

## Chapter 1

# Symptomatic therapy

Richard J. Glassock

### Introduction and overview

Patients with glomerular diseases develop a wide variety of biochemical disturbances and pathophysiologic alterations leading to overt clinical manifestations (Remuzzi, 1993; Glassock et al., 1995, Remuzzi and Bertani, 1998; Schrier and Fassett, 1998; Vaziri, 2003; Floege and Feehally, 2007; Kim et al., 2007; Haraldsson et al., 2008). These occur as a direct result of injury to the capillary wall and disturbances in normal glomerular function, including loss of filtration capacity and excessive transfer of erythrocytes and/or plasma proteins from blood to tubular lumina eventuating in hematuria and/or proteinuria. Proteinuria—which is believed to be the consequence of disturbed glomerular capillary wall permselectivity (Haraldsson et al., 2008)—when substantial, can lead to hypoproteinemia and thereby to a reduction in plasma oncotic pressure. Changes in the synthesis, turnover, and plasma concentration of various proteins and lipids develop and can lead to an imbalance of pro-thrombotic and anti-thrombotic factors promoting a ‘thrombophilic’ state (Vaziri, 2003; Crew et al., 2004; Glassock, 2007). Disturbances in the renal handling of sodium chloride (NaCl) and water are often associated with edema formation and/or hypertension (Perico and Remuzzi, 1993; Schrier and Fassett, 1998). Finally, the rapid or slow loss of the glomerular filtration capacity (glomerular filtration rate, GFR) due to damage of single nephrons (perhaps mediated by filtered proteins and their reabsorption) as well as by the ‘drop out’ of functioning nephrons from the overall population of nephrons in the two kidneys is responsible for ultimate progression to end-stage renal disease (ESRD) in many, but not all, of the primary glomerular disorders (Drummond et al., 1994; Remuzzi and Bertani, 1998; Squarer, et al., 1998; Floege and Feehally, 2007).

Collectively these abnormalities give rise to ‘*syndromes*’ of glomerular disease. These ‘*syndromes*’ can be arbitrarily, but usefully, grouped into five categories which may overlap to some degree; namely, the *acute nephritic syndrome*, *rapidly progressive glomerulonephritis*, *the nephrotic syndrome*, ‘*symptomless*’

**Table 1.1** Symptomatic therapy of nephrotic syndrome

Edema
Hypertension
Hyperlipidemia
'Hypercoagulable state'
Hypoproteinemia/proteinuria
Progressive renal failure
Trace metal deficiencies
Endocrine disturbances
Infectious/immunodeficiency states

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*Treatment of Primary Glomerulonephritis*. Oxford University Press, Oxford.

*haematuria and/or proteinuria, and slowly progressive 'chronic' nephritis* (Glassock et al., 1995). The cardinal features of these syndromes and the diseases to which they are most closely associated are discussed in this monograph. This monograph will deal largely with those glomerular diseases which *primarily* affect the kidneys and in which the extra-renal manifestations are the consequence of the impairment or disturbance of kidney function itself (the so-called *primary glomerular diseases*).

The clinical abnormalities resulting from these disturbances in pathophysiology require management in order to minimize or avoid disabling symptoms, often referred to as *symptomatic therapy*, in order to distinguish the measures employed from those which are used in an attempt to ameliorate the specific underlying disease detailed in the chapters which follow, under the heading of 'Specific therapy.' Several aspects of *symptomatic therapy* will be discussed here (see also Table 1.1), namely:

- ◆ Management of edema arising from altered NaCl and fluid handling by the diseased kidney and the associated disturbances in the Starling forces operating within the peripheral capillaries.
- ◆ Treatment of hypertension developing because of extracellular and intravascular fluid volume expansion and vasoconstriction, possibly related incomplete suppression of the renin–angiotensin system, and other factors (such as reduced vasodilatory capacity and/or reduced vascular compliance).
- ◆ Therapy of hyperlipidemia and the tendency for accelerated atherogenesis;
- ◆ Management of the 'hypercoagulable' or 'thrombophilic' state accompanying hypoproteinemic forms of glomerulonephritis.

- ◆ Non-disease-specific treatment of hypoproteinemia and proteinuria, including protein-deficiency states.
- ◆ Non-disease-specific strategies designed to retard the progression of renal disease (loss of GFR) and prevention of the inexorable development of ESRD.
- ◆ Management of other disturbances, including trace metal deficiencies, endocrine perturbations, immunodeficiency states, and enhanced risk of infection (usually bacterial in origin) occurring in the absence of the use of immunosuppressant agents for ‘specific therapy.’

The extent to which each of these ‘symptomatic’ management principles can be successfully applied to specific glomerular diseases and to individual patients will vary depending upon the extent and magnitude of the underlying biochemical or pathophysiologic disturbances and their interactions with each other.

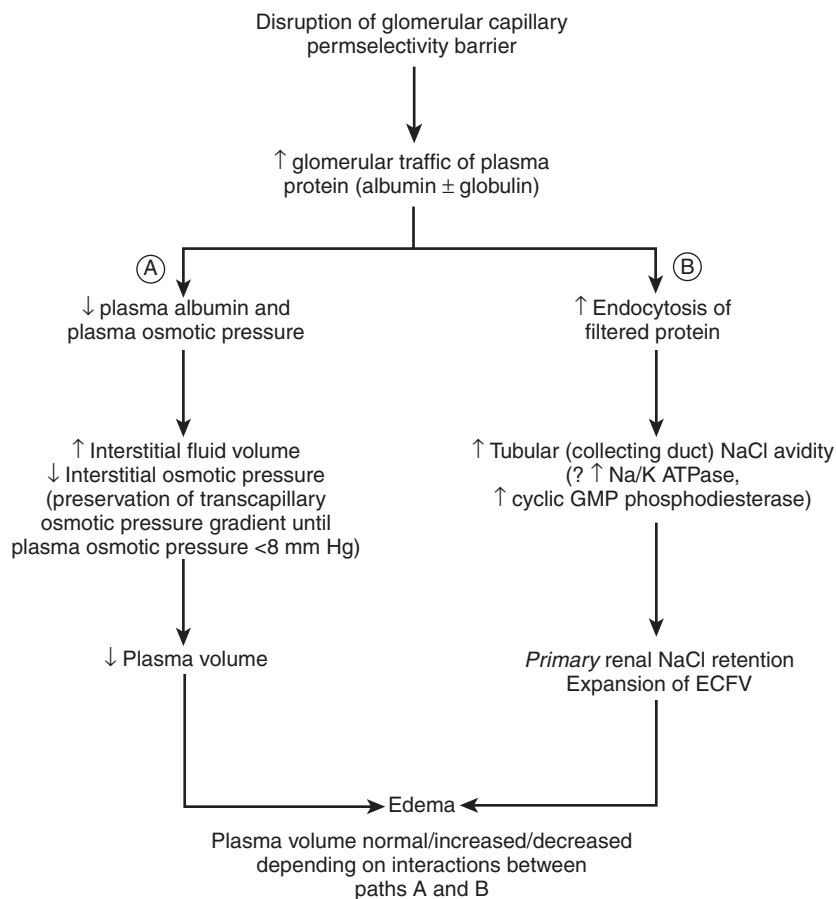
## Edema

### Clinical features, pathogenesis, and pathophysiology

Edema is common in glomerular disease, especially in those accompanied by marked proteinuria (nephrotic syndrome) (Glassock, 1980, 1997; Schrier and Fassett, 1998; Vande Walle and Donckerwolcke, 2001; Kim et al., 2007). The acute nephritic syndrome may also be associated with edema, even when hypoproteinemia is absent or mild, but it is usually less severe than that seen in nephrotic states. Edema in glomerular disease usually first accumulates about the peri-orbital areas (where the interstitial pressure is low) and in dependent sites (ankle, feet, and pre-sacral areas). Pericardial effusions are very rare but pleural effusions and ascites may develop if the disease is severe and prolonged.

In glomerular disease (acute nephritis and the nephrotic syndrome), the occurrence of edema is usually related to hypoproteinemia and/or augmented primary NaCl resorption at distal nephron (collecting duct) sites, conditioned by abnormalities of the Starling forces in the peripheral capillaries governing interstitial fluid formation and its re-uptake. Complicating congestive heart failure, advanced liver disease, pericardial effusions, or obstructions to venous/lymphatic disease may be a concomitant cause of edema in some patients. Except in oliguric patients or those with markedly impaired renal function, reduced NaCl excretion is not usually the consequence of reduced delivery to tubular reabsorptive sites because of impaired GFR per se.

The pathogenesis of edema in glomerular disease in the absence of ESRD or severe acute renal failure is not fully understood (see Fig. 1.1), but considerable progress has been made in unraveling the complex processes underlying edema formation in both the nephrotic syndrome and in acute nephritis (Perico and Remuzzi 1993; Lee and Humphreys, 1996; Schrier and Fassett, 1998; Deschenes et al., 2001; Donckerwolcke et al., 2003; Kim et al., 2006; de Seigneux et al., 2006; Doucet et al., 2007).



**Fig. 1.1** Pathophysiology of oedema formation in nephrotic syndrome. Reproduced with permission from Ponticelli C and Glasscock RJ (eds) (1997). *Treatment of Primary Glomerulonephritis*. Oxford University Press, Oxford.

Two quite distinct pathophysiologic processes appear to be involved:

- ◆ Disruption of the Starling equilibrium at the peripheral capillary level, particularly alterations in the factors governing the permeability of peripheral capillaries participating in the transfer of fluid from the vascular to the interstitial compartment (Joles et al., 1993; Joles and Koomans, 2001). In the nephrotic syndrome these abnormalities contribute to the redistribution of retained NaCl and water from the vascular to the interstitial compartments. If such transfers did not occur the degree of primary NaCl retention seen in nephrotic syndrome would quickly lead to marked intravascular volume expansion and severe hypertension. Primary renal NaCl retention *without* an accompanying marked transfer of the retained fluid to the interstitial space appears to be involved in the development of volume-dependent hypertension observed in the acute nephritic syndrome
- ◆ Marked primary renal NaCl retention occurring at distal (collecting duct) sites (Perico and Remuzzi 1993; Schrier and Fassett, 1998; Doucet et al., 2007) is the proximate cause of the retention of fluid in both nephritic and nephrotic states. Circulating hormones (e.g., aldosterone) play little role in the initiation of the salt-retaining state in these disorders.

While a decrease in plasma osmotic pressure ( $\pi$ ) due to hypoalbuminemia should result in a major displacement of intravascular fluid into the interstitial compartment, this generally does not occur unless the plasma  $\pi$  value falls well below 8 mmHg or 1 kPa (normal about 25 mmHg or 3.3 kPa) because of a corresponding fall in interstitial osmotic pressure, thus maintaining the transcapillary osmotic gradient (Joles et al., 1993; Joles and Koomans, 2001). However, a very *acute* decline in plasma  $\pi$  value, such as might occur in rapidly developing nephrotic syndrome, may not be accompanied by a corresponding rapid decline in the interstitial  $\pi$  value, so a major displacement of fluid from the vascular compartment into the interstitial compartment may occur, leading to profound hypovolemia. In more slowly developing conditions, edema with expansion of the total extracellular volume occurs even when plasma  $\pi$  is only modestly reduced, thus factors in addition to the transcapillary osmotic gradient must be involved in edema formation (Joles et al., 1993; Dorhout Mees and Koomans, 1990; Joles and Koomans, 2001). In the nephrotic syndrome the peripheral capillaries increase the transfer of fluid from the intercapillary space to the interstitial space, irrespective of the fundamental disease causing the abnormal glomerular permeability. Thus, the accumulation of retained fluid in the interstitial space (edema) is the consequence of disturbed Starling forces in the peripheral capillary, but not usually due to

the decrease in serum proteins (chiefly albumin) and thereby the plasma oncotic pressure (Joles and Koomans, 2001). This accounts for the variability in the severity of edema in patients with the nephrotic syndrome, independent of the plasma albumin concentration and the  $\pi$  of the circulating fluids.

