

Gamma-glutamyl transferase (plasma or serum)

1 Name and description of analyte

1.1 Name of analyte

Gamma-glutamyl transferase (plasma or serum)

1.2 Alternative names

Gamma-glutamyl transpeptidase (EC 2.3.2.2)

Abbreviations: γ -GT, GGT.

1.3 NLMC code (to follow)

1.4 Description of analyte

The principal human *GGT* gene is located on chromosome 22. Pre-genome investigations have indicated that the human genome contains additional *GGT* genes or sequences, which has resulted in inconsistencies in nomenclature. Systematic analysis has suggested that there are 13 additional sequences related to that of the *GGT* family, of which six appear to be active. The function and clinical significance of these variants remain unclear at present.

The GGT protein is a heteroduplex entity composed of a light chain and a heavy chain, both derived from a single precursor protein with a MW of 61–64 kDa. The heavy chain possesses an intracellular, a single transmembrane and extracellular domain. The extracellular domain interacts with the light chain which possesses the active site. A number of variants of the GGT protein exist with variations in carbohydrate structure and content that can be separated by electrophoresis.

The enzyme is present within the cell membranes of many tissues including the kidneys, liver, bile ducts, pancreas and heart. It is most prominent on epithelial surfaces. The greatest GGT activity is observed on the luminal surface of the proximal tubules of the kidneys. It is also found in high quantities on biliary epithelial cells of the liver and the acinar cells of the pancreas.

1.5 Functions of analyte

Gamma-glutamyl transferase catalyses the transfer of a glutamyl residue from a donor to an acceptor. The most significant of the donors is glutathione. However, a number of other molecules, such as leukotrienes and cisplatin, possess the gamma-glutamyl structure, necessary to act as a donor. Glycylglycine is the most common acceptor, though again a number of other alternatives exist.

Gamma-glutamyl transferase is most abundant in organs with transport functions such as the kidneys and the liver. It has been observed to be particularly important for maintaining the availability of cysteine. In diets low in sulfur, the levels of GGT activity are increased. It has been suggested that this is to liberate cysteine and implicates GGT as being important in maintaining cysteine availability.

2 Sample requirements and precautions

2.1 Medium in which measured

Gamma glutamyl transferase can be measured in either serum and plasma.

2.2 Precautions re sampling, handling etc.

Non-haemolysed serum is the preferred sample. Use of heparin anticoagulants may cause turbidity, which can interfere with the assay. Citrate, oxalate and fluoride can depress enzyme activity by 10–15%. Activity is stable for one month in samples stored at 4°C and one year at – 20°C.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

There are two main uses for GGT measurement:

- to determine the origin of elevated serum alkaline phosphatase (ALP) activity.
- to assess compliance with treatment in alcohol abuse.

3.2 Limitations

Although GGT has a high sensitivity for hepatobiliary damage it has poor specificity, which limits its clinical utility.

4 Analytical considerations

4.1 Analytical methods

- Early methods for measuring GGT used *L*- γ -glutamyl-*p*-nitroanilide (GGPNA) as a substrate. The product of the reaction is *p*-nitroaniline which is measured at 405 nm. However, the low solubility of the substrate made obtaining saturating concentrations difficult to obtain.
- The current method uses GGT to catalyse the transfer of a gamma-glutamyl group from the donor *L*- γ -glutamyl-3-carboxy-4-nitroaniline to a glycine acceptor. This reaction yields 3 carboxy-4-nitroaniline, which absorbs at 410 nm (Theodorsen reaction) and is typically measured by kinetic spectrophotometry methods, which are inexpensive and precise. The rate of formation of 3 carboxy-4-nitroaniline is directly proportional to the activity of GGT in the sample.

4.2 Reference method

The IFCC reference method uses the modified Theodorsen reaction as described in 4.1.

4.3 Reference materials

Gamma-glutamyl transferase from pig kidney (ERM-AD452 - gamma-glutamyltransferase)

4.4 Interfering substances

Heparin: can cause turbidity

Citrate, oxalate and fluoride: depress activity by 10–15%.

4.5 Sources of error

Haemolysis

5 Reference intervals and variance

5.1.1 Reference interval (adults)

The upper reference limit in adults for is 38 U/L (females) and 55 U/L (males). These limits are two-fold higher in persons of African ancestry.

Smoking – mean 24% higher

Oral contraceptive – mean 10% higher

5.1.2 Reference intervals (others)

Full term neonates have an upper reference limit 6–7 times that of an adult. This declines to adult ranges within 5–7 months. Values are a mean of 24% higher in smokers and can be up to a mean of 10% higher in women taking an oral contraceptive of any type.

