Serum Free Light Chain Testing

In this article we will review immunoglobulins then focus on the metabolism serum free light chains as well as the potential uses of detection of these chains and their ratio.

Immunoglobulin Structure

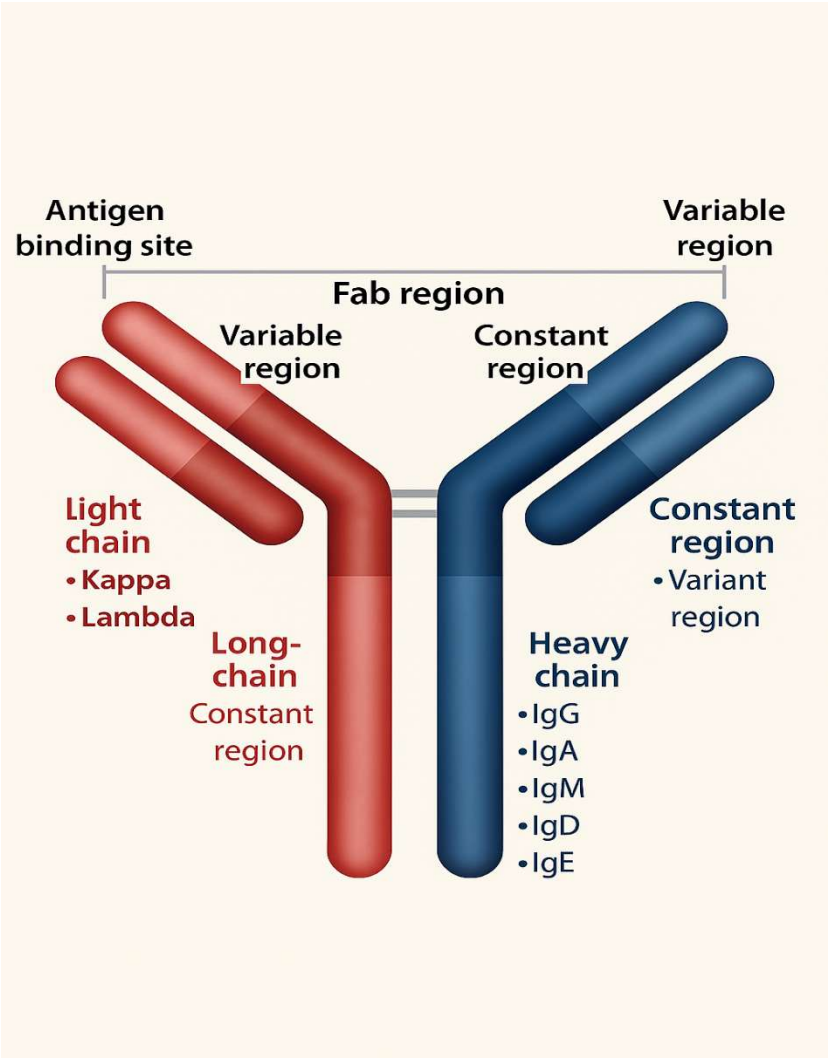
There are five types of immunoglobulins that are produced by plasma cells: IgM, IgG, IgA, IgD, IgE.

They are heterodimeric structures, composed of 4 polypeptide chains: 2 identical heavy chains and 2 identical light chains in a Y shaped structure. The light chains are either kappa (K) or lambda (λ), only one type of light chain is present in each immunoglobulin molecule.

There is a variable amino acid structure at the end of each chain, this is called the variable region/domain. Areas of the structure with little change are called ‘constant domain’.

Each heavy chain has a single variable and 3 constant domains whilst light chains have one each. These variable regions of the light and heavy chains form the part of the immunoglobulin where the antigen attaches.