As a result, it is very clear that edematous patients with hypoproteinemia (hypoalbuminemia) due to glomerular disease may have normal, expanded, or decreased intravascular volume (Joles et al., 1993; Joles and Koomans, 2001). The ‘*underfilling*’ theory of renal NaCl retention in the nephrotic syndrome has been largely discarded, except in unusual circumstances. Those patients with clearly and unequivocally reduced intravascular volume constitute the minority of patients with nephrotic syndrome. Such patients typically have relatively *rapid* development of edema and minimal glomerular structural abnormalities of glomeruli. Expansion of extracellular volume combined with normal or even increased intravascular volume in many patients with nephrotic syndrome points to an important contribution of primary renal processes in NaCl and fluid retention in the edema of nephrotic syndrome (Joles, 1993; Perico and Remuzzi, 1993; Doucet et al., 2007). On the other hand, the hypothesis that the great majority of subjects with the nephrotic syndrome have an ‘*overfilled*’ vascular volume (due to primary renal NaCl retention) can be criticized (Schrier and Fassett, 1998). These critiques have clinical implications as to how aggressively edema is treated with diuretics. Subjects with ‘*underfilling*’ of the intravascular volume in nephrotic syndrome may be very susceptible to decrements in arterial blood pressure or GFR with overly aggressive diuretic treatment of edema.

Strong experimental evidence suggests that primary renal retention of NaCl is caused by intrarenal disturbances rather than by circulating hormonal factors or neural effects (Ichikawa et al., 1983; Doucet et al., 2007). Excess plasma renin activity or elevated circulating aldosterone levels, deficient atrial natriuretic factor production, or activation of the sympathetic nervous system do not fully account for the disturbances in NaCl handling by the kidney observed in nephrotic syndrome (Perico and Remuzzi, 1993; Doucet et al., 2007). Furthermore, renal NaCl retention is related more to the onset and magnitude of proteinuria than the status of intravascular volume or the degree of hypoalbuminemia. Indeed, NaCl retention appears before any reduction in serum protein concentration and a diuresis ensues in the absence of any significant change in serum protein concentration in nephrotic subjects. Infusions of hyperoncotic albumin, in the absence of diuretics, do not increase NaCl excretion, despite a rise in plasma oncotic pressure. Plasma renin activity, although sometimes modestly elevated, may show little clear relationship to intravascular volume thus it is possible that renin–angiotensin system may be stimulated

by intrarenal events rather than necessarily by a depletion of intravascular volume depletion.

The abnormal NaCl reabsorption within the nephron appears to be localized to the distal nephron and collecting ducts (Ichikawa et al., 1983). Post-receptor resistance to the action of atrial natriuretic factor due to enhanced activity of cyclic GMP phosphodiesterase may be involved (Perico and Remuzzi, 1993; Lee and Humphrey, 1996), but the dominant process appears to be an increased activity of  $\text{Na}^+/\text{K}^+$  activated ATPase, perhaps abetted by alteration in the density of epithelial sodium channels (ENaC) in the cortical collecting ducts (Deschenes et al., 2001, Kim et al., 2006, 2007; de Seigneux et al., 2006; Doucet et al., 2007). Increased abundance and apical targeting of the subunits of ENaC have been demonstrated in the cortical collecting ducts in experimental nephrotic syndrome (Doucet et al., 2007). ENaC activation is secondary to hyperaldosteronism (by recruitment of an intracellular pool of channels), but sodium retention and induction of  $\text{Na}^+/\text{K}^+$  ATPase in the cortical collecting ducts are independent of hyperaldosteronism and increased ENaC may not be the rate limited step in renal NaCl retention in experimental models of nephrotic syndrome (PAN nephrosis) (Lourdel et al., 2005). Primary renal NaCl retention can occur in the absence of aldosterone in experimental nephrotic syndrome (Doucet et al., 2007). Due to the *unilateral* retention of NaCl demonstrated in experimental models of nephrotic syndrome (Ichikawa et al., 1983) it is unlikely that any circulating factor is directly involved in primary renal NaCl retention observed in nephrotic states (Doucet et al., 2007).

A distinct linkage exists between abnormal glomerular permeability, increased exposure of tubules to, and subsequent reabsorption of, protein and primary renal NaCl retention. This indicates that enhanced glomerular permeability to protein may govern primary renal NaCl retention at the *individual* nephron level in nephrotic edema. Functional changes in tubular cellular function consequent to expression of factors governing NaCl reabsorption in the collecting ducts (such as Na/K ATPase, ENaC) resulting from abnormally high concentrations of protein (including albumin) in tubular lumina appear to be involved, although this remains controversial (Zandi-Nejad et al., 2004; Yu et al., 2005; Doucet et al., 2007) (see also 'Proteinuria and hypoalbuminemia,' below). Specific filtered proteins (albumin, high-molecular weight proteins) may have differing effects on tubular reabsorptive phenomena. Intrinsic proteins may also have direct effects on NaCl reabsorption. For example, parvalbumin has recently been shown to have effects on the thiazide-sensitive  $\text{Na}^+/\text{Cl}^-$  co-transporter and thus may be involved in both  $\text{Na}^+$  and  $\text{Ca}^{++}$  handling in the distal convoluted tubule (Belge et al., 2007; Zacchia and Capasso, 2008).

It is important to re-emphasize that the proteinuria-driven changes (luminal protein concentration) in cortical collecting tubule sodium avidity operates at the *individual nephron level*. Tubules which are not exposed to abnormal luminal protein concentration (i.e., tubules which are not affected in a focal glomerular disease process involving some but not all nephrons) are capable of excreting NaCl in a normal manner and these ‘normal’ nephrons would be expected to excrete the NaCl retained by the *abnormal* nephrons in the mixed diseased/non-diseased nephron population. This phenomenon may explain why edema is quite uncommon in subjects with very focal and segmental permselectivity defects (e.g., obesity-related glomerulopathy and other ‘secondary’ forms of focal segmental glomerulosclerosis). Tubular reabsorption of NaCl at more proximal sites (proximal tubule and ascending limb of the loop of Henle) is normal in nephrotic states, at least in the absence of acute hypovolemia, diuretics, or advanced decline in GFR. Reabsorption of NaCl at distal convoluted tubule sites where Na<sup>+</sup> and K<sup>+</sup> exchange occurs is also initially normal. Thus, potassium retention or potassium loss is not seen in nephrotic states in the absence of diuretics or aldosterone deficiency. However, potassium retention may be severe in the acute nephritic syndrome, usually because of the attendant secondary hypo-reninemic, hypo-aldosteronism and reduced capacity for K<sup>+</sup> excretion (Don and Schambelan, 1990).

## Therapy

### Mild edema

If edema is mild and well tolerated, the best approach is to reduce dietary NaCl intake to levels below 3g per day (42mM Na<sup>+</sup> or about 0.5–0.6mM/kg/d) (Table 1.2). Bed rest should be avoided because of the tendency of these patients to develop thromboembolic complications (see below). Support stockings and nocturnal leg elevation may be of value in some patients with mild edema. Many patients will not require any more than these simple measures. However, if they are unsuccessful, a diuretic may be added to the regimen (Glasscock et al., 1996). An oral thiazide diuretic (e.g., hydrochlorothiazide 12.5–50mg per day or chlorthalidone 12.5–25mg per day) is a reasonable first choice, providing the GFR is normal or near normal since the effectiveness of this class of agents is blunted when GFR is <30mL/min (Ellison and Wilcox, 2008). If the serum creatinine is elevated (above 1.4mg/dL; 120μmol/L), thiazide-type diuretics are not likely to be very effective. Loop-acting diuretics (furosemide, ethacrynic acid, bumetanide, piretanide, or torsemide) are more effective choices when the GFR is reduced and when edema is troublesome (Brater, 1986; Ellison and Wilcox, 2008). Because of the duration of action, furosemide should be given on a twice-daily regimen. Once-daily administration of loop-acting diuretics is not recommended. Because severe hypoproteinemia

may impair the rate of refilling of the plasma volume, overly vigorous diuresis is to be avoided. Excessive diuresis may also activate the renin–angiotensin system and thereby promote thrombosis (see below). Oral furosemide 40–80mg per day or oral bumetanide 1–2mg per day given in two or three divided doses, along with modest dietary NaCl (3g/d) should suffice in most instances of mild edema.

### Moderate edema

More severe edema may require more intensive regimens, such as high-dose oral furosemide (160–480mg) given in two or three divided doses daily or by continuous intravenous infusion (see below) (Glassock et al., 1995) (Table 1.2). Synergistic combinations of oral furosemide 160–320mg daily or bumetanide 4–8mg daily and the distally acting diuretic, metolazone 2.5–10mg daily, are particularly effective, but may lead to pronounced kaliuresis requiring intensive potassium replacement (Suki and Eknoyan 1992). Very high

**Table 1.2** Management of edema in nephrotic syndrome

#### Mild

Dietary NaCl restriction (to 3–4 g NaCl per day)  
 Support stockings  
 Hydrochlorothiazide 12.5–50 mg per day (if GFR >50 mL/min)  
 Furosemide 40–80 mg per day (if GFR <70 mL/min)

#### Moderate

Continue NaCl restriction, add  
 Furosemide 160–480 mg per day or bumetanide 1–2 mg per day or torsemide  
 40–160 mg per day

#### Severe

Continue NaCl restriction, add  
 Oral or IV furosemide 160–480 mg per day (or bumetanide or torsemide) plus metolazone  
 2.5–10 mg per day

#### Refractory

Continuous IV infusion of furosemide (20 mg/h) or bumetanide (1 mg/h) after a loading dose

or

Hyperoncotic salt-poor albumin (25–50 g) mixed with 120 mg of furosemide

or

Slow continuous veno-venous ultrafiltration using a highly permeable (polysulfone) membrane

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doses of loop-acting diuretics, oral or intravenous, should be used with caution in patients with markedly impaired renal function because of the risks of transient or permanent deafness (Ellison and Wilcox, 2008). Mild diarrhea may also be seen with very high doses of loop diuretics. The natriuretic effects of loop-acting diuretics are related to the urinary concentration of the diuretic (Brater, 1993). The relationship between diuretic excretion rate (in  $\mu\text{g}/\text{min}$ ) and sodium excretion rate (in  $\mu\text{Eq}/\text{min}$ ) is described by a steep sigmoid curve. Different loop-acting diuretics differ only in potency, not in the shape of the curve (Brater, 1993).

Potassium-sparing diuretics, such as spironolactone, eplerenone, triamterene, or amiloride, given alone, are also of limited value but they may blunt the kaliuresis seen with thiazides or loop-acting diuretic and augment the resulting natriuresis when used in combination with other diuretics acting at different sites within the nephron. Thus, they are not usually very effective when used as monotherapy, but they augment the effectiveness of both loop-acting diuretics and thiazide-type diuretics. These potassium-sparing diuretics should be used with great caution or not at all in patients with impaired GFR ( $<25\text{mL}/\text{min}$ ) or when hyperkalemia is present. More rigorous dietary NaCl restriction (1g/d) may also be required for short periods of time, but this will usually not be tolerated (or adhered to) over a period of longer than a few weeks.

### Severe or refractory edema

A severe edematous state (anasarca) in which increasing doses of loop-acting diuretics combined with potassium-sparing diuretics and/or metolazone become increasingly less effective in inducing a natriuresis is relatively common, especially in patients with severe and massive proteinuria ( $>10.2\text{ g per day}$ ), marked hypoalbuminemia ( $<2.5\text{ g/dL}$ ) and/or impaired renal function (serum creatinine  $>2.0\text{mg/dL}$ ) (Glassock, 1997) (Table 1.2).

