Slowing the Progression of Chronic Renal Parenchymal Disease

End-stage renal failure (ESRF) is a major cause of morbidity and mortality in North America as well as in the rest of the world. In addition, the treatment of patients who have ESRF is quite expensive. It is estimated that for an in-hospital hemodialysis patient, the average annual cost is approximately $54,000 in Canadian dollars and a peritoneal dialysis patient's annual care costs approximatel $32,000 in Canadian dollars, whereas a kidney transplant patient costs about $25,000 dollars a year in Canadian dollars. And as renal replacement therapy by hemodialysis, peritoneal dialysis or successful kidney transplantation prolongs survival in ESRF patients, new dialysis patients have been outnumbering those who die from ESRF. To complicate matters further, the number of ESRF patients have been on the rise the last two decades and is expected to continue to rise at a rate of about 6 to 10% per year through the next one to two decades, putting more strain on the national economy, human resources and on an already strained health care system

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Therefore, it makes sense to slow down or delay the progression of chronic renal parenchymal disease, or when possible, to prevent it from happening altogether. In this article, we will review the mechanisms and course of progression of renal injury and elaborate on the currently recommended strategies to delay or halt the progression of chronic renal disease.

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The incidence and prevalence of end-stage renal failure (ESRF), also known as end-stage renal disease (ESRD), have increased greatly in North America and globally. Actually, some authors have called this an epidemic. This term becomes very clear when one looks at the number of patients in Canada, receiving renal replacement therapy (hemodialysis, peritoneal dialysis or renal transplantation). In 1996 that was 17,807 patients. This number is expected to almost double to 32,952 patients by the end of 2005. In the United States, in 1991, there were around 190,000 patients on renal replacement therapy (RRT); this number reached more than 372,000 at the end of 2000 and is expected to be approximately 650,000 by 2010. It is also noted that although the total number of patients receiving RRT is very small compared with the general population (0.02 to 0.06% as it varies from one country to another), dialysis costs that are steadily rising absorb 0.7 to 1.8% of the health services budget. For example, in the United States alone, it is estimated that the cost of RRT will be more than U.S. $28 million by 2010. Medical professionals are expected to provide dialysis for all patients who need it, whereas politicians and health care planners try to contain costs.

Mechanisms of Progression of Chronic Renal Disease

The following pathological mechanisms have been proposed as possible factors, single or in combination, in initiating renal injury and also maintaining it over time, leading to ESRF:

Systematic arterial hypertension (HTN)

It is well-known that HTN is a primary cause of chronic renal insufficiency. Moreover, HTN has been shown to be an important risk factor for the progression of renal disease initiated by other mechanisms, such as chronic glomerulonephritis (Chr. GN) and diabetic nephropathy (DM Nephrop.). Arterial HTN results in increased glomerular capillary perfusion and elevated capillary hydraulic pressure to the glomerulus, which, if remains sustained, can exacerbate pre-existing renal disease by inducing progressive sclerosis of the glomeruli.

Deleterious compensatory responses of surviving nephrons

Clinical studies, as well as animal experiments, have led investigators to formulate that there is a central common pathway theory that states chronic renal diseases progress through focal nephron loss and that the responses of surviving nephrons, which include glomerular hyperfiltration and hypertrophy, although initially serving to compensate for the lost function of the more severely damaged or destroyed nephrons, will eventually prove detrimental to those remaining functioning nephrons. , With time both nephrosclerosis and tubular atrophy will steadily reduce the number of surviving nephrons in a self-perpetuating cycle that ultimately results in ESRF. Nephronal adaptive mechanisms also include: (1) vascular adaptations, including vasodilatation and glomerular capillary hypertension; (2) metabolic adaptations, particularly by the tubular epithelium, resulting from the increased filtration rates in the residual nephrons: a) increased oxygen consumption leading to increased production of oxygen radicals; b) increased ammonia production by residual nephrons. Ammonia reacts with components of the complement system, inducing an inflammatory reaction that leads to direct renal tissue injury and attraction of leukocytes; c) elevated serum oxalate level and elevated calcium-phosphorus product may lead to disposition of these substances in the renal interstitium providing a nidis for inflammation and tissue destruction; d) dyslipidemia is common in chronic renal disease states, especially those in which there is significant proteinuria, and is believed to contribute to the damage in the renal microvasculature.