The heavy and light chains are held together by disulfide bonds and non-covalent interactions. (1)


Antigen binding site
Variable region
Fab region
Variable region
Constant region
Light chain
• Kappa
• Lambda
Long-chain
Constant region
Heavy chain
• IgG
• IgA
• IgM
• IgD
• IgE
Constant region
• Variant region

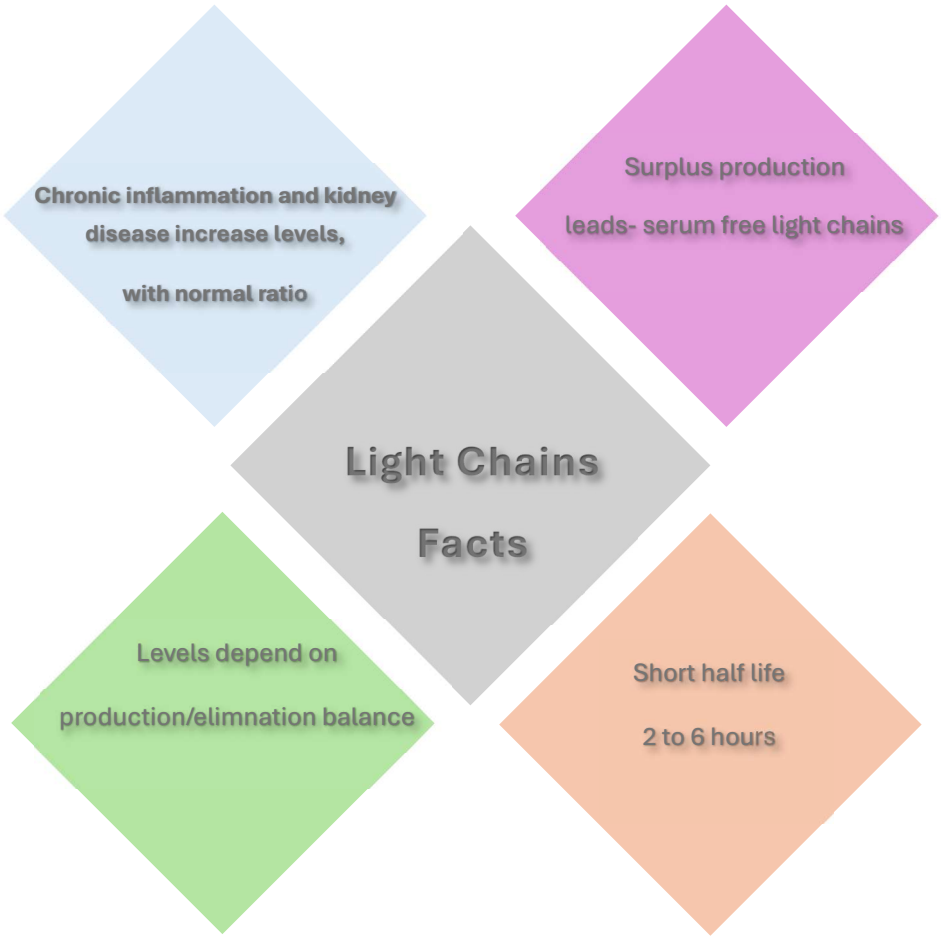
More about Serum Free light Chains

Light chains are usually produced in excess quantities and can be found as free kappa and lambda.