At one time the poor response to loop-acting diuretics (e.g., furosemide) was thought to be caused by binding of the drug to tubule fluid albumin, thereby preventing the action of the diuretic on the luminal side of the ascending limb of the loop of Henle to inhibit the  $\text{Na}^+/\text{K}^+/\text{2Cl}^-$  reabsorptive pathway (Brater, 1993; Kirchner, 1993). This is no longer thought to be the case. An intravenous loading dose of furosemide or bumetanide followed by a slow intravenous infusion of the diuretic over 12–24h (20mg/h for furosemide and 1mg/h for bumetanide) (Brater, 1993) may sometimes be effective, when oral administration is not accompanied by a diuresis.

Excess compensatory ‘upstream’ distal-NaCl reabsorption (sites prior to the cortical collecting duct) may also be overcome by concomitant administration of a thiazide-type diuretic (Paton and Kane, 1977). Hyperoncotic (25%) or

iso-oncotic (5%) human albumin infusions alone are seldom indicated to expand plasma volume, except when a rapid diuresis has resulted in clinical features of a plasma volume deficit, such as hypotension or a low central venous pressure. Such infusions should be used cautiously, if at all, in patients with impaired renal function and intrinsic cardiac disease because of the risk of precipitating congestive heart failure. Because of continued abnormal permselectivity, the infused albumin will be rapidly excreted in the urine (usually within 24–48 h). Thus, the beneficial effects are short lived. The increased filtration of albumin can also result in further injury to the glomerular epithelial cells and or tubule. Indeed, some studies have suggested that use of intravenous albumin may inhibit therapeutic responses to glucocorticoids in minimal change disease (Yoshimura et al., 1992). On the other hand, some investigators believe that intravenous albumin may be regarded as a useful vehicle for augmenting the delivery of loop-acting diuretics to tubular sites of action as mentioned above. A natriuresis can be potentiated by the concomitant administration of a loop-acting diuretic and hyper-oncotic albumin (furosemide mixed with 25% human serum albumin) in equimolar concentrations (Brater 1993; Kirchner 1993), but the effect is usually limited and of short-duration. In addition, some clinical investigators have challenged the usefulness of intravenous albumin in the treatment of nephrotic edema, either alone or combined with diuretics, based on an exhaustive survey of the literature (Dorhout Mees, 1996). Loop-acting diuretics circulate bound to albumin and are delivered to their site of action in the ascending limb of the loop of Henle via the organic anion secretory pathway in the proximal tubule. When hypoalbuminemia is present, both the volume of distribution and the extrarenal catabolism of loop diuretics are increased. Less drug is therefore delivered to secretory sites in the proximal tubule and the urinary excretion is diminished, leading to a blunted effect even at high doses of the drug.

Intrinsic unresponsiveness of the renal tubule and impaired gastrointestinal (GI) absorption of furosemide have also been suggested as potential causes of diuretic refractoriness (Kirchner et al., 1992) but this does not appear to be of major importance, at least in the usual case of nephrotic syndrome. Non-steroidal anti-inflammatory drugs (including aspirin) *antagonize* and angiotensin-converting enzyme inhibitors *potentiate* the action of loop-acting diuretics (Brater, 1990).

In exceptional patients who are truly refractory to all oral or parenterally-based treatments (including high-dose loop-acting diuretics, metolazone and/or amiloride), a course of slow, continuous ultrafiltration using a highly permeable (polysulfone) dialysis membrane and a veno-venous circuit with systemic heparin anticoagulation can be used for temporary relief of anasarca

(Fauchald et al., 1985). Because the edema in the interstitial compartment can be partially mobilized when serum albumin concentration is increased by ultrafiltration, rapid rates of ultrafiltration (3–5 L/h) are usually well tolerated.

## Hypertension

### Clinical features, pathogenesis, and pathophysiology

Elevation of systolic and/or diastolic blood pressure (BP) commonly occurs in patients with glomerular disease (Glasscock et al., 1995). The degree of hypertension is usually worse and the frequency more common in the acute nephritic syndrome and much less prominent in the nephrotic syndrome, unless a severe decrease in the GFR is present. Indeed, severe hypertension (and volume overload) can lead to congestive heart failure and encephalopathy in patients with the acute nephritic syndrome but this seldom occurs in those with the nephrotic syndrome, due to primary glomerular disease. Patients with hypertension due to primary glomerular disease tend not to have the normal decline in BP during sleep ('non-dipper') when studied by 24-h ambulatory BP monitoring (Tamura et al., 2008). The underlying pathophysiology of hypertension in primary glomerular disease remains a subject of intense investigation but several factors appear to be involved, namely:

- ◆ Primary renal NaCl retention leading to expansion of intravascular and extracellular fluid volumes (see above); this is especially important in the acute nephritic syndrome.
- ◆ Intrarenal activation of the renin–angiotensin system despite relative vascular volume expansion; plasma renin activity and plasma aldosterone levels are markedly suppressed in the acute nephritic syndrome, but they may be inappropriately elevated in the presence of extracellular volume overload.
- ◆ Activation of the sympathetic nervous system, perhaps a consequence of the central actions of angiotensin II.
- ◆ The release, at the level of the vascular endothelial cell, of vasoconstrictor substances (e.g., thromboxane or endothelin) or deficiencies in the generation of vasorelaxant factors (e.g., nitric oxide, prostaglandins) may also participate (Campese, 1995; Galla and Luke, 1995).

A more pronounced effect on systolic pressure with widening of the pulse pressure suggests a prominent volume-mediated component and/or an effect of the disease on vascular compliance. Acute post-streptococcal glomerulonephritis is a classic example of volume-mediated hypertension in which the renin–angiotensin–aldosterone system is markedly suppressed (Don and Schambelan, 1990). Chronic forms of glomerulonephritis nearly always show

an admixture of volume-mediated and vasoconstrictor pathophysiology (Galla and Luke, 1995). The concomitant presence of hypertension and nephrotic syndrome may alter the distribution of fluid between the intravascular and interstitial spaces and thus blunt the expected hypertensionogenic effect of fluid retention (Geers et al., 1984). In some exceptional patients with nephrotic syndrome 'secondary' hyperreninemia and hyperaldosteronemia are present without hypertension, indicative of a reduced plasma volume. These patients usually have minimal change nephropathy and the rapid development of nephrotic syndrome (Meltzer et al., 1979).

## Therapy

The management of hypertension accompanying glomerular disease is very important not only to reduce the risks of cardiovascular disease (stroke, myocardial infarction, peripheral vascular disease, congestive heart failure) but also potentially to blunt progressive renal insufficiency (see below). The management of hypertension in glomerular disease is based on two fundamental precepts:

- 1) Dietary NaCl restriction and/or diuretics in order to affect the volume-mediated influence on blood pressure, and
- 2) To reduce the vasoconstrictor effect of an inappropriately activated renin-angiotensin or sympathetic nervous system.

Thiazide or loop-acting diuretics may suffice in many patients but if not accompanied by NaCl restriction will often be ineffective, particularly when short-acting agents such as bumetamide or furosemide are used. When GFR is normal, the natriuretic effect of the furosemide lasts approximately six hours and thus, if this agent is administered on a once-daily basis, *in the absence of sodium restriction*, once the diuretic effect has dissipated, the sodium-avid kidney will reabsorb sodium to an extent that the 24-h balance will be neutral (Ellison and Wilcox, 2008). Diuretics with more prolonged action such as thiazides or chlorthalidone will not have this disadvantage. However, the natriuretic potency of these agents is considerably attenuated when the GFR is <30 mL/min.

If NaCl restriction and/or diuretics do not 'adequately' control blood pressure (see below for a discussion of what constitutes 'adequate' BP control), then additional antihypertensive agents can be added. For a variety of reasons, listed below, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB) or both combined appear to be the agents of choice. A new class of agents, the direct renin inhibitors (e.g. aliskerin), has also been recently introduced and may have a role in the management of hypertension.

The use of drugs interfering with the action of the renin–angiotensin system is preferred because:

- ◆ They tend also to reduce protein excretion, presumably because of their intra-renal hemodynamic and other BP independent effects (Cravedi et al., 2007).
- ◆ They may have renoprotective properties *independent* of lowering BP and even their anti-proteinuric effects, thus reducing the likelihood of future progression to ESRD (see below) (Cravedi et al., 2007; Ruggenti et al., 2008).
- ◆ They are well tolerated and are associated with minimal side effects (except cough [see below] and occasionally anaphylaxis with ACEi) and a good quality of life.
- ◆ They are quite effective, particularly when combined with thiazide and/or loop diuretics and/or NaCl restriction. Hyperkalemia, allergic reactions (including angio-edema), and agranulocytosis are relatively uncommon.

A common troublesome side effect is a dry, non-productive cough associated with the use of ACEi but not with ARB, and is perhaps related to change in bradykinin activity. Cough is seen more commonly in individuals of Asian ancestry but may also be seen in Caucasians. Combinations of ACEi and ARB may produce more side effects, including acute reductions of GFR, when used in patients with underlying cardiac disease (Cravedi et al., 2007). Theoretically, ACEi may also reduce thrombotic tendency because they lower plasminogen activation inhibitor-1 levels (see below) (Kerins et al., 1995). Other antihypertensive agents such as  $\beta$ -adrenergic blockers (propranolol, atenolol), combined alpha/beta blockers (labetolol), central or peripherally acting adrenergic inhibitors (clonidine),  $\alpha$ -1 receptor blockers (doxazosin), dihydropyridine or non-dihydropyridine calcium channel blockers (CCB), and direct-acting vasodilators (e.g., hydralazine, minoxidil, nitroprusside) may also be quite effective in lowering BP (Campese, 1995), but are not preferred as front-line agents in glomerular disease with proteinuria. Non-dihydropyridine CCB (e.g., diltiazem, verapamil) may also reduce proteinuria, but to a lesser extent than ACEi (Gansevoort et al., 1995). Dihydropyridine CCB have little effect on proteinuria or may actually increase protein excretion rates. Dihydropyridine CCB should not be given in the absence of concomitant ACEi or ARB. Combinations of loop-acting diuretics, ACEi and/or ARB, and non-dihydropyridine calcium antagonists may be useful in difficult-to-manage cases. Refractory hypertension requires a multi-drug approach, but control of volume expansion with diuretics and NaCl restriction is a critical component of therapy. Dihydropyridine CCB (nifedipine, nisoldipine, amlodipine) are quite useful

adjunctive antihypertensive agents but they tend not to be associated with a reduction in protein excretion and may aggravate edema (Gansevoort et al., 1995). Furthermore, these latter agents do not appear to have reno-protective actions, independent of BP lowering. Small doses of spironolactone or eplerenone may be very helpful for the control of BP in those subjects (mainly diabetics) who do not respond favorably to thiazides or loop-acting diuretics agents or ACEi/ARB, but caution about hyperkalemia is warranted (Schjoedt et al., 2006).

Agents which can be administered on a once-a-day basis are preferred for chronic therapy. Administration of doses at bedtime may be helpful for subjects with 'non-dipping' BP elevations. Newer anti-hypertensive agents, such as direct renin inhibitors (aliskiren) can also be used (alone or in combination with other angiotensin-II inhibiting agents), but there is only limited short-term little experience in their use in primary glomerular disease with nephrotic syndrome or acute nephritis (Parving et al., 2008). This class of agents would not be expected to be beneficial if plasma renin activity is depressed (see also Table 1.3 for a description of recommendations for treatment of hypertension).