In addition to these adaptive mechanisms, a large number of locally acting specific peptides, such as growth factors, proliferative and fibrogenic peptides, play an important role in the sclerosis and scarring that occur as chronic renal disease progresses. Among the many peptides that have been identified to contribute to the progression of chronic renal disease are platelet-derived growth factor, transforming growth factor-beta and endothelin.

Angiotension II and aldosterone have also been shown to play an important role in the progression of chronic renal disease by, at least partly, interacting and linking with the aforementioned peptides/factors.

Proteinuria

It is well established that proteinuria is a marker of renal disease; the presence of proteinuria or microalbuminuria serves as a marker of glomerular capillary hypertension, since elevated glomerular capillary hydraulic pressure has been associated with impaired glomerular permselectivity of albumin. Recent studies have shown that proteinuria is not only a marker for renal damage but is itself a pathogenic. It has also been recognized that the magnitude of proteinuria correlates with progressive renal impairment in virtually in all types of renal injuries, including diabetic nephropathy, membraneous nephropathy and focal segmental glomerulosclerosis. It is hypothesized that proteinuria renal injury takes place as a result of endocytosis of the filtered albumin via two pathways in the cells of the renal proximal tubules. Following its endocytosis, the albumin is metabolized to a number of intermediate peptides and small proinflammatory molecules, some of which are believed to be cytotoxic, leading to tubulointerstitial injury. In addition, proximal tubule cells that have been exposed to elevated filtered protein produce growth factors associated with the development of glomerulo-tubular fibrosis. It is believed that tubulointerstitial fibrosis correlates more strongly with progressive renal dysfunction in patients with glomerular injury than does glomerular function.

Dyslipidemia

Dyslipidemia is a common association of chronic renal disease and is usually seen from the early stages of renal insufficiency. It is more common, and sometimes severe, in patients with heavy proteinuria/nephrotic syndrome and kidney transplant recipients. Lipid abnormalities and proteinuria usually occur concomitantly, even when the proteinuria is at a nonnephrotic range. Experimental studies suggest that circulating lipoproteins play a direct role in the pathogenesis of glomerulosclerosis and tubulointerstitial injury by adhering to albumin and, therefore, inducing a series of inflammatory reactions leading to renal damage. Among the lipoproteins, apoB-containing lipoproteins are the most nephrotoxic. In a prospective clinical study of non-diabetic patients with primary chronic renal disease, it has been found that raised plasma concentrations of apoB and LDL cholesterol were correlated with faster progression of renal impairment.

Other mechanisms and risk factors

Poor glycemic control in diabetes. A number of studies have demonstrated that poor glycemic control in diabetic patients increases the risk of development of microalburia, which is considered an important marker of incipient diabetic nephropathy. In addition, poor glycemic control appears to hasten the development of frank proteinuria (alubuminuria) in those patients who otherwise have microalbuminuria.

Phosphate and calcium metabolism. It has been documented by Alfrey et al that uniephrectomized rats receiving a high phosphate diet developed renal calcium and phosphate deposition and tubulointerstitial injury within five weeks of nephrectomy, indicating that phos-

phate excess appears to have some intrinsic nephrotoxicity, and moreso in those with reduced nephron mass. A high-phosphate diet also leads to the development of hyperparathyroidism in uninephrectomized rats resulting in increased circulating parathyroid hormone (PTH) levels. The high PTH may independently exacerbate an already impaired renal function by worsening both systolic and diastolic blood pressures, exacerbating glucose intolerance and impairing lipid metabolism.

