



Nephrotic Syndrome

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ABSTRACT

Much information has become available in recent times about the structure of the glomerular basement membrane (GBM), the pathway of filtration of proteins, and the barriers to passage of proteins through the GBM. There is both a size barrier and a charge barrier. The main location of both of these is the slit diaphragm between the foot processes of the glomerular epithelial cells.

Apart from the effects of the disease causing the nephrotic syndrome, proteinuria is itself harmful to the kidney. It leads to focal glomerular sclerosis, tubular damage, apoptosis of tubular cells, and release of cytokines causing chronic interstitial changes and progressive renal failure. Hypoproteinaemia can be associated with oedema, hyperlipidaemia, and a hypercoagulable state.

Changing concepts of management include the understanding that a high protein diet can itself increase proteinuria and is therefore counterproductive. It is also very difficult to correct proteinuria by giving more protein since most of the extra protein is excreted in the urine. It is therefore essential to reduce proteinuria, preferably by curing the condition leading to the nephrotic state, but failing that with the use of ACE inhibitors. Lipid abnormalities are usually reversed if proteinuria can be controlled, but if proteinuria persists it is essential to correct the lipids with appropriate diet and therapy.

Measurement of the urinary protein creatinine ratio in a spot sample of urine is a simple and effective way to monitor the progression of the disease and the success of treatment.

DEFINITION

The traditional definition of the nephrotic syndrome is the association of massive proteinuria with hypoalbuminaemia and oedema. Since there are some patients with massive proteinuria who do not become oedematous, the definition was altered to the passage of 3.5 g protein per 1.73 sq m body surface area in 24 hours. Neither definition should be slavishly adhered to. Proteinuria arises when there is an increase in the permeability of the glomerular capillary to protein. In other words the glomerular clearance of protein increases. A certain amount of blood is cleared of its protein content each minute. If serum albumin is 4.2 g/dl, and if the protein clearance is 0.1 ml/min, the patient will lose 4.2 mg of protein per minute, or 6.048 g of protein per day. When serum albumin falls to 2.1 g/dl, with the same leak of protein, urinary protein will fall to 3.024 g/day, and will fall below the mathematical definition of the nephrotic syndrome. However, the disease and its severity are the same, only it has lasted longer and the patient is more ill. It would

be absurd to withdraw the diagnosis of the nephrotic syndrome. One should therefore combine both definitions with a touch of commonsense.

In any case, the nephrotic syndrome is not a disease entity. It is only a symptom complex that can be produced by many diseases, each with its own treatment and its own course and prognosis. One should recognise that and proceed to make a full diagnosis in every patient so that appropriate treatment may be administered.

THE PATHOGENESIS OF SEVERE PROTEINURIA

The filtration pathway through the glomerulus begins with the capillary endothelium, which has large pores called fenestrae that can easily be traversed by proteins. They can thus reach the glomerular basement membrane (GBM). The GBM behaves as if it has pores, though these pores have not been demonstrated even with the electron microscope. The size of the pores follows

a bimodal distribution, the majority, through which filtration of small molecules takes place (normal glomerular filtration) being small. A very few have a substantially larger diameter, and permit the filtration of proteins. In disease states it is possible for the number of these pores to vary independently of each other, so one can get many more large pores with significant proteinuria, and at the same time there may be far fewer small pores, leading to reduced GFR.

The major barrier to protein filtration, however, lies in the slit diaphragm which bridges the slits between the foot processes of the glomerular epithelial cells, at their junction with the GBM.^{1,2} It has been found that molecules of a protein, nephrin, stretch from opposing foot processes and bridge the gap. They are stabilised in that position by another compound called podocin. Yet another substance, CD2AP, binds nephrin to the podocyte. Any disruption, caused by defective structure due to genetic defects, or to antibodies to one or more components, leads to proteinuria. This knowledge has not yet led to any remedy for the nephrotic syndrome.

Another cause of proteinuria at this level is damage to the epithelial cells. Foot processes fuse and get lifted off the GBM, leaving a wide gap through which protein can leak.

