REVIEW

CHRONIC RENAL FAILURE (CRF) : A HOLISTIC APPROACH

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An increasing number of patients with CRF progress every year to endstage renal insufficiency when they require dialysis replacement therapy. It is imperative that we optimise the management of these patients in view of the associated high morbidity and mortality. The approach to the patient with CRF should be a multidisciplinary one involving doctors (nephrologists) nurses and dietitians. I will highlight in this review a general framework for the management of CRF.

The management of CRF should include the following:

1. Treatment of the underlying disease

2. Prevention of superimposed renal insults

3. Slowing the progression of the underlying nephropathy

4. Treatment of uraemic complications

5. Minimizing the co-morbidity of CRF

6. Optimal referral and initiation of renal replacement therapy (RRT)

1. Treatment of the underlying disease

The management of the underlying nephropathy is relevant early in the course of most chronic nephropathies. Furthermore, primary prevention of CRF could be undertaken in conditions such as diabetes mellitus (DM) and essential hypertension where the metabolic control (hyperglycaemia) (1) and that of hypertension respectively can prevent the onset of renal dysfunction. In other renal diseases, such as glomerulonephritis, early referral and management by immunosuppression when appropriate could lead to remission and a resolution of inflammation before it progresses to renal fibrosis and irreversible CRF. In obstructive uropathy, the prompt relief of the obstruction may prevent long-term irreversible scarring. It is therefore important, for all the above reasons, that patients with proteinuria, haematuria or raised serum creatinine are referred to nephrologists who could thoroughly investigate them and initiate appropriate therapies.

2. Prevention of superimposed renal insults

In addition to the treatment of the underlying renal disorders, it is important to avoid any superimposed injury. Most commonly, patients with CRF have further renal impairment due to drug nephrotoxicity. In particular, patients with CRF are extremely susceptible to the nephrotoxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) (2). In addition, they are prone

to the nephrotoxicity of angiotensin converting enzyme inhibitors (ACEI) as their renal function depends on some angiotensin-dependent glomerular filtration. All too often, these patients are prescribed such nephrotoxic agents without due consideration to their renal impairment, age, or hydration status. Old age and dehydration potentiate the nephrotoxicity of many drugs. A high index of suspicion is therefore required from those attending to patients with CRF in order to avoid or exclude any nephrotoxic drugs. Also attention should be paid to non-prescription agents such as potentially nephrotoxic herbal remedies (3).

3. Slowing the progression of the underlying nephropathy

The progression of chronic renal failure (CRF) to endstage renal insufficiency is the direct consequence of the underlying renal scarring that slowly destroys the renal parenchyma regardless of the cause of the initial insult. Such scarring is characterised histologically by progressive glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis (4). Research has focused over the last quarter of a century on the putative mechanisms and mediators involved in the development and progression of these histological changes. Simultaneously a better understanding of the natural history of kidney diseases has identified some risk factors associated with a poor prognosis. The identification of these risk factors and their elimination may prove to be the key to the future management of patients with CRF. Their control or elimination may also have a direct impact on the underlying histological changes. In this review, I will therefore focus on some well-defined risk factors for the progression of CRF, examine their effect on renal scarring and review the impact of their control on the progression of CRF.

Hypertension

There is little doubt that systemic hypertension accelerates the rate of decline of renal function. Numerous studies have implicated systolic as well as diastolic hypertension (5). It has been suggested that the rate of decline in renal function with time is a function of the severity of hypertension. Patients with mean arterial blood pressure values around 107 mmHg

(140/90 mmHg) have a slow rate of functional deterioration compared to those with higher blood pressure values who progress rapidly towards endstage renal insufficiency (5). Research has also explored the mechanisms through which systemic hypertension can accelerate scarring. It has been suggested that the transmission of systemic hypertension to the glomerular capillary with consequent glomerular hypertension would initiate and accelerate the development of glomerulosclerosis. Systemic hypertension is also associated with renal arterial and arteriolar hyalinosis, sclerosis and narrowing, leading to chronic glomerular as well as tubulointerstitial ischaemia. This would in turn contribute to further glomerulosclerosis and tubular atrophy as well as interstitial fibrosis (4).

Numerous clinical trials in diabetic and non-diabetic nephropathies have shown that the control of systemic hypertension slowed the progression of the underlying nephropathy (6). Recent evidence has also suggested that some anti-hypertensive agents may be more effective than others in slowing the progression of CRF. Interest has focused on the potential therapeutic advantage of angiotensin converting enzyme (ACE) inhibitors (7). These agents have the advantage of reducing systemic as well as intraglomerular hypertension and also reduce proteinuria. Such a key dual beneficial effect may explain the apparent therapeutic superiority of these agents in the control of progressive renal insufficiency in diabetic (8) and non-diabetic (9, 10) nephropathies. This advantage is clear when these agents are compared to beta-blockers or to dihydropyridine calcium antagonists such as nifedipine with no significant effect on proteinuria (11). Further, while the reduction of systemic hypertension per se is associated with a parallel reduction in proteinuria, the effect of ACE inhibitors on proteinuria is apparent early and at high levels of blood pressure. At lower blood pressure levels (MAP < 100mmHg), other antihypertensive agents may also be equally beneficial. Finally, in order to optimise the antihypertensive and antiproteinuric effects of ACE inhibitors, dietary salt restriction is recommended.

