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Therapeutic Concepts of Proteinuria and Intra-Glomerular Hypertension

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Proteinuria is the hallmark of renal disease[1]. Proteinuria can also be used as a prognostic marker. In patients with glomerulonephritis, those with more than 1 gram of protein excretion per day in the urine are more likely to have glomerulosclerosis or scarring of the kidneys on renal biopsy and those exceeding 2 grams a day, a higher incidence of developing renal failure on long-term follow-up[2]. Hitherto, it was believed that proteinuria is the result of damage to the kidneys but recently, evidence suggest that the converse is also true, that proteinuria can also directly cause renal damage[3].

When there is excessive leakage of protein in the renal tubules, the proximal tubular cells (PTC) become overloaded with protein. Lysosomes present in the PTC when they engulf excessive proteins, would swell and rupture and release injurious lysosomal enzymes which cause tubulointerstitial damage and fibrosis and with time, give rise to renal failure. In the second mechanism, protein overload of the PTC also triggers the release of certain growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) which are mitogenic to the PTC. They cause excessive production of collagen as well as interstitial cell proliferation, eventually leading to fibrosis and renal failure. Finally, protein overloading of the PTC causes the activation of transcriptase genes which in turn trigger genes encoding vasoactive and inflammatory mediators, the release of these lead to vasoconstriction and inflammation of the renal tissue with injury and renal failure[3].

Therapeutic reduction of proteinuria in kidney disease is now considered as important as the reduction of BP in hypertensive patients as both are important in the preservation of renal function. Normally, the two kidneys in our body excrete less than 150 mg of protein in the urine a day. We must try to reduce proteinuria to as low a level in our patients, if possible to a level below 0.5 gram a day. One of the best strategies to protect the kidneys against damage due to proteinuria is the use of angiotensin converting enzyme inhibitor (ACEI)[4]. In many renal conditions associated with proteinuria, there exists a phenomenon known as glomerular hyperfiltration (HF)[5] which induces proteinuria apart from the direct immunological effect of the glomerulonephritis (GN) which also causes renal damage with leakage of protein into the urine. HF is a condition which occurs whenever some of the glomeruli are diseased or sclerosed. The surrounding glomeruli which are normal are then subject to excessive blood flow with vasodilatation of the afferent glomerular arteriole. In the efferent glomerular arteriole, there is associated angiotensin II (ATII) mediated vasoconstriction. Therefore with increase in blood flow at the inlet and reduction of blood flow at the outlet, there is excessive amount of blood in the glomeruli which is subject to HF with the result that there is raised intraglomerular (IG) blood pressure or IG HPT. IG HPT is associated initially with increase in single nephron glomerular filtration rate (GFR) with leakage of protein in the urine. With time as a consequence of IG HPT, there is renal damage with glomerular sclerosis and eventually renal failure. ACEI by inhibiting the action of ATII on the efferent glomerular arteriole will cause vasodilatation thereby reducing IG HPT and preserving renal function of the affected glomeruli. About 20% to 30% of our patients given ACEI develop the side effect of a dry irritating cough aggravated whenever they have a respiratory tract infection. For these patients, we recommend an angiotensin II receptor antagonist (ATRA) (Losartan) which does not have the side effect of cough. ATRA competes with the receptor for angiotensin and therefore inhibits the action of angiotensin. It is as effective as ACEI in the reduction of proteinuria and preservation of renal function. When using an ACEI or ATRA, one should initially target for a 50% reduction of proteinuria. In other words, the dose of ACEI or ATRA should be increased gradually if necessary, to its maximum dose for effective reduction of proteinuria.

When administering ACEI or ATRA to patients with renal impairment, especially when the serum creatinine is above 200 mmol/L, one should also monitor the serum potassium as hyperkalaemia may be a side effect of drug therapy since both drugs are not only anti-renin but also anti-aldosterone as well. Aldosterone causes retention of sodium and excretion of potassium. An anti-aldosterone agent would therefore cause potassium retention and as renal failure progresses, such an anti-aldosterone agent may aggravate the hyperkalaemia due to the renal failure itself as the failing kidney excretes less and less potassium as renal failure progresses. Generally, when the serum creatinine is above 500 μmol/L, one should discontinue the use of ACEI or ATRA. At that time, there is not much to be gained in terms of preservation of renal function and the problem of hyperkalaemia

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becomes more obvious. Usually this is the time when the patient would be informed about the need for the creation of an arteriovenous-fistula in preparation for future dialysis when the serum creatinine is about 900 μmol/L. It is therefore a good time to cease ACEI or ATRA therapy.