**Table 1.3** Therapy of hypertension in primary glomerular disease

<b>Goals:</b>	Maintain systolic blood pressure of 120–130 mmHg and diastolic BP of 70–80 mmHg. Do not allow diastolic BP to fall below 70 mmHg if symptomatic coronary artery disease is present
<b>Agents:</b>	<p>Angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) preferred</p> <p>Use NaCl restriction and/or diuretics (thiazides, loop acting, spironolactone or eplerenone) to augment effectiveness</p> <p>Combinations of ACEi and ARB may be used, with careful attention to serum potassium levels</p> <p>Direct renin inhibitors may also be used selectively</p> <p>Adjunctive therapy with calcium channel blockers (CCB) may be used for optimal BP control</p> <p>Change in serum creatinine and potassium levels should be monitored at frequent intervals during the first month of initiating therapy. If serum creatinine levels rise &gt;25% from baseline, therapy may have to be interrupted.</p>
<b>Dosage:</b>	<p>For monotherapy with ACEi or ARB, the maximum tolerated dosage should be used, preferably to assure both daytime and night-time control of BP to desired goals. Ambulatory monitoring of 24-h BP may be needed</p> <p>For combination ACEi and ARB therapy the maximum recommended dosage of each agent should be used, with monitoring of serum potassium levels.</p>

The extent to which BP should be lowered for optimal or 'adequate' control remains a subject of ongoing investigation. For the time being, a goal of 120–130 mm Hg for the systolic BP and 70–80 mmHg for the diastolic BP (mean arterial pressure of around 92 mmHg) appears prudent. Acute lowering of BP to these levels in subjects with encephalopathy (or carotid arterial stenoses) may be hazardous due to reduction in cerebral perfusion. Intravenous, short-acting antihypertensive agents (such as labetalol, enalaprilat, or nitroprusside) may be useful for severe hypertension and associated acute left ventricular dysfunction with congestive heart failure. In more chronic states, it is not known whether lower levels of BP (<120 mmHg systolic or <70 mmHg diastolic) will be associated with any better protection from progressive renal failure and a low diastolic pressure (<70 mmHg) should be avoided in older patients with established coronary artery disease because of the risk of impairing coronary perfusion which is highly dependent on diastolic pressure gradients (Messerli, et al., 2006). Too low BP should also be avoided in those with carotid artery stenoses. 24-h ambulatory BP recordings may be useful to detect 'non-dipping' status, which is associated with a greater degree of left-ventricular hypertrophy and a higher mortality rate from CVD (Hermida, 2007).

## Hyperlipidemia

### Clinical features, pathogenesis, and pathophysiology

Elevation of plasma total cholesterol and triglycerides is commonly found to accompany glomerular disease, especially in those situations associated with heavy proteinuria and hypoalbuminemia (nephrotic syndrome) (Table 1.4) (Vaziri, 2003). The lowering of plasma albumin concentration and the increased protein excretion contribute separately to changes in lipoprotein metabolism in the nephrotic syndrome (Shearer et al., 2001; Vaziri, 2003). The underlying pathophysiology of hyperlipidemia is only partially understood but appears to involve both enhanced synthesis and decreased metabolism of lipoproteins (Joles and Kaysen 1991; Vaziri, 2003). The characteristic perturbation seen in nephrotic syndrome is an increase in low density lipoproteins (LDL), very low density lipoproteins (VLDL), and/or intermediate density lipoproteins (IDL), but no change or a decrease in high density lipoproteins (HDL). Apolipoprotein B and apolipoprotein CIII are increased but apolipoprotein AI, AII, and CII are unchanged. The ratio of apolipoprotein CIII/CII is increased and contributes to a prevailing state of inhibition of lipoprotein lipase. HDL<sub>3</sub> is increased whereas HDL<sub>2</sub> is decreased. The combination

**Table 1.4** Plasma lipid concentrations in nephrotic syndrome**Increased**

Very low density lipoproteins  
 Intermediate density lipoproteins  
 Low density lipoproteins  
 Apolipoprotein B  
 Apolipoprotein CIII  
 High density lipoprotein<sub>3</sub>  
 Lipoprotein (a)  
 Total cholesterol  
 Triglycerides (when serum albumin <2 g/dl)

**Unchanged**

Apolipoprotein AI  
 Apolipoprotein AII  
 Apolipoprotein CII

**Decreased**

High density lipoprotein<sub>2</sub>

See Wheeler and Bernard (1994) and Kaysen *et al.* (1991) for details.

of reduced HDL<sub>2</sub> and increased LDL/IDL increases greatly the *potential* risk for atherosclerotic cardiovascular disease, especially with the concomitant presence of smoking, obesity, diabetes, hyperuricemia, and hypertension. Circulating levels of lipoprotein (a) [Lp(a)] and fibrinogen are also increased in nephrotic syndrome and may have an additive effect on atherogenesis and on the predisposition to thrombotic events (Stenvinkel *et al.*, 1993). The synthesis and cellular expression of LDL receptors is diminished in experimental nephrotic syndrome (Vaziri and Liang, 1996; Vaziri, 2003).

The hepatic synthesis of apolipoproteins A, B, E, and VLDL is often, but not invariably, increased perhaps as a result of decreased serum albumin concentration and plasma osmotic pressure, but other processes are probably also involved (Vaziri, 2003). The catabolism of VLDL and LDL is also greatly reduced in nephrotic syndrome and this does not appear to be the direct consequence of reduced albumin concentration (Vega *et al.*, 1995). Reduced catabolism of apolipoprotein B LDL is also present when increased plasma cholesterol is not accompanied by hypertriglyceridemia, but hepatic production of apolipoprotein B LDL is increased in combined hypercholesterolemia and hypertriglyceridemia (Vega *et al.*, 1995).

It has been suggested that proteinuria per se results in a disturbance of lipoprotein metabolism, perhaps because of the renal generation or urinary loss of a lipoprotein regulatory substance (Garber et al., 1984; Vaziri, 2003). It has long been known that elevated serum lipoproteins can occur even in glomerular proteinuria unaccompanied by nephrotic syndrome or hypoalbuminemia.

These lipid abnormalities (increased LDL, reduced HDL<sub>2</sub>, and increased Lp(a)) have important long-term consequences which deserve careful attention and appropriate management (Radhakrishnan et al., 1993; Appel, 2001), but here is little evidence-based data (such as randomized clinical trials) to guide rational management. Observational and controlled trials have proven atherogenesis to be accelerated in hypercholesterolemic states (high LDL and low HDL cholesterol) and this leads to an increased risk for cardiovascular disease, including angina, myocardial infarction, strokes, and peripheral vascular disease. Concomitant hypertension, heavy smoking, obesity, diabetes (insulin resistance), physical inactivity, and/or a positive family history of coronary artery disease (Radhakrishnan et al., 1993). By inference, it is believed that the abnormal lipid patterns seen in glomerular disease also predispose to accelerated atherogenesis, but this is much less proven than in subjects without glomerular disease. It is also postulated that abnormal plasma lipid concentrations also contribute to progressive glomerular injury (see below) (Keane, 1994). However, the benefits and risks of 'statin' therapy to slow progression of renal disease (independent of its benefits for dyslipidemia) remains unproven and controversial (Rahman et al., 2008; Strippoli et al., 2008; Tonelli, 2008). Further randomized trials in progress will likely resolve this controversy. Statins may have lowering effects on established albuminuria but whether this will translate into better outcomes is unknown (Douglas et al., 2006).

## Therapy

Unfortunately, the management of hyperlipidemia accompanying nephrotic syndrome is only fully successful in restoring the elevated levels to normal values when the underlying cause is remedied and long-term complete remissions of proteinuria are induced (see Table 1.5). Dietary therapy consisting of reduced cholesterol and saturated fat intake is generally relatively ineffective and can make the HDL<sub>2</sub> reductions worse. Restriction of total fat intake has never been proven to alter the natural history of atherogenesis in subjects with the nephrotic syndrome. Even with strict dietary prescription and full compliance, LDL levels will usually fall a maximum of 15–20% from baseline values. The long-term use of agents which interfere with the GI absorption of dietary cholesterol (such as ezetimide [Zetia®]) or exchange resins (e.g. cholestyramine, colestipol, psyllium colloids, oat bran) is incompletely evaluated in nephrotic

**Table 1.5** Therapy of lipid disturbances in nephrotic syndrome

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Prudent diet, low in total cholesterol and saturated fat (relatively ineffective); vegetarian/soy diet

Stop smoking

Modest exercise

Avoid excessive alcohol

HMG co-reductase inhibitors (lovastatin, simvastatin, pravastatin, atorvastatin, rosuvastatin, fluvastatin)

Probuco (may lower HDL<sub>2</sub>)

Bile acid sequestering agents (cholestyramine, colestipol, psyllium colloid)

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syndrome, and they cannot be recommended at the present time. A vegetarian–soy diet supplemented with amino acids may achieve the best results but long-term compliance and overall efficacy of this dietary approach is not well known (D’Amico et al., 1992). Oral administration of bile-acid sequestering agents, such as cholestyramine, colestipol, or psyllium colloid, are able to reduce modestly the total cholesterol but are relatively poorly tolerated and may aggravate underlying vitamin D deficiency.

Fibric acid derivatives (gemfibrozil) and nicotinic acid are more effective for hypertriglyceridemia but are not very useful for the hypercholesterolemia which accompanies nephrotic syndrome (Grundy, 1990). They may also be associated with muscle injury (Bridgman et al., 1972). Nicotinic acid (niacin) will lower both LDL cholesterol and triglycerides and also increase HDL cholesterol but is not well tolerated at the high dosage required. Extended-release preparations of niacin may be better tolerated. Probuco may be a useful agent since it lowers LDL cholesterol concentration by approximately 20–35% and it may have other beneficial effects as an antioxidant (Neale et al., 1994). Unfortunately, it may also modestly reduce HDL<sub>2</sub> levels further.

Hydroxymethylglutaryl co-enzyme A reductase (HMG co-A reductase) inhibitors (‘statins’) are the current treatments of choice for hypercholesterolemia of nephrotic syndrome (Appel, 2001). All currently available preparations (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin,) will lower LDL and total cholesterol by approximately 25–45% (atorvastatin and rosuvastatin are the most potent) despite continued proteinuria. (See Table 1.6 for a listing of preparations and recommended dosage).

**Table 1.6** Hydroxy methyl glutaryl co-enzyme A reductase ('statin') therapy for hypercholesterolemia in the nephrotic syndrome (adults)

◆ <i>Lovastatin</i> :	10–20mg once daily in the evening (80mg/d maximum dosage)
◆ <i>Simvastatin</i> :	20–40mg once daily in the evening (80mg/d maximum dosage)
◆ <i>Pravastatin</i> :	10–40mg once daily (maximum dose 80mg/d)
◆ <i>Fluvastatin</i> :	20–40mg once daily (maximum dose 80mg/d)
◆ <i>Atorvastatin</i> :	10–40mg once daily (maximum dose 80mg/d)
◆ <i>Rosuvastatin</i> :	5–20mg once daily (maximum dose 40mg/d)

These agents cause no changes or only a mild-modest elevation in HDL<sub>2</sub> and are generally well tolerated but rarely they may produce rhabdomyolysis and even acute renal failure, particularly at high dosage or combined with fibric acid derivatives (or possibly cyclosporin). Asian patients might be more susceptible to these effects. Unfortunately, statins have no or very limited effects on Lp(a) or fibrinogen levels (Wanner et al., 1994).

Although lowering serum cholesterol levels with a statin has the *potential* for significantly reducing the risk of coronary heart disease events in patients with and without preexisting coronary heart disease in the absence of nephrotic syndrome or renal disease, their effects on prevention or regression of atherogenesis complicating human glomerular disease or on the progression of renal have not been unequivocally proven in a large prospectively designed randomized clinical trial in nephrotic subjects (Strippoli et al., 2008; Tonelli, 2008; thus, treatment is largely '*on faith*' that modest lowering of an atherogenic lipid (but not to normal ranges) will be accompanied by a lowered risk of subsequent cardiovascular events. (Scandinavian Simvastatin Survival Study, 1994; Tonelli et al., 2004). Meta-analyses of existing trials have suggested that statins may reduce cardiovascular event rate in patients with chronic kidney disease (CKD) (Tonelli, et al., 2006; Tonelli and Pfeffer, 2007), and may also very modestly slow the rate of progression of CKD *not* accompanied by diabetes, hypertension or glomerulonephritis (Sandhu et al., 2006), but as stated above this is quite controversial. Large prospective randomized trials are in progress to test this hypothesis (SHARP, AURORA) and their results are eagerly anticipated.

