygenic hypercholesterolaemia
- mixed hyperlipidaemias
- secondary hyperlipidaemia
 - chronic liver disease (particularly with cholestasis)
 - hypothyroidism
 - chronic kidney disease
 - myeloma
 - alcohol excess (particularly in connection with severe hypertriglyceridaemia)
 - drugs (steroids, retinoids, anti-retrovirals and tamoxifen can induce significant (usually mixed) hyperlipidaemia.

7.1.2 Investigation

Raised concentrations should be confirmed with a repeat, together with measurements of other lipids including triglyceride and HDL-cholesterol, and LDL-cholesterol (usually by calculation); measurements of apolipoprotein may be appropriate. Beta-quantification of lipids using ultracentrifugation can help determine which lipoprotein fractions are raised.

Secondary causes of hypercholesterolaemia must be excluded before initiating specific treatment.

In individuals with possible FH, genetic studies and cascade testing of relatives may be appropriate.

7.2 Low values

7.2.1 Causes

Usually caused by ongoing inflammatory response to injury or disease, including various types of cancer.

7.2.2 Investigation

Investigation of underlying disease if appropriate

7.3 Notes

8 Performance

- 8.1 Sensitivity, specificity etc. for individual conditions
These concepts are inappropriate for cholesterol: hypercholesterolaemia is defined by cut-off points relating to overall cardiovascular risk.

9 Systematic reviews and guidelines

- 9.1 Systematic reviews
Reviews have focused on specific conditions rather than on cholesterol specifically; these reviews are incorporated into guidelines, below.

9.2 Guidelines

1. NCEP ATP (National Cholesterol Education Program, Adult Treatment Panel) <http://circ.ahajournals.org/content/106/25/3143.citation>
2. NICE: Prevention of cardiovascular disease (PH25) 2010
<http://publications.nice.org.uk/prevention-of-cardiovascular-disease-ph25>
3. NICE: Lipid modification (CG67) 2008 (currently being updated:
<http://guidance.nice.org.uk/CG/WaveR/123>)
4. NICE: Familial hypercholesterolaemia (CG71) 2008
<http://www.nice.org.uk/nicemedia/live/12048/41700/41700>.
5. SIGN 97: Risk estimation and the prevention of cardiovascular disease. 2007 <http://www.sign.ac.uk/pdf/sign97.pdf>
6. Joint British Societies' Guideline on Prevention of Cardiovascular Disease in Clinical Practice (JBS2) 2005
http://heart.bmj.com/content/91/suppl_5/v1.full.pdf+html

- 9.3 Recommendations
Incorporated into guidelines, above

10 Links

- 10.1 Related analytes
HDL-cholesterol, LDL-cholesterol
- 10.2 Related tests
Other routinely analysed lipids: triglycerides, apolipoproteins; other tests related to the assessment of cardiovascular risk or secondary dyslipidaemia, e.g. blood glucose, thyroid function, renal function etc.

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