Apart from the structure that provides a size barrier, the GBM has a coating of glycosaminoglycans that provide a charge barrier. These are negatively charged molecules that inhibit the passage of the negatively charged proteins. The earliest damage to the GBM is associated with loss of this negative charge, as a result of which the smaller molecule, albumin, is allowed to filter through though the size barrier restrains larger globulins.

THE ILL EFFECTS OF PROTEINURIA

Progressive renal failure

Irrespective of the disease causing the nephrotic syndrome, proteinuria itself has harmful effects on the kidney. By mechanisms described below, it leads to focal glomerular sclerosis, tubular cell apoptosis and interstitial fibrosis.^{3,4} The more severe the proteinuria, the more rapid the development of chronic interstitial fibrosis and therefore chronic renal failure. It is important to reduce proteinuria.

Focal and segmental glomerulosclerosis

The first part to suffer is the glomerulus. It is clear that proteinuria leads to secondary glomerular sclerosis. Various mechanisms have been postulated. Foot processes fuse and lose their attachment to the GBM, exposing it to the cells of the parietal epithelium, which proliferate, adhere to the GBM, and release cytokines that lead to sclerosis. Some of the protein is absorbed through megalin molecules on the epithelial cells. When the cell is overloaded with protein, cytokines are released that cause proliferation of cells and sclerosis. Proteins also accumulate in the mesangium and induce cytokines that induce cellular proliferation and increased production of matrix, thereby leading to focal sclerosis.

Tubular apoptosis and interstitial fibrosis

Filtered protein is endocytosed by megalin at the luminal border of the cells, and taken up by lysosomes. If the capacity of the lysosomes to digest these proteins is exceeded, they rupture and release their digestive contents into the cytoplasm. Ammonia is

released and activates complement at the basolateral membrane. Complement mediated fibrosis leads to chronic interstitial damage. The lysosomal enzymes digest the cell contents. Damaged cells also release osteopontin and macrophage chemoattractant polypeptide which draw inflammatory cells to the interstitium. Cytokines released by these cells add to interstitial fibrosis. Proteinuria also leads to apoptosis of tubular cells.

Extra-renal effects

Oedema

The traditional view of the nephrotic syndrome is that it leads to hypoproteinaemia, low plasma osmolality with leakage of fluid into the interstitium and underfilling of the circulation. This in turn leads to reduced renal perfusion, release of renin and hence of aldosterone, which retains salt and secondarily water. While this may be true in minimal lesion nephropathy, in most other conditions there is overfilling of the circulation, and other explanations must be found. It has been demonstrated that albumin in the proximal tubular lumen directly stimulates the sodium hydrogen exchanger leading to retention of sodium. In the principal cells of the cortical collecting duct, over activity of Na⁺,K⁺-ATPase and the epithelial Na channel have been demonstrated. There is resistance to the action of atrial natriuretic peptide in the collecting duct, and this adds to sodium retention. The mechanisms of these changes have not yet been determined, but our understanding is surely and steadily improving.

The distinction between under and over fill is important because a patient with overfill should benefit with diuretics, whereas if there is underfill diuretics may lower the circulating blood volume further and make the patient feel weak, or precipitate syncope from low blood pressure.

Coagulation abnormalities⁵

It is not only the plasma proteins that are lost in the urine. Various factors which play a part in the coagulation cascade also leak through. Zymogens (factors IX, XI and XII) normally regulate coagulation activity and are lost in the urine in the nephrotic syndrome. Hypoalbuminaemia stimulates the liver to produce more proteins, and the manufacture of factors V and VIII is increased along with molecules like albumin, as well as factors II, VII and X. Fibrinogen levels are also increased due to greater hepatic synthesis. Antithrombin III is also lost in the urine. In balance, there is loss of anticlotting factors and increased levels of pro coagulation factors, and this renders the patient more prone to intravascular coagulation. Renal vein thrombosis is especially common in membranous nephropathy and in some children with minimal lesion nephropathy. The dangers are of sudden loss of renal function, and of spread to the inferior vena cava followed by pulmonary embolism.

