

Total protein (serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
Total protein

1.2 Alternative names
None

1.3 NMLC code

1.4 Description of analyte
This is a quantitative measurement of the concentration of all proteins present in serum (note that this excludes clotting factors). The major proteins are albumin and the immunoglobulins (principally IgG, IgA and IgM). Many other proteins are included in the measurement but individually none contributes more than 5% of the total, and most much less.

1.5 Function of analyte
For [albumin](#), see separate entry. The immunoglobulins are components of the humoral arm of the immune system.

2 Sample requirements and precautions

2.1 Medium in which measured
Serum; plasma can be used but concentrations are lower owing to the lack of clotting factors. Total protein can also be measured in urine and cerebrospinal fluid.

2.2 Precautions re sampling, handling etc.
1. Plasma protein concentrations increase with excessive stasis during venepuncture; blood should therefore be collected with a minimum of stasis.
2. No other special precautions apply.

3 Summary of clinical uses and limitations of measurements

3.1 Uses
1. Total protein is measured in serum to give an indication of total immunoglobulin concentration since $([\text{total protein}] - [\text{albumin}]) = [\text{globulins}]$ of which the major component is immunoglobulins.
2. Total protein is sometimes included in the 'liver function tests'; some chronic liver diseases cause increases in [immunoglobulins], which increases total protein (though this may be offset by a decrease in [albumin]).
3. Total protein should be measured in suspected humoral immunodeficiency, for which the definitive diagnosis is by measurement of individual immunoglobulins.
4. Total protein can be measured when a patient is suspected of having a paraprotein but is not always high; the definitive investigation for

paraproteinaemia is serum protein electrophoresis. *Note that urine protein electrophoresis should also be performed in suspected myeloma.*

3.2 Limitations

Total protein measurement is of little value without simultaneous measurement of albumin.

4 Analytical considerations

4.1 Analytical methods

Total protein in serum can be measured by a variety of methods, including chemical methods, turbidimetry and nephelometry. The most widely used is a method based on the biuret reaction, in which an alkaline copper (II) solution reacts with peptide linkages to form a complex that absorbs light at wavelength 540 nm. The sensitivity of the reaction can be increased by the addition of phosphotungstomolybdic acid (Folin-Ciocalteu reagent, phenol reagent) (Lowry method), which, together with other modifications, results in increased absorption for a given amount of protein. The reactivity of the various plasma proteins to the biuret reagent is not significantly different, since it is dependent on the number of peptide linkages, not on amino acid composition. The response is linear from [total protein] 15 g/L to at least 120 g/L.

4.2 The reference method is based on the biuret reaction.

4.3 The reference material is purified human serum (ERM/IFCC DA470K: Institute for Reference Materials and Measurements, Belgium).

4.4 Interference

Causes include:

- bilirubin: [bilirubin] 500 $\mu\text{mol/L}$ causes up to 4% negative interference
- haemoglobin: [Hb] 10 g/L causes up to 6% positive interference
- lipaemia causes negligible interference.

4.5 Sources of error. The biuret reaction is a robust procedure and not subject to significant sources of error.

5 Reference intervals and variance

5.1.1 Reference interval (adults): 60 – 80 g/L

5.1.2 Reference intervals (others): lower in the newborn rising to adult values by age 3 years

5.1.3 Extent of variation

5.1.3.1 Interindividual CV: 6.2%

5.1.3.2 Intraindividual CV 3.5%

5.1.3.3 Index of individuality: 0.53

5.1.3.4 CV of method: 0.9%

5.1.3.5 Critical difference: 10%

5.1.4 Sources of variation:

1. Serum [total protein] is affected by hydration state.
2. Serum [total protein] can be up to 10% higher when an individual is ambulant than when recumbent.

6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation

1. Although often included in the standard panel of 'liver function tests' (see 3.1 (1)), [total protein] does not reflect liver *function*, but may, when used to derive [total globulins] *suggest* the presence of an autoimmune component to chronic liver disease. Thus IgM tends to be raised in primary biliary cirrhosis, IgG in autoimmune chronic hepatitis and IgA in alcoholic liver disease. Autoimmune serology and other investigations are required for diagnosis.
2. Serum [total globulins] may be low in patients with humoral immunodeficiency (primary or secondary) but because IgG is the major component, deficiencies of IgA or IgM may not significantly affect [total globulin]. If immunodeficiency is suspected, individual immunoglobulin classes should be measured.
3. Serum [total globulin] is typically, though not constantly, raised in patients with autoimmune disease, chronic inflammation and paraproteinaemia. More specific investigations are required for diagnosis.
4. Serum total protein is often measured 'routinely', i.e. without a specific indication (see 7.1.1 and 7.1.2).