The overall cost of this therapy is relatively high and the long-term benefits and risks uncertain, but most patients are so concerned about elevated total cholesterol and/or LDL levels that treatment can be justified as a means of reducing apprehension. Some evidence has been generated suggesting that statins given alone modestly reduce the level of proteinuria (Douglas et al., 2006), although at high doses in normal subjects they paradoxically increase

albuminuria by interfering with tubular re-absorption of normally filtered protein by a direct action on tubules. Thus, for the present time at least, the indications for the use of statins in CKD, even accompanied by the nephrotic syndrome are the same as for their use in the general population (Clase, 2008).

Regular moderate exercise, a prudent anti-atherogenic diet (low in total cholesterol, low in saturated and transfat, low in fructose and sucrose, high in anti-oxidant content 'Mediterranean' style diet), complete avoidance of smoking, rigorous control of BP (with ACEi and/or an ARB) and obesity may offer as much or more than drug management of serum cholesterol levels (see below) with respect to prevention of cardiovascular disease and slowing the rate of progression of renal disease.

## Hypercoagulability

### Clinical features, pathogenesis, and pathophysiology

It has been known for many decades that patients with glomerular disease and marked (nephrotic range) proteinuria are at increased risk for thromboembolic events ('*thrombophilia*'), such as deep venous thrombosis (DVT), renal vein thrombosis, pulmonary embolism, and arterial thrombi (Vaziri, 1983; Glassock, 2007). This '*thrombophilic*' phenomenon has been attributed to an ill-defined 'hypercoagulable' state in which an imbalance between naturally occurring pro-coagulant/pro-thrombotic factors and anti-coagulant/anti-thrombotic factors promote *in situ* thrombosis in deep veins or arteries (Table 1.7) (Vaziri, 1983; Cameron, 1984; Glassock 2007).

**Table 1.7** Coagulation abnormalities in nephrotic syndrome

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**Increased (prothrombotic)**

Fibrinogen  
 Platelets (and platelet adhesiveness)  
 Plasma viscosity (cholesterol, lipid)  
 Lipoprotein (a)  
 Plasminogen activator inhibitor

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**Decreased (antithrombotic)**

Active protein C  
 Active protein S  
 Antithrombin III

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*Treatment of Primary Glomerulonephritis*. Oxford University Press, Oxford

The biochemical nature of this *thrombophilic* state is probably multifactorial. The plasma concentration of fibrinogen is markedly increased in nephrotic syndrome. When this is combined with a low albumin level it leads to an almost universal increase in the erythrocyte sedimentation rate irrespective of underlying inflammation. A mild thrombocytosis is frequently present. Hypercholesterolemia leads to an increase in plasma viscosity. Urinary losses of proteins C, S, and antithrombin III may predispose to a low plasma concentration of these factors (Vaziri, 1983; Kauffman et al., 1978; Cameron, 1984). A genetically determined background of impaired resistance to activation of factor V (Leiden trait) may also predispose to thrombosis in the presence of these disturbances (Ridker et al., 1995). Elevated Lp (a) levels may also contribute to impaired fibrinolysis (Kronenberg et al., 1996).

Evidence has accumulated linking local activation of the renin–angiotensin system with impaired endogenous fibrinolysis and a pro-thrombotic tendency. Angiotensin IV (AT-IV), a hexapeptide produced by the action of aminopeptidase on angiotensin II (AT-II), promotes endothelial cell synthesis of plasminogen activation inhibitor-1 (PAI-1) via interaction with an AT-IV specific receptor, not via the well recognized AT-I and AT-II receptors (Kerins et al., 1995). Fibrinolysis may thus be inhibited leading to a prothrombotic state. It is possible that TGF $\beta$  (transforming growth factor  $\beta$ ) is also involved in this interaction since angiotensin II is a strong promoter of TGF $\beta$  synthesis in tissue and TGF $\beta$  stimulates PAI-1 synthesis (Border and Noble 1994). Angiotensin-converting enzyme inhibitors may reduce PAI-1 synthesis and because of concomitant elevated bradykinin levels, endothelial cell synthesis of tissue plasminogen activator (tPA) is enhanced (Kerins et al., 1995). The net effect of ACEi is to tilt the tPA/PAI-2 ratio in favor of a pro-fibrinolytic rather than a pro-thrombotic state. Angiotensin II receptor antagonists (ARB) would not be expected to have as favorable an effect on this ratio, and could even theoretically promote increased PAI-1 levels, because of high AT-II (and thereby AT-IV) levels (Johnston 1995). Similarly, diuretics which promote activation of the renin–angiotensin system and thereby the AT-II and AT-IV levels could also promote a pro-thrombotic state by altering PAI-1 levels. High PAI-1 levels are known to be associated with increased risk of recurrent myocardial infarction in survivors of acute coronary thrombosis (Ridker et al., 1993).

Excess mortality from cardiovascular events in nephrotic syndrome could theoretically be explained, at least in part, by both hyperlipidemia-related increased atherogenesis and a pro-thrombotic state induced by elevated PAI-1 levels driven by an activated renin–angiotensin system. Other concomitant processes such as anti-phospholipid auto-antibodies (usually seen in connection

with systemic lupus erythematosus) and anti-plasminogen auto-antibodies seen in systemic vasculitis (Wegener's granulomatosis) may greatly affect the tendency to thrombosis in these diseases (Merkel, et al., 2005; Bu et al., 2008). Anti-enolase auto-antibodies, strongly associated with membranous nephropathy and exerting an anti-fibrinolytic effects, could also be involved in the marked tendency of this disorder for thrombosis (Wakui et al, 1999).

Many of the disturbances associated with the thrombophilic state in nephrotic syndrome are correlated with the magnitude of depression of serum albumin levels (Kauffman et al., 1978; Glassock, 2007). The concentration of albumin may therefore be used as 'surrogate' to approximate the magnitude of the 'hypercoagulable' state and thereby the potential risk of thromboembolic events. Serum albumin concentrations <2.0–2.5g/dL appear to be associated with an increased risk of thromboembolism. High levels of fibrinogen, low plasminogen activity, low antithrombin III, and high levels of PAI-1 may also predict the tendency for thrombosis (Glassock, 2007). A preceding thrombotic event (such as a DVT), recent abdominal, gynecologic or orthopedic surgery, recent trauma, the presence of a lupus anticoagulant (anti-phospholipid antibody), an anti-plasminogen antibody, systemic vasculitis (Wegener's granulomatosis), prolonged inactivity, obesity, and a family history of 'thrombophilia' (such as might be present with a factor V Leiden trait) are all predisposing factors for thrombotic events. The presence of *one or more* of these predisposing factors should influence the decision regarding use of measures to prevent thrombosis (oral anti-coagulation with warfarin or use of heparin or enoxaparin) in individual patients (Glassock, 2007).

It also must be appreciated that the tendency for thrombosis is not uniform among the primary glomerular diseases leading to the nephrotic syndrome. The disorders most prominently associated with thrombophilia are membranous nephropathy (MN), membrano-proliferative glomerulonephritis (MPGN) and minimal change nephropathy (MCN) (see Chapters 5, 7, and 9) (Glassock, 2007). The reasons underlying these disparities are incompletely understood. Membranous nephropathy has been best studied (Glassock, 2007). DVT and renal vein thrombosis (RVT) may develop. The combined burden of both DVT and RVT in MN has been estimated to be about 45% in MN. The development of RVT in MN is highly variable with reported prevalences ranging from 1.6% to 60%. The development of DVT is highly dependent on serum albumin concentration. A DVT prevalence of <3% has been reported in those with a serum albumin >2.5g/dL and 40% in those with a serum albumin level of <2.5g/dL (Bellomo and Atkins, 1993). In many cases the DVT or RVT are asymptomatic. Ventilation-perfusion lung abnormalities can be found in about 10% of asymptomatic patients without any overt RVT

or DVT and in about 20% of those with RVT alone accompanying the nephrotic syndrome. Higher values have been reported when pulmonary angiography is used for diagnosis. Thus, all patients with nephrotic syndrome should be considered at increased risk for thrombotic events, but those with MN, MPGN, and MCN appear to be at the highest risk. DVT is the most common, but spontaneous arterial thrombosis (pulmonary artery, axillary artery) may also occur when the nephrotic syndrome is very severe (Glassock, 2007).

## Therapy

Management of the thromboembolic complications of the ‘*thrombophilic*’ state accompanying nephrotic syndrome in glomerular diseases may be divided into *prophylactic* and *therapeutic* strategies. As stated above, certain categories of renal diseases appear to be at higher risk for thromboembolic events, not entirely explained by the magnitude of proteinuria or hypoalbuminemia. Such patients may be candidates for *prophylactic* anticoagulation with long-term oral warfarin or short-term anticoagulation with parenteral high molecular weight heparin or low molecular weight heparin derivatives, or even oral or parenteral direct anti-thrombin (hirudin-like) agents in order to prevent thromboembolic phenomena (DVT, RVT, pulmonary embolism, arterial thrombosis). The latter agents (direct thrombin inhibitors) have not yet received an evaluation for safety and efficacy in nephrotic subjects. Decision analyses as well as systematic reviews have shown that an approach using oral warfarin theoretically will reduce the overall risk for serious thromboembolic events (e.g., pulmonary embolism) in excess of the induction of serious bleeding manifestations (Sarasin and Schifferli 1994; Glassock, 2007) in subjects with nephrotic syndrome due to MN. However, no prospective, randomized controlled studies have ever examined the overall efficacy and safety of a prophylactic approach to anticoagulation for patients with the nephrotic syndrome judged clinically to be at ‘high-risk’ for thromboembolic phenomenon, including those with MN. It is noteworthy that thromboembolism is rare in the ‘placebo’ arm of reports of controlled trials of therapy in MN (Glassock, 2007). Whether prophylactic oral warfarin anticoagulation is indicated in other glomerular diseases associated with hypoalbuminemia is unknown. Short-term prophylactic, low-dose, subcutaneous heparin or enoxaparin may be indicated in patients with severe nephrotic syndrome who are massively edematous and who are placed at bed rest or hospitalized for diuresis, trauma, surgery, or congestive heart failure.. Low molecular weight heparin should be used with caution in subjects with reduced renal function and only with appropriate dosage adjustment. Low-dose oral aspirin could also theoretically be of benefit but this has not been proven in a randomized clinical trial. A profound

reduction in antithrombin III levels may be associated with resistance to the heparin anticoagulant effect. Patients with the Leiden trait (see above) may be at special risk and therefore may be candidates for a prophylactic approach (Glassock, 2007). A family history of venous thrombosis should always be sought and if positive, serious consideration should be given to prophylactic anticoagulation. The risk of anticoagulation cannot be overlooked, especially in the elderly and those with CNS or GI lesions (Glassock, 2007).

*In summary*, the decision to employ *prophylactic* anticoagulation in subjects with the nephrotic syndrome is dependent upon:

- ◆ The nature of the underlying disease (e.g. membranous nephropathy)
- ◆ The severity of the nephrotic state (especially the level of serum albumin).
- ◆ The presence or absence of other predisposing factors (e.g., immobility, CHF, obesity, a family history of thrombophilia).
- ◆ A prior history of thrombosis.
- ◆ The risks of anticoagulation (e.g., a central nervous system lesion, a prior history of GI bleeding, advanced age).