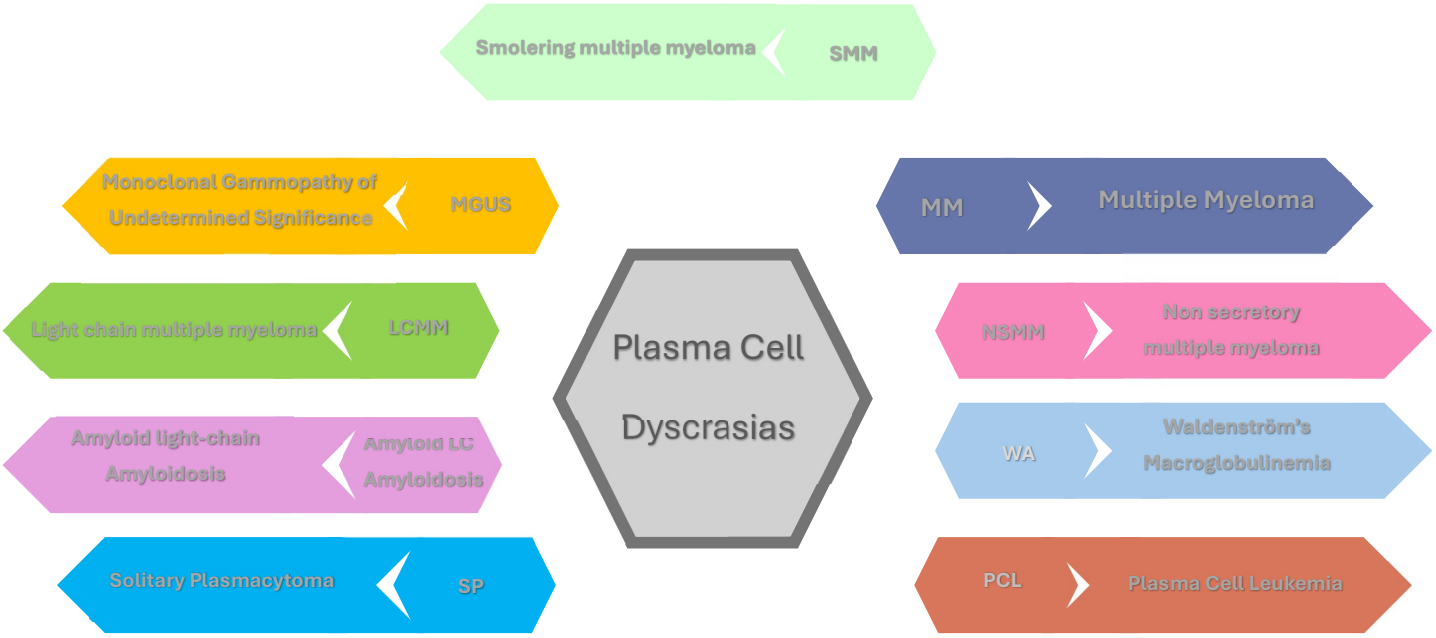
Surplus serum free light chains (sFLC) are released into the circulation; they have a half-life of 2 to 6 hours which is secondary to rapid renal clearance. This short half-life as compared to the longer half-life of intact immunoglobulins, make them useful markers for monitoring disease progress and treatment response. (2)

The levels of sFLCs in circulation are dependent on the balance between their production by the plasma cells and elimination by the kidneys. Normally only small quantities of protein enter the urine; this means that the levels of sFLC are mainly a reflection of production. Levels 30 to 40 times normal can occur in kidney disease and in polyclonal immunoglobulin excess secondary to chronic inflammation; though the ratio of serum kappa to lambda would remain within normal range (in contrast to monoclonal production where the ratio would be altered). (2)

Chronic inflammatory conditions such as: SLE, RA, Sjogren's syndrome, rhinitis, asthma, food allergies, COPD, inflammatory bowel disease, MS, to name a few, can therefore result in elevated sFLC.


Chronic inflammation and kidney disease increase levels,
with normal ratio
Surplus production
leads- serum free light chains
Light Chains
Facts
Levels depend on
production/elimnation balance
Short half life
2 to 6 hours

What happens in Plasma Cell Dyscrasias?



There is a range of plasma cell dyscrasias with a variation in severity. Monoclonal gammopathy of undetermined significance (MGUS), is the mildest of these conditions though it can progress to smoldering multiple myeloma (MM) or symptomatic MM. (3)

People may also be diagnosed with light-chain MM, symptomatic MM, non-secretory MM. Primary amyloidosis is also referred to as light-chain amyloidosis; additionally, macroglobulinemia, solitary plasmacytoma and plasma cell leukemia are also considered plasma cell dyscrasias. (3)

In these conditions plasma cells produce intact immunoglobulins or FLCs of a single type, either kappa or lambda chains or both. (3)

Either form of excess is referred to as monoclonal protein (M) or as a paraprotein. This paraprotein is measured and monitored to diagnose and assess treatment response.