When using ACEI or ATRA, it is useful to know that occasionally both drugs can, on initial use, cause an elevation of serum creatinine or even a temporary worsening of renal function. This is because since their action is a reduction of IG HPT with decrease in single nephron GFR, the total GFR decline among the glomeruli may translate into a worsening of the serum creatinine. Fortunately in many patients, this is a transient phenomenon and with continued therapy, as proteinuria decreases, the renal function should improve or stabilise at its original level of renal impairment and the long term benefits of therapy will become evident as the progression of renal failure is retarded compared to patients who are not on therapy.

In the choice of any therapeutic agent today one should be concerned not only with the restoration of normal physiology of the organ but also the therapeutic remodelling of the particular cell, tissue or organ involved. One strives not only to preserve the function but also the architecture or structure of the cell as all these will eventually translate into long term end organ mortality statistics. Hence in the therapy of hypercholesterolaemia, one chooses an agent which not only normalises the cholesterol level but also its ability to reduce cholesterol plaques and remodel the damaged endothelial cell. Similarly in the choice of an anti-hypertensive agent, a desirable drug would not only normalise blood pressure with minimal or no side effects to ensure patient compliance, but it should also remodel and protect the cardiac and vascular tissue.

In the therapy of proteinuria, one should therefore choose not only a nephrotherapeutic but also a nephroprotective agent. As an exercise let us consider an ACEI and and a calcium antagonist (Ca Antag) except short acting Nifedipine or SANIF which deserves a special mention later on. ACEI is the preferred choice not only because of its potent anti-proteinuric effect with nephroprotection but it achieves the desired therapeutic effect by decreasing IG HPT by reversing angiotensin II mediated vasoconstriction at the efferent glomerular arteriole thereby decreasing IG HPT and proteinuria. Note that ACEI achieves its effect intra-renally[6]. This means that ACEI can cause a reduction of proteinuria in patients with normal BP without hypotension, in contrast to Ca Antag, which can reduce proteinuria only if there is significant lowering of systemic BP, meaning that to achieve significant lowering of proteinuria it has to reduce significantly systemic BP. Hence it is not a suitable anti-proteinuric agent in patients with normal BP.

Apart from this, ACEI exerts direct nephrocellular benefit not found in Ca Antag. ACEI decreases glomerular basement membrane (GBM) permeability and improves metabolism of mesangial cells, both effects of great benefit in patients with IgA nephritis and diabetic nephropathy where the GBM and mesangial cells are involved. In addition, a note of caution should be added with regards to short acting Nifedipine (SANIF). SANIF inhibits proximal tubular reabsorption of protein. Hence patients given SANIF may experience a worsening of proteinuria and it may also counteract the protein lowering effects of ACEI when used together with ACEI as an anti-hypertensive agent. A further note of caution to the use of SANIF as an anti-hypertensive agent is that its use has been associated with certain undesirable side effects of activation of the sympathetic and renin angiotensin system[6] and may therefore not be the ideal therapeutic agent for patients with hypertension.

In conclusion, recent studies have highlighted the important contribution of filtered urinary protein to deterioration of renal function. In depth analysis of proteinuria may assess the degree of glomerular and tubular involvement and help in prognostication of an individual patient with proteinuria. One should consider not only the quantity but also the quality of the urinary protein. This is especially so if there is presence of significant amounts of low molecular weight (LMW) proteins in the urine. In this respect, Woo et al[7] reported that the presence of LMW proteins in the proteinuric SDS-PAGE patterns of patients with IgA nephritis was significantly associated with higher rates of chronic renal failure after 6 years of follow-up. There was a significant correlation between the LMW patterns and tubular atrophy and tubulointerstitial lesions. This work has since been confirmed by other workers[8] and today the presence of LMW proteinuria has been established as an adverse prognostic factor.

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