26 - An overview of the kidney and monoclonal free light chains

26.1. Introduction

This chapter covers the normal renal handling of FLCs and the role of monoclonal FLCs in a range of renal pathologies including cast nephropathy, AL amyloidosis and light chain deposition disease (LCDD).

26.2. Renal clearance of free light chains

FLCs are present in similar concentrations in the vascular and extravascular compartments. As a consequence, the vascular compartment may contain only 15-20% of the total amount of FLCs in the body. The serum concentrations of $\kappa$ and $\lambda$ FLCs are dependent upon the balance between production and clearance (Chapter 3). Although $\kappa$ FLCs are normally produced at a rate approximately twice that of $\lambda$ FLCs, the renal clearance of monomeric $\kappa$ FLCs is faster than dimeric $\lambda$ FLCs. This accounts for the observed differences in their serum half-lives ($\kappa$ sFLCs: approximately 2 hours; $\lambda$ sFLCs: 4 - 6 hours) and their serum concentrations (Chapter 3 and Section 6.1). The molecular weight cut-off for glomerular filtration of circulating macromolecules is around 60 kDa. Therefore, whilst sFLCs are rapidly cleared from the blood by the kidneys, larger serum proteins such as albumin (66 kDa) and transferrin (81 kDa) are only filtered to a limited extent and their serum concentrations are not dependent upon kidney function.

After filtration by the glomeruli, FLCs and other proteins enter the proximal tubules and bind to brush border membranes via low-affinity, high-capacity receptors called cubulin and megalin. Binding results in internalisation of the bound proteins followed by proteolysis within the tubular epithelial cells. Subsequently, the constituent amino acids are returned to the circulation across the basolateral membrane. Reabsorption of FLCs by the proximal tubule is highly efficient and a normal 24-hour urine collection will only contain around 10 mg of polyclonal FLCs.

Whilst the concentration of serum creatinine is a useful guide to kidney function, the glomerular filtration rate (GFR) is a more accurate measure. Estimated GFR (eGFR) values can be derived from various different calculations. Currently, the most widely used calculation is the one proposed by the Modification of Diet in Renal Disease (MDRD) study group, which incorporates serum creatinine along with age, sex, and ethnicity in the equation to produce an eGFR. More recent calculations may be more accurate than the MDRD equation for kidney function measurement; in particular the CKD-EPI equation may replace MDRD in routine clinical practice in the near future.

26.3. Renal impairment and free light chains

Renal impairment is characterised by the reduced ability of the kidneys to excrete waste and maintain the electrolyte balance. This encompasses both acute kidney injury (AKI) and chronic kidney disease (CKD). CKD is very common, with 8.5% of the population having baseline impairment of kidney function (stage 3 - 5 chronic kidney disease, defined by an eGFR of <60 ml/min/1.73m$^2$). This has usually occurred over a period of years and is associated with diseases such as hypertension, cardiovascular disorders or diabetes. AKI affects between 13 and 18% of all people admitted to hospital and the severity of the AKI is defined according to the amount by which serum creatinine has increased within a 48-hour period. It is usually reversible but is associated with a major increased mortality risk in those affected. In patients who present with AKI of unknown cause the underlying pathology may be multiple myeloma (MM) and they should be rapidly screened for monoclonal gammopathy (Section 27.2).

In patients with renal impairment, the reticuloendothelial system becomes the dominant mechanism for the clearance of FLCs and other proteins from the blood. With decreased renal clearance, the relative concentrations of $\kappa$ and $\lambda$ sFLCs become increasingly influenced by production rates, leading to minor decreases in the sFLC ratio in the absence of monoclonal
gammopathy. Application of a modified renal reference interval for patients with renal impairment may increase the specificity of the $\kappa/\lambda$ sFLC ratio for detecting monoclonal FLC production (Section 6.3). If there is complete renal failure, the serum half-life of both FLCs will be the same and may be prolonged to 2 - 3 days, resulting in significant increases in serum concentration for both light chains.

### 26.4. Nephrotoxicity of monoclonal FLCs

Plasma cell dyscrasias are often associated with kidney disease (Figure 26.1). In many cases, this is caused by the nephrotoxicity of the individual monoclonal FLCs produced by a B-cell clone. In a study of 1595 newly diagnosed MM patients, Yadav et al. found that higher sFLC concentrations were associated with an increased incidence of renal impairment at diagnosis, and patients with sFLC>800 mg/L had the highest risk of severe renal impairment (eGFR < 30 ml/min/1.73m²) (Figure 26.2).

Consistent with this, the International Myeloma Working Group recommended sFLC analysis as part of a panel of laboratory tests to diagnose renal impairment in patients with MM, both at diagnosis and during follow-up (Section 25.3.7).