Lipid abnormalities⁶

Cholesterol and phospholipid levels rise early, triglyceride late in the course of the disease. HDL cholesterol may be normal or sometimes low. I do not have the space to discuss the mechanisms. Hyperlipidaemia contributes to early atherosclerosis, and leads to coronary artery disease. It may also contribute to focal glomerular sclerosis and progression of chronic renal failure.

Table 1 : Causes of the nephrotic syndrome. Apollo Hospital. 2502 patients in 20 years.

Cause	Percentage
Minimal lesion nephropathy	35.4
Diabetic nephropathy	19.3
Focal and segmental glomerular sclerosis	10.4
Membranous nephropathy	9.9
Mesangial proliferative glomerulonephritis	7.4
Systemic lupus erythematosus	5.8
Membranoproliferative GN	5.4
Others	6.4

THE DIAGNOSIS OF THE NEPHROTIC SYNDROME

As I wrote in my introduction, I do not believe it is necessary to quantitate urinary protein excretion to make a diagnosis of the nephrotic syndrome. The clinical picture should suffice, together with a demonstration of massive proteinuria. However, some indices are essential to assess the response of a patient to treatment, and to monitor the progress of the disease. These include serum urea, creatinine and albumin, and urinary protein excretion. While a 24 hour urine collection is the gold standard, it is inconvenient and therefore repeated estimation will face some resistance from the patient. It has been demonstrated in numerous studies that the protein creatinine ratio done on a spot sample of urine correlates well with the 24 hour urine protein, provided serum creatinine is 1.5 mg/dL or less. This alone is inadequate to follow up a patient, since, as discussed earlier, protein excretion could fall because the patient has gone into renal failure or because serum albumin levels have fallen. The combination of serum urea, creatinine and albumin with the urine protein creatinine ratio is therefore the most convenient and accurate way to follow up a patient.

Is it necessary to establish the diagnosis in a patient with the nephrotic syndrome? In 1983, a very influential nephrologist of the USA suggested⁷ that there was no necessity to bother with renal biopsy to make a diagnosis, at least initially, since every patient could be given a trial of steroids, and only those who failed to respond would need investigation. I am convinced that this opinion does not hold good for India, and did a study that bears out my conviction.⁸ The risks of infection and other side effects are too great, and it is better to have a firm diagnosis before one embarks on treatment. The most common causes of the nephrotic syndrome in my unit are listed in Table 1. Minimal lesion nephropathy could be diagnosed in a child with the nephrotic syndrome, who does not have hypertension, microscopic haematuria or azotaemia. Diabetic nephropathy may be accepted in a patient with long standing, poorly controlled diabetes and diabetic retinopathy. Systemic lupus erythematosus requires a typical symptomatology of fever, skin rash and joint pains, and positive serology for lupus. In all other instances, renal biopsy is called for. It is especially important as only minimal lesion nephropathy and focal sclerosis respond to steroids alone. All the others require alkylating agents in addition, and even focal sclerosis requires a prolonged course of steroids. I will not

go into the other causes of the nephrotic syndrome since all of them together account for only 6.4% of the patients.

THE MANAGEMENT OF THE NEPHROTIC SYNDROME

Diet

When one sees a patient with hypoalbuminaemia, the temptation is to give him a very high protein diet to compensate for the losses. It took the medical profession many years to realise that this is counterproductive. It does not work and it may be positively harmful. We have already seen that proteinuria itself damages the glomerulus as well as the tubule, and a high protein diet increases glomerular filtration and proteinuria.⁹ There have been many explanations advanced, but the one that appeals to me most is the following: the macula densa has the capacity to sense the sodium and chloride content of urine flowing through the distal tubule. When the content is high, glomerular filtration is reduced by a process known as tubulo-glomerular feedback, and when it is low glomerular filtration increases. The bulk of filtered sodium is reabsorbed in the proximal convoluted tubule. There are many sodium transporters, through most of which sodium passes in linkage with some other substance. One of the transporters conveys sodium with amino acids. A person on a high protein diet will excrete a lot of amino acids in the urine, and the reabsorption in the proximal tubule will lead to increased reabsorption of sodium. Reabsorption of chloride runs in parallel with sodium, though the mechanisms are not as well understood. Excessive reabsorption of sodium in association with amino acids leads to less sodium and chloride passing the macula densa, and therefore to greater glomerular filtration. In other words, a high protein diet increases glomerular filtration and with it the excretion of protein, and greater risk of progressive glomerular and tubulointerstitial damage. Besides this, greater proteinuria makes it more difficult to correct the serum protein level, so a high protein diet does not work and is positively harmful. One should give the patient normal quantities of protein, and if there is renal failure protein intake should in fact be restricted as in any patient with renal failure.