The final decision can only be made on a case-by-case basis (Glassock, 2007).

Patients who have already experienced a thromboembolic event, such as DVT or pulmonary emboli, should probably be treated with long-term oral warfarin, after an initial course of intravenous standard high or low molecular weight heparin, unless some serous contraindication exists. Warfarin should never be administered alone, without initial heparin anticoagulation, because deficiency in active protein C and/or S may increase the risk of warfarin-induced skin necrosis. The warfarin should be continued for as long as the patients have hypo-albuminemia and heavy proteinuria. The precise 'cut-off-point' for continuing or discontinuing warfarin is unknown, but I believe that it would be prudent to consider withdrawal of warfarin after at least six months of therapy if serum albumin is above 3.0g/dL and urine protein is <3.5g per day. The international normalized ratio (INR) for prothrombin time should be followed with the goal of maintaining the INR at about 1.8–2.0. Values over 3.0 are associated with a marked increase in the risk of bleeding, particularly in the elderly. Values for INR between 2.0 and 2.9 are associated with a low risk of bleeding (about 5/100 patient years of treatment, but this risk may be higher in elderly subjects).

Initially, a search for an origination site of the thrombosis (DVT and/or RVT) in patients with an *overt* pulmonary embolus may not be very useful, since long-term anticoagulants will be used irrespective of the source of emboli. Patients with repeated episodes of pulmonary emboli despite anticoagulation

should probably receive percutaneously placed inferior vena cava filters positioned above the renal veins.

The investigation of patients having *no* clinical, laboratory, or radiologic evidence of a thromboembolic event for the existence of a *covert* thrombosis, such as a RVT or asymptomatic DVT, is probably not routinely warranted especially if prophylactic warfarin is to be administered in any case, based on the individualized assessment of risks and benefits. Non-invasive screening studies, such as duplex Doppler ultrasonography, computed tomography, or magnetic resonance imaging are relatively sensitive and specific for RVT but contrast venography is the standard used for these comparisons (Rostoker et al., 1992). In most situations a non-invasive test would be considered adequate and renal venous angiography is seldom required. At present, despite the demonstrated utility of these non-invasive studies, there is little reason to investigate asymptomatic patients for occult renal-vein or DVT since a *negative* non-invasive screening study at a particular point in time does not mean that a thrombosis cannot develop later. A *positive* non-invasive screening study, even in the absence of an *overt* pulmonary embolus, would likely be an indication for consideration of anticoagulation, but there are no studies to evaluate the safety or efficacy of such an approach to investigation and treatment in asymptomatic patients (Glassock, 2007).

## Proteinuria and hypoalbuminemia

### Clinical features, pathogenesis, and pathophysiology

The mechanisms underlying proteinuria and hypoalbuminemia in glomerular disease have been the subject of many recent reviews (Haraldsson et al., 2008). Proteinuria in glomerular disease is believed to be a consequence of a breakdown in the permselectivity barrier of the glomerular capillary wall (comprised of the endothelial cell, glomerular basement membrane, and the slit-pore diaphragm of the podocyte), although this time-honored concept has been recently challenged by some experimental observations suggesting a role for impaired, proximal tubular reclamation of normally filtered proteins (Russo et al., 2007). Plasma proteins, principally albumin but including other plasma proteins as well, are allowed to pass through the glomerular capillary wall and into Bowman's space in variable amounts. The reabsorption of the filtered proteins is governed by the activity of cubulin and megalin in the brush border of the proximal tubular epithelial cell. The maximum tubular protein reabsorptive capacity is quickly exceeded resulting in overt proteinuria, which can range from barely above normal (200mg per day) to massive (>20g per day). Values >3.5g per day in the adult signify nephrotic-range proteinuria (Glassock

et al., 1995). The overall quantity of protein excreted above 3.5g/d has little diagnostic significance per se although 'massive' proteinuria (>20g/d) is most commonly seen in amyloidosis, focal and segmental glomerulosclerosis (FSGS, collapsing variant), MN, and MCN. The excretion of higher molecular weight proteins in the urine (IgG, IgM- 'non-selective' proteinuria) is thought to represent a more severe permselectivity defect and a greater degree of glomerular pathologic alterations (such as is seen in FSGS). The depression in serum albumin concentration and total-body albumin mass is the result of both increased renal catabolism and urinary excretion of albumin accompanied by an augmentation of hepatic albumin synthesis which is insufficient to offset catabolic and excretory losses (Kaysen et al., 1986; Kaysen 1993b). Alteration in the plasma and interstitial distribution of albumin may also contribute to altered plasma concentration. Hypoalbuminemia is not the inevitable consequence of nephrotic-range proteinuria. Modest levels of nephrotic-range proteinuria (4–8g per day) can be well tolerated by well-nourished, robust individuals and serum albumin concentrations may remain normal presumably because of augmented hepatic synthesis (or alternatively to slower rates of transfer of albumin into the interstitial space). Urinary protein excretion rates are influenced by dietary protein intake, transglomerular hydraulic pressure gradients, by serum protein concentrations and GFR (Kaysen, 1993a). Increased dietary protein intake will augment urinary protein excretion and vice versa (Hutchinson et al., 1995). Lowered glomerular capillary pressure, as a result of ACEi or ARB induced efferent glomerular arteriolar dilatation, will lower urinary protein excretion (Heeg et al., 1987; Gansevoort et al., 1995; Hutchinson et al., 1995; Hemmeler et al., 1996). Abnormal traffic of filtered protein along and through tubular epithelial cells can induce a phenotypic transformation in these cells which then promote local inflammation and fibrosis, contributing to the progressive nature of renal disease (Abbate et al., 2006).

The degree of proteinuria seen in glomerular disease is generally classified according to quantity. Non-nephrotic or '*sub-nephrotic*' proteinuria is defined as protein excretion between 1 and 3.5 g/d while '*nephrotic*' proteinuria is judged to be present when >3.5g of protein are excreted per day in an adult (or 40mg/h/m<sup>2</sup> in a child). Protein excretion above the normal level (about 150–200mg/d) but <1 g is generally regarded as 'asymptomatic' proteinuria. Measurement of protein excretion based on 24-h (timed) collections of urine has largely been abandoned, because of the inaccuracies in urine collection. Estimation of urinary total protein (or albumin) excretion can be satisfactorily obtained by collection of a first-voided morning specimen and by analyzing it for protein (or albumin) concentration (by chemical or immunochemical means) and also for creatinine concentration. The protein to creatinine (or albumin to creatinine) ratio in g/g, mg/g, or mM/ $\mu$ M

can then be calculated. The values for the first morning specimen (obtained after overnight recumbency) will generally be less than that obtained during the day with normal upright activity—so one should always collect serial specimens at the same time of the day and under similar condition of hydration. However, even with meticulous care, the protein excretion rate in patients with glomerular disease can spontaneously vary over time, perhaps due to differences in physical activity, salt intake, or dietary protein intake. This sample-to-sample biologic variation is usually <20–25%. A total protein to creatinine ratio of >3.0g/g generally indicates a ‘nephrotic range’ proteinuria while values of <0.2g/g would be regarded as normal. One must be sure to exclude ‘tubular’ proteinuria or ‘overflow’ proteinuria associated with primarily tubular disease or the presence of lower-molecular weight monoclonal proteins (light chains) respectively before concluding that the proteinuria is of ‘glomerular’ origin. Tubular and glomerular proteinuria can co-exist. Elevated  $\beta_2$  macroglobulin excretion relative to albumin excretion is a feature of tubular proteinuria. The ‘quality’ of the proteinuria, believed by some to have diagnostic, prognostic, or therapeutic significance, can be determined by measuring the rate of IgM,  $\alpha$ , or  $\beta_2$  microglobulin excretion, by assessing the fractional excretion of IgG (FE IgG) or by comparing the IgG to transferrin clearance in ‘spot’ urine samples (Bazzi et al., 2003; D’Amico and Bazzi, 2003; Deegens and Wetzels, 2007; Hofstra et al., 2008). The significance of these estimates of the ‘selectivity’ of proteinuria will be discussed further in the individual chapters which follow. I should also point out that the magnitude of proteinuria has different associations with the likelihood of progression of disease according to the individual diseases and is also influenced by gender (Cattran et al., 2008). The same amount on 24-h proteinuria has much different associations with the rate of decline in GFR in membranous nephropathy, focal glomerular sclerosis and IgA nephropathy.

## Therapy

It is obvious that the best approach to the management of proteinuria and hypoalbuminemia in patients with glomerulonephropathies is to identify and correct the underlying disease. However, as pointed out in later chapters dealing with specific glomerular diseases (Chapters 4–11), this is not always possible. Exogenous infusion of hyperoncotic (salt-poor) human serum albumin will transiently increase the serum albumin concentration but in the absence of any change in glomerular permselectivity, the infused albumin will be rapidly excreted in the urine, perhaps with adverse effects on glomerular and tubular structure and function.

Therefore, except in unusually difficult circumstances, such as profound edema (anasarca) unresponsive to loop-thiazide-potassium sparing diuretic

combinations (see 'Edema,' above) this approach is not routinely recommended. Dietary measures which supplement oral protein intake are also often quite unsuccessful since urinary protein excretion almost invariably increases and total body albumin pools do not increase (Kaysen 1993b; Kaysen et al., 1998). Concomitant administration of ACEi and/or ARB will frequently reduce protein excretion rate by 30–60%, depending upon the dose and prevailing NaCl intake (Gansevoort et al., 1995; Talal and Brenner, 2001; Pisoni et al., 2002). As noted above, these effects are probably mediated by intra-renal hemodynamic alterations independent of systemic arterial BP levels, but other specific effects of angiotensin II inhibition on glomerular permeability can also participate. The antiproteinuric effects of ACEi, but not ARB may be partially dependent on elevated bradykinin levels (Hutchinson et al., 1995). In addition, a fall in systemic arterial BP appears to initiate the antiproteinuric effects of ACEi/ARB but the magnitude of the persistent antiproteinuric effect of ACEi/ARB are independent of the extent of BP reduction (Gansevoort et al., 1995). Modest protein restriction, combined with sufficient dosage of ACEi/ARB in the presence of restricted NaCl intake and/or diuretics, can not only reduce protein excretion rates but can also increase the total body albumin pool and serum albumin concentration (Kaysen 1993b). In addition, as noted previously, diuretic responsiveness may be restored in edematous patients with the use of these agents along with NaCl restriction. The addition of an inhibitor of the action of aldosterone (spironolactone or eplerenone, but not other potassium sparing diuretics, such as amiloride), even in rather low doses not associated with a prominent risk of hyperkalemia, can also lead to an additive anti-proteinuric effect, it is not yet clear whether this effect is independent of the systemic arterial BP lowering effects of such agents.

Combinations of ACEi and ARB given in maximum recommended dosages appear to have a greater anti-proteinuric effect compared to monotherapy with individual agents also given in maximum recommended dosage (Kunz, et al., 2008). However, this effect may be 'disease-dependent' and is not seen in all primary glomerular diseases. 'Supra-maximal' doses of some angiotensin inhibiting agents may also have augmented anti-proteinuric effects compared to 'conventional' doses even though blood pressure is not further reduced (Pisoni et al., 2001, 2002). The anti-proteinuric response to ACEi and ARB, alone or combination, varies among the categories of primary glomerular diseases (for example, the anti-proteinuric response to ACEi/ARB is poor in MN), and it is difficult to predict in individual patients what the response to this therapy will be in advance of a 'trial' of treatment, in adequate dosage. However, if urine protein excretion falls to 'sub-nephrotic' levels or below (partial remission) on such treatment and remains at or below this level, it is *likely* that the prognosis, in terms of progression to ESRD, is improved (Trojanov et al., 2004, 2005; Reich et al., 2007).