The pattern of renal injury in plasma cell dyscrasias varies considerably, and is influenced by structural properties of the individual monoclonal FLC, particularly the variable domain, as well as environmental factors such as pH or local proteolysis. Renal disorders that are associated with plasma cell dyscrasias may be classified into two major groups according to the predominant type of injury: glomerular or tubulo-interstitial (Table 26.1).
### Renal disease

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<td>AL amyloidosis (Chapter 28)</td>
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<td>Fibrils (Congo red positive)</td>
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<td>Cryoglobulinaemia</td>
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<td>Microtubules (or rarely crystalline)</td>
<td>Hypertension, proteinuria, nephrotic syndrome, haematuria, CKD, acute nephrotic syndrome</td>
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<td>Monoclonal immunoglobulin deposition diseases (Chapter 29)</td>
<td>LCDD: FLC HCDD: truncated HC (α most common) LHCDD: FLC +truncated HC</td>
<td>Nodular glomerulosclerosis, linear amorphous deposits along tubular basement membranes</td>
<td>Hypertension, proteinuria, nephrotic syndrome, haematuria, CKD</td>
</tr>
</tbody>
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AKI: acute kidney injury; HC: heavy chain; CKD: chronic kidney disease; HCDD: heavy-chain deposition disease; LHCDD: light- and heavy-chain deposition disease

### Table 26.1. Main renal disorders related to monoclonal immunoglobulin deposition or precipitation

Tubulo-interstitial disorders include cast nephropathy, acute tubular necrosis and Fanconi syndrome. Cast nephropathy is the most frequent cause of severe AKI in MM patients, causing up to 90% of cases. This pathology is discussed in detail in Chapter 27 along with issues relating to diagnosis and preservation of renal function in MM patients. A less common cause of AKI in MM is acute tubular necrosis. In this condition, proximal tubular injury is associated with an acute ischaemic or toxic event. In some MM patients, endocytosis of nephrotoxic FLCs may directly cause proximal tubular cell injury and necrosis. Fanconi syndrome may be due to proximal tubule dysfunction secondary to reabsorption of FLCs that are resistant to proteolysis and crystallise within epithelial cell lysosomes. This dysfunction leads to a loss of solutes, including phosphate, glucose, amino acids and bicarbonate and is characterised by renal tubular acidosis. Interestingly, this is nearly always associated with FLCs of the VK1 subgroup, derived specifically from only two germline genes: IGKV1-39 and IGKV1-33. Leung and Behrens recently published a comprehensive review of myeloma-related kidney disease. A similar spectrum of kidney disease can occur in Waldenström’s macroglobulinaemia (Chapter 32), but the proportion of patients with kidney involvement is lower.

AL amyloidosis and LCDD are often associated with glomerular damage, albuminuria and progressive renal impairment. Whilst LCDD is frequently associated with MM (65%), AL amyloidosis is less frequently observed (10 - 20%) The kidney is the organ most affected in LCDD, with severe renal impairment evident in the majority of cases at presentation. The kidneys are adversely affected in approximately 75% of AL amyloidosis patients, the majority of whom present with heavy proteinuria, often with a nephrotic syndrome. AL amyloidosis and LCDD are considered in more detail in Chapters 28 and 29 respectively.

Finally, it is important to note that more than one histological pattern can exist in the same kidney. The most common combinations are cast nephropathy with acute tubular necrosis, and cast nephropathy with LCDD.

### 26.4.1. Monoclonal gammopathy of renal significance

A new term, "monoclonal gammopathy of renal significance (MGRS)" was proposed by Leung and colleagues to describe a group of haematological disorders associated with kidney disease that fail to meet the standard definitions for MM or...
lymphoma. In such cases, the renal impairment is often linked to the underlying haematological disorder. Their definition included AL amyloidosis (Chapter 28), type I and II cryoglobulinaemias (Section 34.2), monoclonal immunoglobulin deposition disease (MIDD; Chapter 29) and Fanconi syndrome 

The intention was to make a clear distinction between MGUS (Chapter 13), a benign asymptomatic condition, and MGRS, which may be associated with significant morbidity and mortality. Supportive information was published by two studies: Steiner et al. studied the long-term outcome of MGRS patients compared to MGUS patients without renal impairment, and concluded that MGRS patients had a significantly higher risk of progression to MM. Johnson et al. reviewed data from 425 patients with MGUS, and found that an abnormal sFLC ratio and elevated involved sFLC concentrations were associated with an increased risk of developing renal disease. Yadav et al. and Correia et al. recommend the use of sFLC analysis when screening for MGRS.

Figures

**Figure 26.1. Renal injury caused by FLCs.**

LCDD immunofluorescence magnification x150 [Copyright © 2007 Karger Publishers, Basel, Switzerland](#).

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- 26.4. Nephrotoxicity of monoclonal FLCs

**Figure 26.2. Higher sFLC levels are associated with more severe renal impairment.**
Distribution of renal impairment across sFLC concentration categories. As sFLC rises above 800 mg/L, the proportion of patients presenting with severe renal impairment increases. Adapted from Yadav et al.\(^{[14]}\)

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- Key updates

References


diagnosis in patients with multiple myeloma. BMC Nephrol 2018;19:178