Having established that the control of systemic hypertension is the key to slowing the progression of CRF, the question is what is the

optimal level of blood pressure control? The answer to this question has become apparent over the last few years. It depends on the patient we are treating, in particular his race and the severity of his proteinuria. There is ample evidence to suggest that systemic hypertension in blacks is associated with a worse prognosis and a faster rate of decline in renal function when compared to whites. With that in mind, it became apparent that in order to protect black patients from hypertensive renal injury, it is imperative to lower their blood pressure more aggressively than that of white patients (12). The Modification of Diet in Renal Disease (MDRD) study showed that conventional blood pressure control (130/80 mmHg; MAP 98 mmHg) was inisufficient to slow the decline in renal function of blacks who required levels of MAP around 92 mmHg (120/70 mmHg) to achieve similar protection to their white counterparts (12). The other variable to take into consideration when we treat a hypertensive renal patient is proteinuria. The MDRD study also showed that the higher the proteinuria the more aggressive our antihypertensive treatment and the lower our target blood pressure should be (13). In this study, patients with proteinuria < 1g/24h had a slow rate of functional decline when blood pressure was reduced to 140/90mmHg (102-107 mmHg). On the other hand, patients with proteinuria between 1 and 3 g/24h required a tighter blood pressure control with target levels around 98 mmHg (130/80 mmHg). Finally, patients with heavy proteinuria (>3g/24h) required even lower blood pressure levels (MAP 92 mmHg; 120/70mmHg) to achieve the same level of protection as those with lower proteinuria (13). It is therefore imperative to tailor our antihypertensive therapy to the patient we treat with reference to his/her race and level of proteinuria.

Proteinuria

It has been known for many years that the severity of proteinuria predicts the rate of decline in renal function (14). Only recently has it been suggested that proteinuria may not only be a prognostic marker of declining renal function but also that it may directly be nephrotoxic, thus contributing to the decline in renal function. Within the glomerulus and the proximal renal tubules, it has been suggested that the trafficking of proteins contribute to glomerulosclerosis and tubulointerstitial fibrosis respectively (15). Within the glomerulus, the uptake by mesangial cells of excessive amounts of filtered proteins can lead to their overload, proliferation and ultimately, mesangiosclerosis (15). In the tubules, recent in vitro experimentation has shown that the exposure of proximal tubular cells to proteins stimulate their proliferation or apoptosis as well as stimulating their release of pro-inflammatory and pro-fibrotic mediators.

Proteinuria may therefore be an important risk factor for the progression of renal disease. Clinical data suggest that its reduction by either dietary or pharmacological means is beneficial. With that in mind, a prominent role has been attributed to ACE inhibitors which appear to have selective anti-proteinuric effects by the reduction in glomerular capillary hypertension and the glomerular basement membrane permeselectivity (7). It is imperative that we minimize proteinuria if we want to slow the progression of chronic renal failure. Furthermore, as mentioned above, the severity of proteinuria is a guide for our antihypertensive management.

Lipids

Hyper- and dys-lipidaemia are common in patients with CRF. It was suggested many years ago that hyperlipidemia may not only be a consequence of CRF but that it may contribute to its progression (16). Since this hypothesis was put forward it became apparent that there is a correlation between the severity of hyperlipidemia and the rate of decline in renal function (17). More specifically, high circulating levels of apolipoprotein B have been associated with a fast rate of functional decline and poor prognosis (17). Experimental data showed that the reduction of hyperlipidemia by diet or drugs slows the progression of CRF and prevents glomerulosclerosis. Lipids are potentially toxic to glomerular as well as tubular cells, stimulating their death through apoptosis and their release of pro-inflammatory and profibrotic mediators (18).

It therefore makes good clinical sense to aim to reduce and correct the hyperlipidaemia in CRF in order to slow the progression of renal insufficiency and also in order to minimise cardiovascular complications. To date, no published clinical trial has proved this assumption. Those undertaken have been too

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small or with a short follow-up period, thus failing to establish the benefit of reduction of hyperlipidaemia on progression. This should not deter us from treating our hyperlipidaemic patients with CRF, as at least such an intervention may reduce their cardiovascular morbidity and mortality. After all, cardiovascular diseases constitute the major cause of death of patients with endstage renal failure.

Smoking

Smoking has been overlooked until very recently as a risk factor for patients with CRF. It has been known for many years that smoking exacerbates hypertension. More recently, it has been shown that smoking increases proteinuria in diabetic nephropathy. A retrospective clinical observation in patients with CRF suggested a dose-dependent increased risk of endstage renal failure (ESRF) associated with smoking (19). In this study, heavy smokers had an up to ten fold increased risk of ESRF (19). Preliminary observations suggest that stopping smoking reduces the severity of proteinuria in diabetic patients.