6.2 Confounding factors

Serum [total protein] is affected by the patient's state of hydration; meaningful interpretation of results requires that a patient's hydration state is normal.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes:

- dehydration ([albumin] likely to be elevated also)
- chronic infection/inflammation e.g. osteomyelitis, endocarditis.
- autoimmune disorders e.g. rheumatoid disease, systemic lupus erythematosus (but not 'organ-specific' autoimmune diseases, excepting autoimmune hepatitis)
- paraproteinaemia (myeloma and other causes).

7.1.2 Investigation

A high [total protein] in a normally hydrated patient suggests high [immunoglobulins]. Unless there is an obvious cause (e.g. chronic infection, chronic liver disease) serum protein gel electrophoresis (see 10.2) is required.

Typical patterns observed include:

- a polyclonal increase (no discrete bands, characteristic of chronic inflammation and autoimmune disorders)
- one or more (oligoclonal) bands on the background of a polyclonal increase (an occasional finding in autoimmune disease or infection)
- a monoclonal band or paraprotein (characteristic of haematological malignancy, especially myeloma but sometimes due to monoclonal gammopathy of uncertain significance (MGUS). With malignant paraproteins, the concentration of normal immunoglobulins may be decreased (pale-staining background); this is termed immune paresis.

7.2 Low values

7.2.1 Causes

Low [total protein] only occurs as a result of conditions causing low values of the major components, i.e. [albumin](#) and the immunoglobulins (particularly IgG). A low [total protein] but normal [albumin] may be the first indication that a patient has humoral immunodeficiency.

7.2.2 Investigation

Low [albumin] will be apparent from its specific measurement. Suspected immunoglobulin deficiency is diagnosed from measurements of the individual immunoglobulin classes (IgG, IgA, IgM).

7.3 Note

Measurement of total protein is of little value on its own but can suggest a need for further investigation to arrive at a specific diagnosis.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

Total protein measurements are of no diagnostic value on their own and hence there are no relevant data.

9 Systematic reviews and guidelines

9.1 Systematic reviews

None identified

9.2 Guidelines

None identified

9.3 Recommendations

The Guidelines for Blood Transfusion Services in the UK recommend that serum albumin and total protein should be measured in potential plasma donors at their initial visit but provide no indication of a cut-off value at which they should be prevented from becoming donors. [Total protein] and [IgG] remained within the reference interval in a group of plasma donors providing 500– 600 mL plasma at weekly intervals for six months (Ciszewski TS, Ralston S, Acteson D *et al.* Protein levels and plasmapheresis intensity. *Transfus. Med.* 1993;3:59-65).

10 Links

10.1 Related analytes

Specific assays are available for many individual plasma proteins. Examples, with the condition(s) in which their measurement may be useful include:

- α_1 -antitrypsin (α_1 -antitrypsin deficiency)
- α -fetoprotein (tumour marker, see 10.2.3)
- apolipoproteins (dyslipidaemias, cardiovascular risk assessment)
- caeruloplasmin (Wilson's disease)
- C-reactive protein (inflammatory disorders)
- ferritin, transferrin (iron deficiency and storage disorders)
- haptoglobin (haemolytic disorders)
- prealbumin/transthyretin (nutritional status)

- immunoglobulins (humoral immunodeficiency).

10.2 Related tests

1. Gel electrophoresis of serum separates the constituent proteins into discrete bands. Characteristic but non-specific patterns are associated with various conditions; the only diagnostic use of this technique is to detect paraproteins (monoclonal immunoglobulins). Paraproteins are found in many patients with myeloma and malignancies of B-cell origin, but can be benign (monoclonal gammopathy of uncertain significance, MGUS).
2. Enzymes present in plasma, either because it is where they function or are present as result of a pathological disturbance, are considered under individual headings.
3. Many tumour markers (proteins characteristic, but not diagnostic, of malignancy) are measurable in serum. They are considered under individual headings.

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