In approximately 20% of patients with MM, only free light chains or low levels of intact immunoglobulin levels can be found. These serum free light chains may be undetected by serum protein electrophoresis resulting in false negative results for multiple myeloma in 1/8 of patients if serum protein electrophoresis is used as the only diagnostic test. (4) It should be noted that serum immunofixation is 10 times more sensitive than protein electrophoresis however in light chain conditions, there may not be sufficient free light chains to be detected by serum immunofixation or serum protein electrophoresis. (2)

Notably the median levels of monoclonal kappa and lambda that would be needed to be present in the serum before Bence Jones proteins could be detected in the urine were found to be 113 mg/l and 278 mg/l in a study implying that low serum levels would therefore be undetected. (2)

As it relates to light chain multiple myeloma, which is approximately 20% of myeloma cases, it may be undetected with use of serum protein electrophoresis alone in up to 40% of patients. (2)

With non secretory MM, present in 1 to 5 % of all MM patients, monoclonal proteins are not detected with in the serum or urine by immunofixation though immunoglobulins can be found on examination of the bone marrow in a fraction of these patients. Use of serum FLC testing is particularly beneficial in this group with increased detection using this testing method. (2)

AL amyloidosis and light chain deposition disease, sFLC is an important technique with the sFLC ratio having diagnostic sensitivity ranging from 75 to 98% for AL amyloidosis. Abnormal ratios have been found in the majority of light chain deposition disease patients as well (88 to 100) %. (2)

What do the Current Guidelines Recommend?

Measurement of serum free light chains is recommended along with electrophoresis- both for detection, monitoring treatment response and remission and assessment of prognosis of multiple myeloma and other plasma cells dyscrasias. (3)

Both the levels of each serum free chain and the ratio of serum free kappa to serum free lambda would allow determination of clonality along with the other markers aid in the accurate diagnosis and effective monitoring of patients. (3)

The normal serum free light chain ratio is 0.26-1.65. (2)

The table below summarizes possible results and interpretations for kappa, lambda and ratios. (5)

Result	Interpretation
Kappa, lambda and ratio are within normal range	Normal /no comment
Kappa and/or Lambda outside of reference range, but ratio within range	Likely causes include inflammation or abnormal renal function

sFLC ratio 1.66 to 3.1 within expected range in chronic kidney disease (CKD)	sFLC ratio falls within reference range for CKD. If patient is known to have CKD-no further action If not known to have CKD- consider MGUS, myeloma or amyloidosis. Recommend discussion with referral to clinical haematology if there are features of MM If no features of MM- recheck immunoglobulins and electrophoresis in 2 to 3 months and refer to haematology if 25% or more change. Refer urgently if symptoms develop
sFLC ratio > / 0.1 and < 0.7 but outside of reference range	Abnormal ratio. Consider MGUS, myeloma or amyloidosis.Refer if there are features of MM. If no features of MM- recheck immunoglobulins and electrophoresis in 2 to 3 months and refer if more than 25% change is noted Refer urgently if symptoms develop
sFLC ratio <0.1 or >7	Significant change in the sFLC ratio, urgent referral to haematology suggested

If there are minor changes in kappa and lambda levels and the ratio is normal, consider assessing for inflammation or renal disease unless there are obvious features of MM. If, however, there are minor changes in the ratio and there are no symptoms or signs that suggest MM, the tests can be repeated in 2 to 3 months and the patient monitored.

Table taken from- Demystifying serum free light chains- a guide for primary care-Manchester University NHS Foundation trust

1. ThermoFisher Scientific. Immunoglobulin Structure and Classes.

2. Jenner E. Serum free light chains in clinical laboratory diagnostics. Clin Chim Acta. 2014 Jan 1;427:15-20. doi: 10.1016/j.cca.2013.08.018. Epub 2013 Aug 30. PMID: 23999048.

3.Rao M, Lamont JL, Chan J, et al. Serum Free Light Chain Analysis for the Diagnosis, Management, and Prognosis of Plasma Cell Dyscrasias: Future Research Needs: Identification of Future Research Needs From Comparative Effectiveness Review No. 73 [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012 Sep. (Future Research Needs Papers, No. 23.) Background. Available from: https://www.ncbi.nlm.nih.gov/books/NBK137791/

4. Australian Clinical Labs. Free light chains and Multiple Myeloma – What, When and Why. *Published September 2024*