The effects of ACEi/ARB on protein excretion rates may not be observed for several weeks and usually continue for several weeks when the drug is discontinued. The antiproteinuric effects of ACEi may also be related to polymorphisms in the ACE gene (Yoshida et al., 1995). Patients with the DD polymorphism tend to have higher levels of plasma renin activity and plasma angiotensin II concentrations and may respond better to an ARB than to an ACEi (Hadjadj et al., 2007) but this has not been as well established for the primary glomerular diseases as in diabetic nephropathy. Chronic administration of an ACEi may be associated with ‘escape’—defined as a loss of the effect of ACEi on angiotensin II levels and aldosterone secretion rates (Werner et al., 2008). This phenomenon may have consequences for long-term use of agents in this class as monotherapy of proteinuria in glomerular disease.

Non-steroidal anti-inflammatory drugs (NSAID, e.g., indomethacin, meclofenamate, ibuprofen, celecoxib) also exert a dose-dependent, antiproteinuric effect which is potentiated by NaCl depletion and which is independent of a change in GFR (Pisoni et al., 2001). The effects may be additive to the effects of ACEi in some circumstances but are more rapid in onset and quickly dissipate when the drug is discontinued. NSAID will also interfere with the action of loop-acting diuretics and may, at times, cause acute renal failure, due to an interstitial nephritis or acute tubular necrosis. The combination of ACEi and NSAID may also produce serious hyperkalemia. For reasons of undesired side effects, NSAID are seldom used for their anti-proteinuric effects.

Omega<sub>3</sub> polyunsaturated fatty acids (O3FA; e.g., eicosapentaenoic and docosahexanoic acid) may have a renoprotective actions in certain diseases (see also Chapter 8 on IgA nephropathy), but these appear to be independent of any effect on protein excretion.

In very unusual and fortunately rare circumstances, ablation of renal function by administration of nephrotoxic agents (medical nephrectomy) may become necessary if continued massive proteinuria results in severe life-threatening malnutrition (Glasscock et al., 1995). Surgical bilateral nephrectomy or intentional arterial embolic infarction of the kidneys is almost never performed for massive proteinuria in current times.

## **Reduction in GFR and progressive renal failure**

### **Clinical features, pathogenesis, and pathophysiology**

Many glomerular diseases are associated with an acute or even progressive, albeit variable, degree of depression of GFR. In the acute nephritic syndrome the loss of GFR may be quite abrupt and spontaneously reversible, even in the

absence of 'specific' therapy. In the syndrome of rapidly progressive nephritis the loss of GFR may be abrupt or more insidious and, in the absence of specific therapy, the development of ESRD may be inexorable. In the nephrotic syndrome the loss of GFR is highly variable and some cases progress to a picture of the 'chronic' nephritic syndrome. Patients with 'symptomless' hematuria and/or proteinuria, by definition, have a normal GFR at the onset or presentation of disease, but in some instances, slow progression to ESRD may subsequently be observed.

The pace of development and progression of abnormal GFR varies widely among patients and between diseases and is determined by a multitude of factors (Jaber and Madias, 2005). These include:

- ◆ The severity of the initial insult to glomerular architecture (proliferation, necrosis, obliteration of capillary network, obstruction or misdirection of the flow of the glomerular ultrafiltrate, and reduction of the trans-capillary hydraulic conductivity [Lp or Kf]).
- ◆ The pathophysiologic response to injury (including maladaptive glomerular capillary hypertension/hypertrophy).
- ◆ The continued activity of the underlying disease process.
- ◆ Concomitant systemic biochemical and circulatory abnormalities (such as hyperlipidemia and hypertension).
- ◆ The noxious effect of proteinuria and/or hematuria on tubulointerstitial structure.
- ◆ The activity and dysregulation of the balance of mediator systems (such as complement, TGF $\beta$ , platelet-derived growth factor, and PAI-1).
- ◆ The loss of angiogenic factors contributing to capillary 'drop-out.'
- ◆ The underlying genetic milieu.

Each of these interact to determine the rate and manner of changes in individual nephron filtration rate as well as the extent and pace of nephron loss and thereby the concomitant decline in GFR and its potential for reversibility (Meyer et al., 1995). *The level of renal function at the time of discovery of disease and during follow-up, the magnitude, quality, and duration of proteinuria, the severity of systemic and glomerular capillary hypertension and their control, and the extent of capillary loss, podocyte deficiency, tubular atrophy, and interstitial fibrosis stand out as major predictors of the long-term outcome of disease with respect to the eventual occurrence of ESRD.* Once a proportion of the functioning nephron mass is lost, a vicious cycle of events, unrelated to the initiating processes, is brought into play. Intra-glomerular hypertension, glomerular hypertrophy, visceral epithelial cell (podocyte) injury, and tubulo-interstitial damage are principal components

of these processes. Until we have a full and complete understanding of how the various pathophysiologic, cellular, and molecular events participate in progressive disease, our approach to ameliorating progression will remain relatively empiric, but as knowledge of these mechanisms improve so does the prospects for a rational and specific therapeutic approach to reduction, arrest, or even reversal of the progressive disease process (generically called 'reno-protection') (Pisoni et al., 2001). Indeed, systematic clinical efforts to this end (called 'renal remission clinics') are growing (Ruggenti et al., 2008).

Increased filtration of protein and its eventual partial reabsorption by the proximal tubule is thought to play a major role in progression of renal injury (see Remuzzi and Bertani, 1998, for a review). Such events can lead to marked phenotypic changes in the tubule and the development of interstitial inflammation and fibrosis. The precise nature of proteins involved in stimulating this sequence of events and how injury to the glomerular filtration barrier produces their undesired effects is a subject of intense research interest (Remuzzi and Bertani, 1998; Kriz and LeHir, 2005; Zandi-Nejad et al., 2004). *Nevertheless, a reduction in urinary protein excretion (by whatever method) can slow the rate of progressive loss of GFR in many renal diseases (Ruggenti et al., 2008).*

Assessment of GFR is the *sine qua non* for evaluating the degree of renal functional depression and its progression. Classically, serial measurements of serum creatinine concentrations have been used for this purpose. In recent years, formulae have been devised to use serum creatinine concentration to 'estimate' true GFR, since measurement of the 'true' value may not always be practical, e.g., estimated GFR (eGFR), corrected for body surface area (e.g., to standard body surface area of  $1.73\text{m}^2$ ) using the modification of diet in renal disease (MDRD) abbreviated equation (see Table 1.8 and [http://www.kidney.org/professionals/KDOQI/gfr\\_calculator.cfm](http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm) for an online Internet based calculation method) (Stevens et al., 2006). This formula, derived from subjects with CKD, takes into account variables of age, gender, and race. These factors are added as 'surrogates' for the estimation of endogenous creatinine generation, a requirement for translation of serum creatinine levels into estimated clearance or GFR values. The MDRD abbreviated formula is widely used but not well verified in diverse populations (according to diet, body habitus, ancestry, or geography) and the derived eGFR tends to have a negative bias (underestimate true GFR) at values above  $60\text{mL}/\text{min}/1.73\text{m}^2$  and in the presence of obesity. The estimates of eGFR by the MDRD formula are not very accurate relative to true GFR, particularly at GFR levels  $>60\text{mL}/\text{min}/1.73\text{m}^2$  (Froissart et al., 2005; Issa et al., 2008). For accurate results the MDRD eGFR also requires that the serum creatinine be 'calibrated' to the standards used in the derivation

**Table 1.8** Estimation of the glomerular filtration rate (eGFR) by the modification of diet in renal disease (MDRD) abbreviated equation and the estimation of the endogenous creatinine clearance (C-G –Ccr) by the Cockcroft–Gault formula

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$$\text{MDRD eGFR (mL/min/1.73m}^2\text{)} = 186.3 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$$


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$$\text{C-G Ccr (mL/min)} = (140 - \text{age in years}) \times (\text{weight in kg})/72 \times \text{serum creatinine in mg/dL} (\times 0.85 \text{ if female})$$


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of the equation. Serum creatinine values are reproducible within laboratories but vary considerably between laboratories. This state of affairs will continue until a universal ‘gold-standard’ approach to quantifying serum creatinine concentration is adopted on a world-wide basis. This appears to be a likely outcome of intense efforts over the next few years (Levey et al., 2007).

Another formula, to estimate the creatinine clearance is the Cockcroft–Gault equation (which takes into account age and body weight and estimates creatinine clearance not adjusted for standard body surface rather than GFR) (Cockcroft and Gault, 1976). Creatinine clearance may be significantly altered in the present of proteinuria, due to augmented tubular creatinine secretion (Branten et al., 2005). Creatinine clearance or its estimation by the Cockcroft–Gault formula tends to provide values which are higher than true GFR, especially when marked proteinuria is present, at least when values are >60mL/min. Current recommendations are to use the MDRD equation for estimating eGFR in monitoring patients with primary glomerular disease, but due to biases caution should be exerted in interpreting the results of serial measurements of eGFR using the MDRD formula (Xie et al., 2008). The determination of whether the values obtained are normal or abnormal should also take into account the expected decline in GFR with aging and the fact that GFR is lower in females than in males, even after correcting for differences in body surface area (Wetzels et al., 2007). Non-creatinine based methods for estimating GFR, such as the serum cystatin C concentration, are also gaining favor as they eliminate the variability of endogenous creatinine production and extra-renal elimination that complicate the MDRD and Cockcroft–Gault equations (Hoja et al., 2008). Application of cystatin C measurement for eGFR is not yet widespread or well-tested in primary glomerular disease of various etiologies.

## Therapy

Obviously, eradication or control of the *underlying* disease process itself represents the best chance for improving GFR and preventing progression

providing it can be accomplished prior to the induction of irreversible or self-perpetuating injury. Falling short of this, consideration should be given to the employment of non-specific strategies designed to ameliorate the pathophysiologic processes contributing to progressive renal damage, such as glomerular capillary (maladaptive) hypertension, proteinuria, glomerular and interstitial fibrosis, and capillary 'drop-out.' *Renoprotective agents* are a class of therapeutic compounds which affect these processes by slowing further nephron loss and delaying the development of the ESRD, quite independent of control of the basic disease process itself (Pisoni et al., 2002; Ruilope, 2008). Control of systemic and/or intracapillary hypertension, reduction of plasma lipid concentrations, inhibition of thrombosis, retardation of fibrogenesis, promotion of angiogenesis to counteract capillary loss, alteration of the regulation of cell cycle/cell growth could all be properly classed as potentially *renoprotective* strategies. ACEi and ARB both have renoprotective properties, independent of their BP lowering effects, as do certain non-dihydropyridine calcium channel-blocking agents (e.g., diltiazem, verapamil). Additional agents, including dihydropyridine calcium antagonists, do not have renoprotective actions, even though they reduce systemic arterial BP. Theoretically, HMG co-reductase inhibitors (statins) and NSAID may also be renoprotective, but randomized controlled trials are lacking (Tonelli, 2008). NSAID should be used with great caution and in the lowest effective dose in patients with primary glomerular disease as they have a propensity to induce acute interstitial nephritis and may also produce a sudden fall in GFR because of hemodynamic effects.

Systematic reviews, meta-analyses, and observational studies have suggested a rather modest but variable renoprotective action for statins (Strippoli, 2008). Randomized controlled trials are in progress (SHARP, AURORA). Modest protein restriction (0.6–0.8 g/kg/d) combined with an ACEi/ARB *may* slow the rate of progression of renal disease in patients with heavy proteinuria and reduced GFR (25–50 mL/min) (see below) (Klahr et al., 1994; Levey et al., 2006; Mandayam and Mitch, 2006; Menon et al., 2008), but protein malnutrition is a potential hazard of such an approach in patients with nephrotic syndrome. The benefit appears to be magnified by the concomitant use of ACEi/ARB.