Calcium-phosphate deposition is a frequent histologic finding in end-stage kidney biopsies, irrespective of the underlying etiology of the renal failure. Calcium levels in end-stage kidneys have been found to be nine times greater than levels in control kidneys. Furthermore, the severity of renal parenchymal calcification was found to correlate with the degree of renal functional impairment. Calcium deposition is believed to induce renal injury essentially by uncoupling of mitochondrial respiration and generation reactive oxygen radicals. Potentially renal calcium deposition can also lead to progression of renal disease by increased vascular smooth muscle tone, messangial cell contractility, cell growth and proliferation, increased synthesis of extra cell matrix and immune cell modulation.

Other risk factors include cigarette smoking, male gender, high dietary protein intake, African-American race, ureteric reflux and unresolved persistent acute renal injury.

Strategies Recommended for Slowing the Progression of Chronic Renal Disease

Control of arterial hypertension (HTN)

It has been well recognized that HTN can lead to primary renal damage or exacerbate renal damage from secondary causes, such as DM nephropathy. Moreover, it has also been shown that adequate treatment of systemic HTN ameliorates and slows the progression of chronic renal disease. There are two practical issues related to control of HTN in patients with chronic renal disease. First, what is the optimal (lowest) blood pressure that needs to be achieved? Second, which anti-hypertensive agents should be used to control HTN in this group of patients? As to the blood pressure (BP) level, the Modification of Diet in Renal Disease (MDRD) study has provided a reasonable evidence that BP levels less than 125/75 mmHg or mean arterial BP of 90 mmHg significantly delayed the progression of renal injury, moreso in diabetic patients and those with proteinuria of 1 gm or more per 24 hours. In patients with proteinuria level of 3 gms or higher per 24 hours, a mean arterial BP of 91 mmHg (or BP 125/75 mmHg) slowed the rate of decline in glomerular filtration rate (GRF) by over 40% (6.7 ml per minute vs. 10.2 ml/minute decline in patients with BP of 130/80 or mean arterial BP of 96). This goal BP is also in keeping with the JNC-VI report that recommends a target BP of 125/75 in patients with chronic renal insufficiency. As for which anti-hypertensive agent is most effective, all clinical trials over the past two decades had shown that angiotension-converting enzyme inhibitors (ACE-Is) are the single class of agents that provides the most renoprotective effect, especially in diabetic patients and those with heavy proteinuria. The beneficial effect of ACE-Is in slowing the progression of chronic renal disease has been documented in those patients who have HTN, as well as in normotensive patients. Recent evidence also indicates that most angiotensin-receptor blockers (ARBs) also have the same renoprotective effect as that of ACE-Is. Indeed there are early reports indicating that combining these two classes anti-hypertensive agents in the same patient had resulted in significant reduction of proteinuria than by using either agent alone. In addition to the blood pressure-lowering and proteinuria-lowering effects of ACE-Is and ARBs, blocking angiotension II preferentially decreases vasoconstriction of the efferent arteriole, resulting in decreased intra-glomerular pressure; it may also result in blocking the proliferative effects of angiotension II on the mesangium and inhibiting inflammation and fibrosis. The ACE-Is extensively studied include enalapril, captopril, benazepril and ramipril, and the ARBs include valsartan and candesartan. However, most, if not all, ACE-Is and ARBs seem to exert the same degree of renoprotection. Adding non-dihydropyridine calcium channel blocker, such as verapamil to enalapril, has resulted in around 25% more drop in proteinuria in diabetic patients with heavy proteinuria. Implementing a low salt diet and using diuretics are important additional measures in achieving optimal control of HTN.

