Introduction

Chronic kidney disease (CKD) is a highly prevalent and costly disease, and is therefore an important public health concern. Through the years, there has been a quest to treat patients with CKD using various strategies to retard progression to end-stage renal failure (ESRF). This article offers a long-term perspective with examples of clinical trials that have contributed to the management of CKD.

The 1960s

In the 1960s, dietary restriction of protein and phosphate was the key component to delay progression of renal failure. The Giovanetti[1] diet consisted of only 18 grams of high biologic value protein. Hypertension was said to be well controlled as long as a blood pressure (BP) of 140/90 or below was achieved; any pressure above this was considered as hypertension and necessitated therapy. Essential hypertension was considered benign, and only malignant and renal hypertension were believed to cause progression to end-stage renal failure (ESRF). A low-protein diet and good control of hypertension were key factors in delaying the progression to ESRF.

The 1970s

In the 1970s, protein restriction to 30 grams a day (0.6 g/kg BW) became popular with the description of renal injury related to glomerular hyperfiltration.[2] Keto acid analogs and essential amino acid diets were
often prescribed. This period also saw the use of cyclophosphamide, prednisolone, and Imuran in the treatment of nephrotic syndrome and other forms of glomerulonephritis. The documentation of platelet and endothelial cell injury in the glomeruli led to the introduction of an antiplatelet agent (dipyridamole) and anticoagulants (heparin, warfarin). These agents helped to retard progression to ESRF.

The 1980s

In the 1980s, controlled trials of dietary protein and phosphate restriction were performed, and the belief that high parathormone levels were one of the main causes of renal deterioration was held. However, none of the trials were vigorous enough to demonstrate that protein restriction was beneficial in renal retardation. There was the concern that a 0.6 g/kg BW protein diet could lead to malnutrition, and a 0.8 g/kg BW protein diet was recommended. The control of hypertension was recognized as the single most important factor in retarding progression to ESRF.

ACE inhibitor (ACEI) was introduced as a therapy that could cause efferent arteriolar vasodilatation and thereby decrease intraglomerular hypertension in glomerular hyperfiltration. This could retard the progression of chronic renal failure. Hypercholesterolemia was also recognized as a contributing factor to renal injury, as it was toxic to the mesangial cells. The control of lipids and cholesterol was advocated.

Steroids and cytotoxic drugs were prescribed for nephrotic proteinuria, as an immunological basis was implicated in heavy proteinuria. In a controlled trial involving 52 pairs of patients with IgA nephritis using cyclophosphamide, antiplatelet and antithrombotic agent (low-dose warfarin), Woo et al. demonstrated that the treatment group had slower deterioration of renal failure 8 years later compared to those on no treatment.

The early 1990s

In the early 1990s, hyperfiltration injury in kidney disease was considered as the main cause of renal deterioration and the role of enalapril was recognized in retarding progression to ESRF in diabetic nephropathy and IgA nephritis. Proteinuria was also documented as directly nephrotoxic, contributing to proximal tubular cell injury leading to glomerulosclerosis. Angiotensin II receptor antagonists (ATRA), introduced in the mid-1990s, were an alternative for those patients who could not tolerate ACEI because of cough. Cyclosporine A was introduced in the therapy of glomerulonephritis with nephrotic syndrome. Steroids (low dose) were introduced to reduce tubulointerstitial fibrosis in glomerulonephritis. Hypertensive nephrosclerosis resulting from essential hypertension was documented as an important cause of ESRF, second only to diabetes mellitus which had become the leading cause of ESRF in the USA and other developed countries.
The late 1990s

In the late 1990s in Singapore, diabetic nephropathy accounted for 52% of patients with ESRF, with chronic glomerulonephritis (GN) accounting for 29% and hypertensive nephrosclerosis 9%. Each year, there were about 750 new patients with ESRF. Retarding the progression to ESRF through these three main causes of ESRF will address 80% of patients destined for ESRF.

For patients with diabetic nephropathy (Diab Nx), strict control of blood sugar and use of ACEI could help retard the progression of Diab Nx. ACEI was important to prevent the development of Diab Nx in those patients found to have microalbuminuria. Patients with persistent microalbuminuria that did not respond to ACEI formed the group that would progress to established Diab Nx with progressive renal failure. The importance of good blood pressure control was emphasized as one of the key features to retard progression of renal failure. In addition, control of hypercholesterolemia was important to prevent renal damage and to decrease cardiac morbidity and mortality. Antiplatelet and antithrombotic therapies were also used. In 1996, with the introduction of the angiotensin II receptor antagonist (ATRA) losartan in Singapore, it was found that this could help reduce proteinuria as well as control hypertension.