As a class, renoprotective agents such as ACEi/ARB should be considered in the management of *all* forms of glomerular disease accompanied by persisting proteinuria which have a demonstrated potential to progress to ESRD, providing contraindications to their use do not exist (e.g., hypersensitivity, hyperkalemia, bilateral renal arterial stenosis). Patients with heavy and persistent proteinuria, those with impaired GFR, and those whose renal biopsies demonstrate tubular atrophy and/or interstitial fibrosis should be considered as

potential candidates for such treatment. Systemic arterial hypertension requires vigorous therapy, preferably with ACEi, ARB, and/or non-dihydropyridine CCB (see ‘Hypertension,’ above). The goal should be to reduce BP to the lowest level possible, usually 120–130/70–80 mmHg, around a mean arterial pressure of 90–92 mmHg, without impairing quality of life or inducing disabling symptoms. At times, three or even four drugs may be needed.

It must be recognized that the degree to which ACEi and/or ARB reduce proteinuria or delay the progression of declining GFR vary considerably between and among the individual diseases to be discussed in this monograph. Thus, for example, a dosing regimen of an ACEi or ARB alone (or perhaps in combination) may be much more effective in IgA nephropathy than in MN. Unfortunately, very few large, long-term studies have been conducted in homogeneous groups of patients to provide us with information regarding the likely ‘responsiveness’ of the individual diseases to such therapy. In addition, the precise ‘optimal’ goals for proteinuria reduction have not been well defined for each entity. We do suspect that they will not be the same, since the relationship of the magnitude of persistent proteinuria to prognosis varies among the primary glomerular diseases (see Table 1.9) (Cattran et al., 2008). In other

**Table 1.9** The relationship of time averaged proteinuria (in g/d) to the progression of renal disease (in decline of eGFR in mL/min/year) in three primary glomerular diseases (adapted from Cattran et al., 2008)

	Decline in eGFR (mL/min/year)					
	Time averaged proteinuria					
	<1g/d	1–2gs/d	2–3g/d	3–5gs/d	5–7g/d	>7g/d
<b><i>IgA nephropathy:</i></b>						
Males	<1	3.8	6.1	7.0	10.7	na
Females	<1	3.0	6.0	9.1	9.8	na
<b><i>Focal segmental glomerulosclerosis:</i></b>						
Males	2.1	2.5	3.1	4.0	10.9	18
Females	2.7	2.8	5.0	5.6	9.8	12
<b><i>Membranous nephropathy:</i></b>						
Males	1.3	1.5	1.6	1.4	4.0	12.0
Females	0.9	1.6	1.4	1.5	4.8	7.3

Adapted from Cattran, et al., (2008). The impact of sex on primary glomerulonephritis. *Nephrol Dial Transplant* 23:2247–2253.

words, reduction of proteinuria from 4 g a day to 2 g per day (a 50% reduction) may have differing effects on the rate of subsequent progression of renal disease in each primary glomerular disease entity. It does appear that reduction of proteinuria is more dose-dependent when an ACEi or an ARB is used than hypertension and that 'supra-maximal' doses (above those recommended by regulatory agencies and manufacturers) of these agents might have further beneficial effects on proteinuria without further lowering of blood pressure (Pisoni, 2002; Weinberg et al., 2003). Combinations of an ACEi and an ARB are possibly more effective than either given alone in maximal recommended doses (such as in IgA nephropathy, less well understood in other lesions), but side effects (such as hyperkalemia) need to be monitored more closely. If combinations of an ACEi and an ARB are to be used at all it would be appropriate to limit their use to patients with proteinuria >1.0g/day (Epstein, 2009). One should also be cognizant of the potential risks (hyperkalemia and sudden declines in GFR). The addition of spironolactone or eplerenone, in low dosage, appears to have an additive effect on BP control and proteinuria reduction in patients who fail to achieve goal BP or proteinuria with ACEi and/or ARB, but again caution must be exercised regarding the risk of hyperkalemia in these combinations (Schjoedt et al., 2006; Chrysostomou et al., 2006; Epstein 2006). When using ACEi and/or ARB for their anti-proteinuric effects, one must pay careful attention to the need for concomitant NaCl restriction and the addition of diuretic appears to potentiate the anti-proteinuric (and anti-hypertensive) action of these agents. Not uncommonly, the serum creatinine may rise following initiation of therapy with an ACEi and/or ARB. This rise is largely due to blunting of the intra-glomerular maladaptive capillary hypertension and a reduction in the transcapillary hydraulic pressure gradients favoring filtration (due to efferent glomerular arteriolar dilatation). When the rise in serum creatinine is <25% (e.g., a serum creatinine increases from 2.0mg/dL to 2.3mg/dL) one need not stop or modify therapy. However, progressive increase in serum creatinine above this threshold (e.g., a serum creatinine increases from 2.0mg/dL to 2.6mg/dL), then the regimen should be interrupted. Such patients may have an underlying bilateral renal arterial stenosis or a unilateral stenosis in a solitary functioning kidney. ACEi and/or ARB can be used to retard progression even when the GFR is substantially reduced, but the risks of hyperkalemia may require more intense monitoring (Hou et al., 2006).

## General management principles

Patients with glomerular disease should be encouraged to consume a prudent diet, low in saturated fats, trans-fatty acids, cholesterol, and in NaCl content (6g per day in the absence of edema or 3g per day in the presence of edema). Caloric intake should be sufficient to maintain ideal body weight, around

35 kcal/kg. Caloric restriction is indicated in obese subjects with BMI >30kg/m<sup>2</sup>. Protein intake should be 0.8–1.0g/kg per day plus any urinary protein losses if the GFR is >70 mL/min. Modest protein restriction to the level of 0.6–0.8g/kg per day plus urinary losses could be used for patients with reduced GFR so long as malnutrition is not present. Protein should be of high biologic value and red meat should be discouraged. Fish, white meat, fruits, and colored vegetables should be encouraged. A vegetarian/ Mediterranean diet is best if the GFR is reduced. Increased protein intake (above 1.0–1.2g/kg per day) is usually accompanied by increasing urinary protein excretion and has little or no effect on albumin stores (see above). Total fat should be limited to <30% of total calories. Saturated fat should represent no more than 10% of total calories. Cholesterol intake should be limited to 200mg per day. Modest alcohol consumption (<60mL of 30–40% ethanol daily) is permitted. Supplementation of the diet with O3FA is permissible, but the benefits are uncertain.

Supplementation of the diet with antioxidant vitamins (e.g., vitamin C, ascorbic acid) is reasonable, but in the absence of malnutrition, supplementation with soluble vitamins B1, B2, B6, B12, or folate is not necessary, but no harm would be done if such vitamins were given in doses equivalent to minimum daily requirements (especially to older patients). A normal intake of the fat soluble vitamin E and K is suggested and supplementation is not needed. Vitamin D supplements (ergocalciferol, cholecalciferol) are useful in patients with heavy proteinuria since they are often deficient in 25-hydroxy vitamin D2 or D3 and may have a mild form of secondary hyperparathyroidism due to urinary losses of vitamin D combined with its receptor protein (Goldstein et al., 1977). Estrogen, androgen, and glucocorticoid-binding proteins are all excreted in the urine in excess in heavily proteinuric subjects (Harris and Ismail 1994). Mild hypogonadism and altered glucocorticoid metabolism may ensue but usually these abnormalities do not require active intervention. Copper, zinc, and iron are all excreted in the urine in patients with heavy proteinuria and deficiencies of these metals may occur (Harris and Ismail 1994). Copper supplementation can be helpful for leg cramps. Zinc supplementation may be useful for dysgeusia, impotence, or poor wound healing. Iron supplementation is only indicated if iron deficiency is documented. Oral or IV iron preparations may not be efficacious if serum transferrin levels are very low due to excessive urinary losses not offset by enhanced hepatic transferrin synthesis (Prinsen, et al., 2001). Oral calcium intake should be at least 1500mg/day and supplementation of dietary calcium may be necessary. Phosphate intake need not be restricted unless GFR is <25mL/min. Phosphate-binding compounds (calcium carbonate, calcium acetate, sevelamer hydrochloride or carbonate, lanthanum carbonate) can be prescribed if serum phosphorus is elevated. Aluminum-containing compounds should be avoided.

While less frequently observed now than prior to the steroid-treatment era (circa 1960), infections remain a troublesome problem particularly among children and in developing countries (Glassock et al., 1995). Not infrequently, spontaneous bacterial peritonitis may complicate severe edema/ascites in children (Rubin et al., 1975). Encapsulated *Streptococcus* and *Hemophilus* species (e.g., *S. pneumoniae*) are frequently implicated, and in pediatric patients with severe edema and ascites a prophylactic approach with oral penicillin or IM benzathine penicillin (Bicillin®) is indicated. Pneumococcal immunization programs may also reduce the incidence of this dreaded but now rare complication of nephrosis in children. The occurrence of fever, abdominal pain, and ascites is an indication for emergent paracentesis with culture and leukocyte counts. Cellulitis may become severe in profoundly edematous patients and demands vigorous therapy with advanced generation cephalosporins and/or anti-staphylococcal agents (e.g., nafcillin, methicillin, vancomycin, linezolid, daptomycin). Other localized and systemic infections, such as bacterial pneumonia, urinary tract infection, infectious diarrhea, or meningitis, can be treated in a standard fashion, taking into account the potential effects of hypoalbuminemia and/or reduced GFR on pharmacokinetics and pharmacodynamics of individual agents. In patients who have or are receiving therapy with immunosuppressive agents, special care must be given to evaluation for opportunistic infections such as candidiasis, tuberculosis, toxoplasmosis, cryptococcosis, cytomegalovirus, herpesvirus, BK virus, or JC virus. Patients at high risk for human immunodeficiency viral (HIV) infection should always be studied with an appropriate serologic test for HIV antibody or by polymerase chain reaction (PCR) for virions.

IgG deficiency can arise, either from excessive urinary losses, extrarenal catabolism, or perhaps impaired synthesis (Giangiacomo et al., 1975). Sometimes this can be severe enough to impair the defense against bacterial infection (usually with encapsulated organisms). Exogenous polyvalent intravenous or intramuscular Ig replacement could be considered if bacterial infections are severe and recurrent. Vaccination with live, attenuated viruses are ordinarily well tolerated (but should be used with great caution in heavily immunosuppressed patients), however, protective humoral immune responses may be impaired, particularly when renal failure is present (Garin et al., 1983). Some vaccines (e.g. Varicella) are well tolerated and highly effective even in the face of nephrotic syndrome (Furth et al., 2003) Although cell-mediated immunity may be impaired in patients with heavy proteinuria and/or mild renal insufficiency, there is no tendency for opportunistic infections unless severe renal failure is present or unless patients are receiving concomitant immunosuppressive therapy (Glassock et al., 1995).

Regular aerobic or anaerobic exercise, and even engagement in competitive sport activities requiring short-time exposure to vigorous exercise, are not contraindicated. Indeed, such activity may promote fibrinolysis and prevent thrombotic events in those with the nephrotic syndrome. On the other hand, short-periods of bed rest may be advised for those with acute glomerulonephritis during periods of active NaCl retention and serious hypertension and edema. Prolonged bed rest does not improve the chances for recovery from acute nephritis. Forced and extended periods of inactivity in overtly nephrotic subjects may have disastrous consequences by augmenting DVT or even pulmonary embolization. It is well appreciated that vigorous prolonged exercise (such as in marathon running) can result in an increase of proteinuria and/or hematuria. This effect is quite transient. While theoretically this can be harmful, no prospective studies have yet demonstrated that modest, regular exercise has any deleterious (or beneficial) effects on the progression of primary glomerular disease. Regular swimming may be the best advice, since it may be good for maintaining conditioning and does not apparently have any adverse effects (other than the potential for drowning or hypothermia).

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