For the same reasons, it is harmful to give a patient intravenous infusion of albumin. The effect is to pour the albumin from the bottle into the toilet bowl using the patient as a conduit. Albumin is indicated only in the short term when hypoalbuminaemia is so severe that the patient is unable to stand because of orthostatic hypotension.

Salt intake should be restricted in keeping with the oedema and the blood pressure, and saturated fats should also be restricted. Diuretics may be used if oedema is massive and troublesome, but I prefer to tackle the cause of the nephrotic syndrome as far as possible.

Treat the cause of the nephrotic syndrome

I do not have the space to deal with this in detail. For minimal lesion nephropathy, most Indian nephrologists use the protocol recommended in the Western literature.¹⁰ I believe this delivers too massive a dose for Indian conditions and have evolved a lower dose and shorter courses that I have found effective with far fewer side effects (Table 2).

Table 2 : My protocol for the management of minimal lesion nephropathy

1. Put the patient on prednisolone, the dose being 2 mg/kg body weight per day in a single dose each morning if the body weight is below 15 kg, 1 mg/kg if the weight is above 30 kg, and 30 mg if the weight is between 15 and 30 kg.
2. Check urine protein once a week. When proteinuria comes to nil, taper off prednisolone by 5 mg every three days and thus stop it. If the dose of prednisolone is above 50 mg, taper off by 10 mg every three days.
3. Approximately 30% of patients will not relapse, 30% will have a few relapses, and 30% are frequent relapsers.
4. If the patient develops oedema again, confirm the presence of proteinuria and wait for one week. Spontaneous remission occurs in 4% of patients in my experience.
5. If oedema and proteinuria persist for one week, start on prednisolone again as indicated above.
6. Up to three attacks may be treated in this fashion in any 12 month period. If the patient has a fourth attack within a year, he may receive prednisolone again as before, but in addition may receive cyclophosphamide in a dose of 2.5 mg/kg body weight, rounded off to the nearest 25 mg, given each morning. The leucocyte count may be checked once a week, and cyclophosphamide may be withheld if the count falls below 4000/cmm. Once that happens, the count may be checked every day and cyclophosphamide may be restarted when the count rises above 4000 again. If this happens within one week, the same dose may be given, but if it takes more than a week to recover the dose may be reduced to approximately 75% of the original dose.
7. Prednisolone may be tapered off when proteinuria disappears but cyclophosphamide may be continued for eight weeks, and then abruptly stopped.
8. Cyclophosphamide usually induces permanent or at least a longer remission. If relapse occurs after a course of this drug, treatment may be with prednisolone as indicated above.
9. If an alkylating agent is indicated again, it is unwise to repeat cyclophosphamide. The patient may be given chlorambucil in a dose of 0.2 mg/kg, continued for eight weeks with the same precautions as with cyclophosphamide.
10. If, at any time, the patient should receive prednisolone in appropriate dosage for eight weeks without response of proteinuria, he or she should undergo a renal biopsy to establish the accurate diagnosis and treat accordingly.
11. A very small number of patients will have minimal lesion nephropathy proved on biopsy, respond to steroids and will relapse whenever steroids are withdrawn. They are classed as steroid dependent, and will require long continued steroids. The minimal effective dose should be used.

There is no specific treatment for diabetic nephropathy, and the non-specific measures of ACE inhibitors must be used. My protocol is detailed below.