Reduction of proteinuria

Several clinical trials have shown that the rate of deterioration in chronic renal dysfunction was faster in patients with high grade proteinuria, greater than 1 gm per day, than for those with low-grade proteinuria, less than 1 gm per day. The acceleration of renal disease progression in patients with type 1 and 2 diabetes correlated with the level of baseline proteinuria. Even in patients with controlled essential HTN with no evidence of renal disease, the onset of proteinuria was a marker of future decline of renal function. The MDRD study demonstrated that baseline proteinuria was an independent risk factor for progression of renal disease in nondiabetic patients, and the degree of proteinuria reduction might be a measure of the effectiveness of BP control. All in all, the evidence from human studies, as well as experimental animals, has shown that proteinuria of greater than 1 gm per day is associated with progression of renal disease. Therefore, it is very important to reduce the degree of proteinuria to less than 1 gm per day or lower and keep it at that level. Different pharmamacologic agents have been used to lower the level of proteinuria to less than 1 gm per day.

ACE Inhibitors

ACE-Is have been shown in a number of studies that they do consistently reduce proteinuria more effectively than conventional anti-hypertensive therapy with similar effect on BP. They seem to exert their antiproteinuric effect partly through reducing both systemic and intraglomerular pressure. However, the antiproteinuric effect is more gradual than the hemodynamic effects,

suggesting that a gradual improvement of glomerular perselectivity contributes to the antiproteinuric effect of ACE-Is. In one study, the anti-proteinuric effect of ACE-Is was documented in the absence of an effect on blood pressure, suggesting specific favorable renal effects as well. This antiproteinuric effect occurs irrespective of the level of renal function, pretreatment BP level, severity of proteinuria and underlying renal disease. As indicated above it seems that all ACE-Is have similar renoprotective, antiproteinuric and BP-lowering effects. However, in patients with renal impairment, ACE-Is may abruptly worsen the already compromised renal function, especially in those with renovascular disease or intrarenal renal damage. Thus, it is recommended to check serum creatinine about seven to 10 days following the initiation of ACE-Is. An elevation in serum creatinine by up to 15 to 20% above the baseline may be accpeted, especially if it remains stable on subsequent testing. If the rise in serum creatinine is more than 20% of the baseline creatinine level, then ACE-Is should be discontinued. Another risk of ACE-Is therapy in patients with renal insufficiency is the development of hyperkalemia. This can be prevented or minimized by discontinuing potassium supplement and potassium-sparing diuretic and also measuring the serum potassium level shortly after starting these drugs. In most instances, these compounds are well-tolerated and have particularly beneficial effects.

Angiotension-II receptor blockers (ARBs)

ARBs albeit have been in clinical use for a shorter duration than ACE-Is, have also been shown to be as effective as ACE-Is in controlling HTN, reducing proteinuria and in providing renoprotection in patients who have chronic renal disease, such as DM nephropathy. It also appears that combining the two groups of agents (each in smaller doses than if it were to be used alone) in the same patient may provide a more antiproteinuric affect than by using either agent alone.

Most studies on renal insufficiency patients to date have been performed with losartan; however, other ARBs, including valsartan and irbesartan, are currently studied in clinical trials dealing mostly with patients who have diabetes and diabetic nephropathy. The side effect profile for ARBs may be similar to that of ACE-Is, but probably less severe, as both elevation of serum creatinine and mild to moderate degree of hyperkalemia have been reported in patients who have renal impairment on ARBs. Hyperkalemia due to ARBs is usually mild but can be aggravated by the concomitant use of ACE-Is. Cough, which has been reported to occur in 5 to 20% of patients on ACE-Is, has not been reported to be a problem in those treated with ARBs.

Calcium channel blockers (CCBs)

CCBs can also reduce proteinuria; however, not all CCBs do so. The nondihydropyridine CCBs, such as verapamil and diltiazem, have been shown to reduce proteinuria in proteinuric patients with non-insulin dependent DM (NIDDM) with the same antiproteinuric effect as that of ACE-Is and greater than that of beta blockers. On the other hand, dihydropyridine CCBs, such as nifedipine, nicardipine and nitrendipine, have been shown to be much less effective in reducing proteinuria, and, in some instances, have been reported to lead to increased proteinuria. Combining ACE-Is and non-dihydropyridine CCBs has been shown to have a synergisitc effect leading to a more significant lowering of proteinuria.