It has been postulated that ACEI/ATRA (ACE inhibitor/angiotensin receptor antagonist) may decrease proteinuria in patients with glomerulonephritis by its action on the glomerular basement membrane. Woo et al. performed a study to examine the relationship between the response of patients with IgA nephritis (IgA Nx) to ACEI (enalapril)/ATRA (losartan) therapy by decreasing proteinuria and its effect on the selectivity index (SI) in these patients. Forty-one patients with biopsy-proven IgA Nx entered a control trial, with 21 in the treatment group and 20 in the control group. The entry criteria included proteinuria of 1 g or more and/or renal impairment. Patients in the treatment group received ACEI (5 mg)/ATRA (50 mg) or both with three monthly increases in dosage. In the control group, hypertension was treated with atenolol, hydralazine, or methyldopa.

After a mean duration of therapy of 13±5 months, in the treatment group there was no significant change in serum creatinine, proteinuria, or SI; but in the control group, serum creatinine deteriorated from 1.8±0.8 mg/dL to 2.3±1.1 mg/dL (p<0.05). Among the 21 patients in the treatment group, 10 responded to ACEI/ATRA therapy determined as a decrease in proteinuria by 30% (responders), while the other 11 did not (nonresponders). Among the responders, SI improved from a mean of 0.26±0.07 to 0.18±0.07 (p<0.001), indicating a tendency towards selective proteinuria. This was associated with an improvement in serum creatinine from a mean of 1.7±0.6 mg/dL to 1.5±0.6 mg/dL (p<0.02), and a decrease in proteinuria from a mean of 2.3±1.1 g/day to 0.7±0.5 g/day (p<0.001).

After treatment, proteinuria in the treatment group (1.8±1.6 g/day) was significantly less than in the control group (2.9±1.8 g/day) (p<0.05). The post treatment SI in the responder group (0.18±0.07) was better than that of the nonresponder group (0.33±0.11) (p<0.002). Eight out of 21 patients in the treatment group who had documented renal impairment had an improvement in their renal function compared to two in the control group (x² = 4.4, p<0.05). Of the eight patients in the treatment group who improved their renal function, three normalized their renal function.
Woo et al's study suggests that ACEI/ATRA therapy may be beneficial in patients with IgA Nx with renal impairment and nonselective proteinuria, as such patients may respond to therapy with an improvement in protein selectivity, a decrease in proteinuria, and an improvement in renal function. It is important to note that in this study, patients with renal impairment could normalize renal function as a result of the therapy. ACEI/ATRA therapy probably modifies pore size distribution by reducing the radius of large nonselective pores, causing the shunt pathway to become less pronounced and thus resulting in less leakage of protein into the urine.

The 2000s

In the 2000s, combination therapy with ACEI and ATRA has been advocated for patients with proteinuria associated with Diab Nx, glomerulonephritis and hypertension. The objective is to reduce proteinuria to less than 1 g a day.[14]

In 2000, the USA National Kidney Foundation recommended a target BP of 130/80 in the treatment of hypertension.[15] Lowering systolic BP to 120 mmHg was associated with improved patient and kidney survival (Pohl).[16] Lewington,[17] in his study of 1 million subjects with no cardiovascular (CVS) disease, reported that by decreasing SBP to 115 mmHg and DBP to 75 mmHg, there was a linear association between decreasing SBP and DBP and reduced risk of CVS mortality. However, Pohl[16] reported that SBP reduction to less than 120 mmHg did not provide added renoprotection: he found that SBP<120 mmHg was associated with accelerated loss of renal function because of comorbidities in these patients. In 2003, the 7th Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure in the USA[18] stated that a BP above 115/75 mmHg was associated with higher incidence of an adverse CVS outcome.

Sarnak et al.[19] reported on the effect of a lower BP on the progression of kidney disease, i.e. a long-term follow-up of the modification of diet in renal disease study. This study had the longest follow-up and the highest degree of statistical power demonstrated. The MDRD (modification of diet in renal disease) study achieved BP separation of 8/3 mmHg, 126/77 versus 134/80 over 2 years during an average of 6 years follow-up. ESRF and all-cause death was reduced by 23% in the group with lower BP.