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 3.4%

5.1.3.2 Intraindividual CV: 42.2%

5.1.3.3 Index of individuality: 0.29

5.1.3.4 CV of method: 3%

5.1.3.5 Critical difference: 40%

5.1.4 Sources of variation

Consumption of drugs such as barbiturates, oral contraceptives and NSAIDs can cause elevated GGT activity; so, too do smoking and alcohol consumption. Some individuals possess a genetic predisposition to an elevated GGT with no apparent pathological consequences.

6 Clinical uses of measurement and interpretation of results

6.1 Indications and interpretation

GGT is a sensitive marker for liver dysfunction as it is elevated in most patients with liver disease regardless of cause. Elevations are observed earlier and are more pronounced than those of other liver enzymes in cases of obstructive jaundice and metastatic neoplasms. Levels can become elevated to >30 times ULN in cases of intra- or post-hepatic biliary obstruction. More mild elevations, 2–5 times ULN, are observed with infectious hepatitis, rendering it less diagnostically useful. GGT is most often used as part of a liver function test panel to:

- identify the cause of elevations in ALP. ALP can be increased as a result of cholestasis but is also produced from the placenta in the 3rd trimester and from bone, particularly during adolescence and in bone disease. An elevation in ALP along with elevated GGT confirms the source of the ALP as the liver
- act as a marker of alcohol and drug consumption. GGT should be measured before starting treatment with acamprosate, oral naltrexone or disulfiram to establish a baseline for compliance.

6.2 Confounding factors

The specificity of GGT is compromised as it is known to be elevated in other non-liver disease states (i.e. pancreatitis, diabetes, obesity).

7 Causes of abnormal results

7.1 High values

- Elevated levels of GGT can occur as a result of alcohol consumption. Isolated elevations in serum GGT are suggestive of alcohol abuse or alcoholic liver disease. GGT is not specific for alcohol abuse although isolation of GGT isoforms has been proven to offer more specific information but is not used clinically.
- Numerous drugs have been shown to cause elevations in serum GGT. They include barbiturates, phenytoin, NSAIDs, aspirin and benzodiazepines.
- An elevation in serum GGT has high sensitivity for liver neoplasms, viral hepatitis and fatty liver disease. However, its clinical utility is limited by its poor specificity.

- In recent years, GGT has been recognised as a prognostic marker for cardiovascular disease, with elevations in GGT being associated with an increased risk of a cardiovascular event. It is steadily becoming an important addition to the multimarker approach to cardiovascular risk evaluation.

7.1.1 Investigation

- Gamma-glutamyl transferase should be measured in anyone suspected of drug or alcohol abuse. It should also be measured before treatment for alcohol dependence to obtain a baseline to assess compliance.
- In cases of suspected cholestasis GGT should be measured in conjunction with ALP to confirm the origin of elevated ALP.
- Serum GGT can be measured in combination with a liver function panel when assessing other forms of liver dysfunction particularly obstructive jaundice and metastatic neoplasms.

7.2 Low values

Depressed serum GGT levels are not commonly observed but are a feature of familial intrahepatic cholestasis type 1 (FIC1).

7.2.1 Investigation

Hyperbilirinaemia due to cholestasis with low or normal serum GGT activity is suggestive of FIC1 deficiency. Liver biopsy will often appear normal in the early stages of this condition but fibrosis of the portal tracts develops as the disease progresses. Testing for bi-allelic variations in the *ATP8B1* gene is required to confirm this diagnosis.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

GGT is not typically used to assess individual conditions but rather as guide to determine the source of abnormal ALP values.

9 Systematic reviews and guidelines

9.1 Systematic reviews

Whitfield JB, 2001. Gamma-Glutamyl Transferase. *Critical Reviews in Clinical Laboratory Sciences* 2001;38:263–355, doi: 10.1080/20014091084227.

Mason JE, Starke RD, van Kirk JE. Gamma-Glutamyl Transferase: A Novel Cardiovascular Risk Biomarker'. *Preventive Cardiology* 2010;13:36–41. doi: 10.1111/j.1751-7141.2009.00054.

Dufour RD. Liver Disease. In Burtis CA, Ashwood ER, Bruns DE, Border BG. (eds), *Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics*. 6th edn. St Louis USA: Elsevier Health Sciences; 2014.

9.2 Guidelines

Alcohol – problem drinking. National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summaries, 2015. <https://cks.nice.org.uk/alcohol-problem-drinking#!scenario:1>

9.3 Recommendations

None

10 Links

10.1 Related analytes

Alkaline phosphatase

GGT is typically used to identify the source of elevated ALP levels and act as indicator of liver dysfunction.

10.2 Related tests

None

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