Other anti-hypertensive agents

Beta blockers in small studies have been shown to exert a slight reduction in proteinuria that appears to be more related to their blood pressure-lowering effect. Among the diuretics, one study has found a reduction in microalbuminuria in NIDDM patients, but there was no effect on proteinuria (or microalbuminuria) with hydrochlorothiazide and chlorthalidone.

Non-steroidal anti-inflammatory drugs (NSAIDs).

NSAIDs have been used to lower proteinuria via their effect on renal prostaglandins. Their antiproteinuric effect is proportional to their effect on the production of renal prostaglandins and without affecting BP level. The reduction in proteinuria by NSAIDs is usually associated with afferent arteriolar vasoconstriction, which results in reduced glomerular hydrostatic pressure, which in turn results in reduced GFR. Therefore, while patients are on NSAIDs, renal function and potassium level should be monitored.

Combination Therapy

Combining different classes of pharmacologic agents with different mechanisms of action may have an addictive proteinuria-lowering effect. In addition, implementing dietary measures, as will be discussed later, will maximize the antiproteinuric effect of pharmacologic treatment.

Lipid lowering

A number of studies have shown a relationship between hyperlipidemia and progression of renal disease. Moreover, diverse classes of lipid-lowering agents have shown to retard the progresson of chronic renal injury in experimental animals. Among the lipid-lowering agents studied are the 3-hydroxy-3-methyglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, including lovostatin, simvastatin and pravastatin, which effectively reduce total cholesterol, LDL cholesterol, ApoB and triglyceride levels in renal patients with and without proteinuria, but their effect on HDL cholesterol appears to be highly variable among patients. A number of studies have shown a relationship between hyperlipidemia and progression of renal disease. Moreover, diverse classes of lipid-lowering agents have shown to retard the progresson of chronic renal injury in experimental animals. Among the lipid-lowering agents studied are the 3-hydroxy-3-methyglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, including lovostatin, simvastatin and pravastatin, which effectively reduce total cholesterol, LDL cholesterol, ApoB and triglyceride levels in renal patients with and without proteinuria, but their effect on HDL cholesterol appears to be highly variable among patients. Fibric acid derivatives

appear to be the most effective agents in lowering triglycerides in renal patients, but their efficacy in reducing total cholesterol and LDL cholesterol levels appears limited. It is also noted that in proteinuric patients, significant reduction of proteinuria appears to be associated with improved lipid profile resulting in reduced levels of total and LDL cholesterols and triglycerides, as well as lipoproten (a). These salutary effects on lipids were observed with using ACE-Is, ARBs and indomethacin, and they seem to be proportional to the degree of proteinuria reduction independent of the agents used to achieve this reduction.

Low protein diet

The controversy over the contribution of low protein (or protein-restricted) diet in slowing the progression of chronic renal disease continues in the medical literature. A number of small human studies and experimental studies have demonstrated that protein-restricted diet has a significant renoprotective potential. Several clinical trials have attempted to assess the renoprotective role of low protein diet, but the results are confusing. A recent meta-analysis of multiple trials has suggested that dietary protein restriction does retard the progression of chronic renal injury. In addition, the MDRD study has demonstrated that long-term, three years, administration of a low-protein diet providing 0.6 to 0.8 gm/kg/day to a cohort of patients with nondiabetic chronic renal disease was associated with a beneficial effect in delaying the progression of renal disease.