The effects of microalbuminuria is another important area relating to renal and CVS mortality. Microalbuminuria is defined as 20–200 mg albumin excretion in the urine a day. Less than 20 mg has been said to be “normal.” There is ample data to suggest that albuminuria in the “normal” range carries a significant risk of vascular events.[20] The degree of albuminuria reduction in response to treatment is a primary determinant of both renal and CVS outcomes. More than 2 mg/g creatinine of albumin excretion is significantly associated with CVS death, myocardial infarct, strokes, and high BP. This is applicable to both diabetics and nondiabetics.
It has been shown that reduction of microalbuminuria slows progression of renal disease.\textsuperscript{[20]} Every halving of albumin excretion was associated with an 18% lower risk of CVS death. A 20% to 50% reduction in albumin excretion at 6 months was associated with a 50% lower risk of ESRF. If the albumin excretion rate was reduced by more than 50%, there was a decrease in relative risk of ESRF by 75%.\textsuperscript{[21]} CVS risk follows a continuous positive relationship with albumin excretion, and lowering albuminuria independently lowers the risk of renal and CVS events. “Normal” is not normal. We should identify the level of BP and albumin excretion below which treatment is no longer beneficial.\textsuperscript{[20]}

Apart from control of hypertension and reduction of proteinuria, another area of great interest is the role of high levels of cholesterol in renal damage. This role was first documented in the 1980s,\textsuperscript{[5]} but it has only recently been better documented with evidence to demonstrate that the control of hypercholesterolemia can help in retarding progression to ESRF.

In a recent publication, Tonolo \textit{et al}.\textsuperscript{[22]} provided new evidence that simvastatin maintains steady patterns of the glomerular filtration rate (GFR) and improves the albumin excretion rate (AER) and the expression of slit diaphragm (SD) proteins in type II diabetes. In a 4-year study of 86 microalbuminuric, hypertensive type II diabetics, comparing the effects of 40 mg/day of simvastatin (group I) versus patients treated with 30 g cholestyramine/day (group II), it was found that patients in group II had a GFR decay per year of 3 ml/min/1.73 m$^2$ compared to those in group I whose GFR was stable.

Both groups showed a significant decrease of LDL cholesterol after simvastatin and cholestyramine therapy. The albumin excretion rate (AER) decreased in group I, but not in group II ($p<0.01$). The percentage of patients who had steady normoalbuminuria during the fourth year of follow-up instead of microalbuminuria was threefold higher during simvastatin treatment than during cholestyramine treatment (29% versus 8%, $p<0.01$). Overt proteinuria developed in 15% of cholestyramine-treated patients and in 4% of simvastatin-treated patients ($p<0.01$).

Finally, the simvastatin-treated group also had markedly improved mRNA expression of SD proteins. It was postulated that the improvement attributed to the simvastatin-treated group could be due to the decreased overproduction of reactive oxygen species. But, whatever the mechanism, the authors believe that the study supports the renoprotective role of simvastatin against the development of ESRF.\textsuperscript{[22]}

Woo and Lau,\textsuperscript{[23]} in a recent 5-year controlled trial of 75 IgA nephritis (IgA Nx) patients with 37 in the treatment group and 38 in the control group, studied the ACE gene ID genotype to compare the effects of ID polymorphism on the response to ACEI/ATRA therapy. In the control group, hypertension was treated with atenolol, propranolol, hydralazine, or methyldopa. The patients in the treatment group were treated with enalapril (ACEI) or losartan (ATRA). The post trial serum creatinine in the control group was significantly worse than in the treatment group (serum creatinine 5.0±2.8 mg/dL versus 2.4±2.0 mg/dL, $p<0.001$). The post trial proteinuria in the control group was worse than in the treatment group (1.9±1.0 g/day versus 1.1±0.9 g/day, $p<0.002$). There were 21 patients with ESRF in the control group compared to only 7 in the treatment group ($x^2=5.4$, $p<0.005$). Treatment seems to reduce the number of patients progressing to ESRF. For those with II genotype, there was significantly less patients with ESRF in the treatment group when compared to the control group ($p<0.02$). For those with the ID and DD genotypes, there was no difference in the renal outcome between the treatment and control groups.
Woo and Lau,[23] concluded that ACEI/ATRA therapy was effective in retarding disease progression in IgA Nx; however, treatment significantly reduced the incidence of ESRF only in patients with the II genotype, not in those with the ID or DD genotype. Their subsequent work confirmed that it was the ATRA, not the ACEI, that contributed to improved renal function. Patients responsive to ATRA therapy can retard progression to ESRF by up to 32 years. Mild renal failure can be reversed with possible regression of glomerulosclerosis because of glomerular remodeling by ATRA. This is especially so in patients on treatment with supranormal doses of losartan[24] at 200 mg to 300 mg a day.

**Conclusion**

It is apparent from this review article that three important strategies are necessary to prevent progression to ESRF: control of hypertension, treatment of proteinuria, and treatment of hypercholesterolemia. It is also obvious that through the years, therapeutic intervention has been offered increasingly earlier to patients with CKD. In the past, therapy was started only when patients developed renal failure; in recent years, therapy is offered much earlier and more aggressively, whether it is in terms of reduction of BP, proteinuria, or high cholesterol. Early therapeutic intervention must continue to be the keynote if we are to solve the problem of the increasing number of patients who fall prey to ESRF year after year.

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