I would give a trial of prednisolone for all patients with focal glomerular sclerosis. Treatment is as for minimal lesion nephropathy, but since proteinuria will not disappear in a short time, it has to be maintained longer. I would assess protein excretion every month, and continue steroids as long as there is

progressive decline in the leakage of protein. Once it stabilises, steroids may be tapered off and ACE inhibitors introduced.

Membranous nephropathy responds to the Ponticelli regimen¹¹ in 69% of my patients, and to ACE inhibitors in 53%. The difference is not statistically significant, and either treatment may be used. If one fails, the other may be instituted.

The therapy of mesangial proliferative glomerulonephritis (the most common cause of which is IgA nephropathy) and membranoproliferative glomerulonephritis is still disputed. I have found some patients with IgA nephropathy to respond to cyclophosphamide and prednisolone, but side effects are common and serious. If there is no response, it might be more effective and safe to use ACE inhibitors.

Nephritis due to systemic lupus erythematosus almost always responds to prednisolone and cyclophosphamide. The readers are referred to the reference cited for details of therapy.¹²

ACE inhibitors (ACEI) for the nephrotic syndrome

ACEI have many actions in the nephrotic syndrome. The major effect may be haemodynamic. Reduced renal perfusion due to chronic renal disease and to reduced circulating blood volume stimulate the renin angiotensin system. Angiotensin II (A II) is released in the glomerulus. The first arteriole it comes in contact with is the efferent arteriole, which is also more richly endowed with A II receptors than the afferent arteriole. Preferential contraction of the efferent arteriole raises intraglomerular pressure and therefore both GFR and the leak of protein, both of which accelerate the decline in renal function. AII is also a growth factor and leads to proliferation of glomerular cells, and secondary release of cytokines leading to sclerosis and to interstitial fibrosis. ACEI counteract these effects, reduce proteinuria, and slow progression of renal disease, besides having an antihypertensive effect. On the other hand, reduced GFR can worsen renal failure, and the suppression of aldosterone could cause hyperkalaemia.

I would start by estimating renal function (serum urea and creatinine), proteinuria (urine protein creatinine ratio if creatinine is below 1.5 mg/dL, 24 hour urine protein if it is above) and its effects (serum protein and albumin). I would then start with 2.5 mg of enalapril twice daily. After one week, I would check serum urea and potassium. Urea may be allowed to rise by one third (e.g. 75 mg to 100 mg) and potassium to 5.5 mEq/L. One should expect a rise in urea since GFR falls. This is the effect we are aiming for, and is not harmful if within limits. I prefer to use urea rather than creatinine to judge this effect since, if GFR is normal, the rise in creatinine would be small and may be within the limits of laboratory fluctuation. BP should also fall, and should be allowed to fall to between 100 and 110 mm systolic, provided the patient does not have troublesome orthostatic hypotension. There is no lower limit to the diastolic pressure. Enalapril may be increased by 5 mg every week (2.5 mg twice). When the dose of enalapril reaches 20 mg/day (10 mg twice daily), I would reassess renal function and urinary protein excretion. If there is some improvement in proteinuria without excessive decline in GFR, I would raise the dose in stages to 40 mg/day. There is no upper limit to the dose, and I have reached 200 mg in some patients, as long as there are no side effects.

There is no point in increasing the dose if there is no progressive reduction in proteinuria.

Once further increments cause no added benefit, the same dose of enalapril may be maintained and losartan may be added in a dose of 25 mg twice daily, increasing by 25 mg per week to 100 mg per day. Assessment of benefit may be done at every 100 mg level. I have some patients taking 300 mg of losartan per day. I should point out that the majority of patients would reach the maximum effective dose much below these levels, and it is futile to increase the dose once there is no progressive benefit. I use enalapril and losartan since these are the cheapest drugs in their class, and no added benefit has been found with more expensive congeners.