However, a number of factors may have contributed to this modest renoprotection, including well-controlled HTN, over 40% of patients were already on ACE-Is, almost 25% of patients had polycystic kidney disease and few or none had DM. In another meta-analysis of 13 randomized trials, the authors concluded that although dietary protein restriction retards the rate of renal functional decline, this renoprotective effect was of relatively weak magnitude that better therapies are needed to slow the rate of progression of renal disease. Practically speaking, while protein restriction seems to be a less powerful tool for retarding the progression of chronic renal disease than, for example, antihypertensive therapy one would still offer it to patients as yet another strategy of favorably altering the course of their renal disease. Therefore, dietary protein restriction may be initiated (a) when serum creatinine is over 2 mg/dl (170 umol/L) and not sooner, (b) restrict daily protein intake to 0.6 to 0.8 gm/kg body weight per day, (c) recommend the use of high biological value protein and (d) monitor patients' nutritional status by measuring their serum albumin and total proteins. Protein restriction in patients on glucocorticoid therapy is not recommended, as it can worsen the adverse effects of glucocorticoid on protein catabolism.

Other adjuvant therapeutic strategies

Control of blood glucose in diabetes. Strict control of blood glucose also appears to delay the onset and progressoin of renal disease in type 1 diabetes patients. As microalbuminuria is a hallmark of incipient DM nephropathy, almost all patients with urinary albumin excretion of 30 to 300 mg/day progress to frank proteinuria (macroalbuminuria) in a period of five to 10 years. Therefore, delaying the onset of microalbuminuria may prevent, or delay, the development of DM nephropathy. The Diabetes Control and Complications Trial (DCCT) had shown that intensive control of blood glucose, with goal hemoglobin AIC < 6.0%, reduces the mean risk of developing microalbuminuria in a cohort of normoalbuminuric type 1 diabetes. In addition, intensive blood glucose control appears to delay the onset of albuminaria in patients with microalbuminuria. Pharmacologically, several studies have demonstrated that the use of ACE inhibitors decreases the progression of microalbuminuria to frank proteinuria.

Control of calcium and phosphorous abnormalities by dietary measures and pharmacologic interventions may provide addintional renoprotection in patients with chronic renal disease.

Smoking cessation. Studies have shown that diabetics who smoke are at increased risk of microalbuminuria. In patients with type 1 and type 2 DM, GFR fell two times faster in those who smoked than in those who did not. Even in non-diabetic renal disease, such as polycystic kidneys or IgA nephropathy, the risk of progression to ESRF was much higher in smokers than in non-smokers.

Chronic Renal Insufficiency Clinics

The chronic renal insufficiency (CRI) clinics, also called progressive renal insufficiency, PRI clinics) are multi-disciplinary clinics, in which patients with moderate to severe chronic renal impairment, regardless of its etiology, are being assessed, followed and managed with the goal of slowing the progression of their underlying chronic renal injury for the longest time possible, or, in some cases, even reverse their impaired renal function either to normal, which is the ideal, or to its baseline. In these clinics, patients are evaluated and followed by a nephrologist, a renal nurse, a renal dietician, a pharmacist and a social worker, where they can learn about the nature of their renal disease, investigated for any potentially reversible aggravating factors and treated accordingly and learn about the interplay of diet and drug therapy in the management of their renal disease. In addition, those patients who are destined for dialysis will receive the necessary education regarding types of dialysis and kidney transplant and have their dialysis access created in preparation for starting dialysis.

Summary

The incidence and prevalence of ESRF are already high and are expected to continue to rise over the next two decades. Given the fact that ESRF is associated with substantially high health costs, poor quality of life, as well as high morbidity and mortality, preservation/maintenance of residual renal function n patients with chronic renal insufficiency should be an important goal for public health programs. Therefore, aggressive approach to chronic renal insufficiency is recommended. This will include looking for reversible factors and treating them, control of HTN using ACE-Is and/or ARBs with or without other agents, lowering urine proteins to less than 1 gm/day

treating hyperlipidemia and hyperglycemia, stopping smoking and following a protein-restricted diet. Follow-up of their patients in multidisciplinary CRI clinics has also been shown to be an important part of the overall management of these patients, as it improves their compliance with different therapies and provides a venue to monitor for any side effects or complications that might result from those therapies. For those whose renal function continues to deteriorate, education and proper, timely planning for renal replacement can be accomplished through CRI clinics.

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