If blood pressure falls too low, the dose of enalapril and losartan may be maintained and indomethacin added, starting with 25 mg twice daily, and increasing by 25 mg every week. NSAIDs reduce glomerular filtration by blocking the action of prostaglandins that are vasodilator. The vasoconstriction of the afferent arteriole that results leads to reduction of GFR and with it proteinuria, while raising the blood pressure. One must monitor blood urea and serum potassium once a week as for ACEI, and withdraw the drug or reduce the dose if there is progressive deterioration. The effect on proteinuria may be measured once a month and the dose should be increased only if there is a beneficial effect. Once BP rises to satisfactory levels, the dose of ACEI may be increased again.

It is possible to reduce proteinuria substantially, often to normal levels, by these measures in the majority of patients.

Treatment of hyperlipidaemia

I would not rush to treat hyperlipidaemia in the average patient with the nephrotic syndrome, since lipid levels often normalise once proteinuria is controlled. If it proves impossible to induce a remission of the nephrotic syndrome, it is necessary to use a lipid lowering agent, and I would use a statin. I have found rosuvastatin to be especially effective. It should be remembered that the toxicity of all protein-bound drugs is increased when serum albumin levels are low, so one should start with the minimum dose, monitor the patient for side effects, and increase the dose gradually. Hyperlipidaemia may itself contribute to progressive worsening of renal function and to proteinuria, so control of lipids is desirable apart from the prevention of progressive atheromatous change.

Coagulation abnormalities

I would not ordinarily administer anticoagulants for the nephrotic syndrome. While the incidence of renal vein thrombosis has been variously reported to be between 7 and 70% of patients, it is rarely of clinical significance. However, once renal or other venous thrombosis is detected, the patient should be maintained on anticoagulant therapy to minimise the risk of pulmonary thromboembolism. Patients with membranous nephropathy are supposedly more prone to develop this complication, which should be suspected whenever a patient has a sudden decline in renal function with no obvious explanation.

FOLLOW UP

Even if you achieve a complete remission, please remember that there may be underlying disease activity and progressive subclinical deterioration is possible. Every patient should be cautioned to check BP, urinary protein excretion and renal function (blood urea and creatinine) once a year throughout his life.

REFERENCES

1. Johnson RJ. New insights into the pathogenesis of proteinuria. *Am J Kidney Dis* 2000;36:214-219.
2. Tryggvason KI. Unraveling the mechanisms of glomerular ultrafiltration: Nephron, a key component of the slit diaphragm. *J Am Soc Nephrol* 1999; 10:2440-2445.
3. Burton C. The role of proteinuria in the progression of chronic renal failure. *Am J Kidney Dis* 1996;27:765-775.
4. D'Amico G, Bazzi C. Pathophysiology of proteinuria. *Kidney Int* 2003; 63:809-25.
5. Llach F. Hypercoagulability, renal vein thrombosis, and other nephrotic complications of the nephrotic syndrome. *Kidney Int* 1985;28:429-439.
6. Kaysen GA. Hyperlipidaemia in the nephrotic syndrome. *Am J Kidney Dis* 1988;12:548-551.
7. Kassirer JP. Is renal biopsy necessary for optimal management of the idiopathic nephrotic syndrome? *Kidney Int* 1983;24:561-575.
8. Mani MK. Is renal biopsy necessary in the management of the nephrotic syndrome? *J Ass Physicians India* 1989;37:752-754.
9. Wiseman MJ, Hunt R, Goodwin A, Gross JL, Keen H, Viberti GC. Dietary composition and renal function in healthy subjects. *Nephron* 1987;46:37-42.
10. Nephrotic syndrome in children: a randomized trial comparing two prednisone regimens in steroid-responsive patients who relapse early. Report of the International Study of Kidney Disease in Children. *J Pediatr* 1979;95:239-243.
11. Ponticelli C, Passerini P. Treatment of membranous nephropathy. *Nephrol Dial Transplant* 2001;16 Suppl 5:8-10.
12. Flanc RS, Roberts MA, Strippoli GF, Chadban SJ, Kerr PG, Atkins RC. Treatment of diffuse proliferative lupus nephritis: a meta-analysis of randomized controlled trials. *Am J Kidney Dis* 2004;43:197-208.