As with hyperlipidaemia, the detrimental effects of smoking on health and cardiovascular diseases are well established and should justify recommendation of stopping by patients with CRF, who are at increased cardiovascular risk.

It is clear from the above that the management of patients with progressive CRF should include a tight and optimal control of systemic hypertension. This should be associated with a reduction of proteinuria. In addition, it is imperative to chose anti-hypertensive agents that do not affect the lipid profile adversely. A concomittant reduction in hyperlipidaemia is recommended. For the correction of hypercholesterolaemia, the prescription of an HMG-CoA reductase inhibitor may have the additional advantage of affecting the progression of renal scarring through other pathways involving the inhibition of cellular proliferation and collagen synthesis (20). Finally discontinuation of smoking is advised.

Diet

Experimental evidence suggest that diets high in protein, saturated fat or salt are potentially nephrotoxic. With this in mind, dietary protein, fat and salt restrictions have been proposed to slow the progression of CRF. Clinically, the most popular has been low protein diets. Those seemed to be effective in early clinical trials, however better controlled and randomised studies failed to substantiate such an assumption. In particular the MDRD study failed to show a convincing benefit (21). However, elaborate secondary analysis of this study as well as meta-analyses including the MDRD and other studies suggested a marginal benefit (22, 23).

Recent clinical trials have suggested that dietary supplementation with fish oil (eicosapentaenoic acid) slows the progression IgA nephropathy (24, 25). However, a metanalysis of major studies on fish oil supplementation and progression failed to confirm such a beneficial effect (26).

Dietary salt restriction has been shown to be synergistic with ACE inhibition in reducing proteinuria and blood pressure (27, 28). This would suggest a restriction in salt intake in hypertensive patients and in those treated by ACE inhibitors.

4. Treatment of uraemic complications

Uraemic complications are numerous. These affect the well being and health of patients with CRF. They contribute to a large extent to their symptoms. They need to be addressed early in the course of CRF in order to prevent their progression and the associated morbidity.

Anaemia

It is clear that the majority of patients with CRF suffer from some degree of anaemia. The anaemia of CRF is not without its complications, in particular increased cardiovascular morbidity. It has been well established that anaemic patients with CRF have a higher incidence of left ventricular hypertrophy (LVH) with an associated increase in left ventricular mass index (LVMI) (29). Those parameters are well known risk factors associated with increased morbidity and mortality in patients with endstage renal insufficiency (30). Treatment of renal anaemia aiming for a haemoglobin level of around 10-12g/dl is therefore recommended. Thus attention should be paid to correct any haematologic deficiency, in particular iron deficiency. Early in the course of CRF, oral iron supplementation may

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be sufficient. However, later on oral iron is poorly absorbed and it is recommended that patients receive parental iron therapy (31). Recent clinical trials suggest that there is no advantage in dialysis patients with ischaemic heart disease to aim at haemoglobin (Hb) levels higher than 12g/dl (32). With this in mind, the same targets of 10 to 12 g/dl of Hb should be aimed for in pre-dialysis patients with anaemia. If this is not achieved with iron supplementation, it is advisable to consider recombinant human erythropoietin therapy to improve the anaemia and minimise its cardiovascular complications (33).

Renal osteodystrophy (ROD)

Renal osteodystrophy is multifactorial in aetiology and has a wide range of manifestations. It is known to start early in the course of CRF, thus warranting early intervention to prevent its progression and complications. The prevention of ROD is based on the correction of its precipitating factors namely hyperphosphataemia and hypocalcaemia. For that an early reduction in dietary phosphate intake is advisable. Also early supplementation with calcium and vitamin D may reverse the initial hyperparathyroidism. At this stage serum intact parathyroid (PTH) levels should not exceed 75 pg/ml (34). Treatment with phosphate restriction, calcium and vitamin D supplementation should aim to bring serum PTH levels to this level. Suppression of hyperparathyroidism may also have beneficial repercussions on the cardiovascular system and related morbidity (35). Finally, correction of metabolic acidosis should be sought as it is a major contributor to renal osteodystrophy in patients with CRF.

Malnutrition

Advanced uraemia is often associated with some degree of anorexia, weight loss and undernutrition. Malnutrition in patients with ESRF starting dialysis leads to increased morbidity and shortened life expectancy (36). It is therefore very important to avoid malnutrition in patients with CRF. For this careful dietary advice is necessary and avoidance of zealous protein restrictions is imperative. Also correction of metabolic acidosis should be sought as this is a major contributor to hypercatabolism in patients with CRF.

5. Minimizing the co-morbidity of CRF

Morbidity and mortality in RRT depends to a large extent on co-morbid conditions associated with CRF. Those include diabetes mellitus, cardiovascular disease, chronic obstructive airway diseases and malnutrition.

While many such co-morbid conditions are difficult to prevent, others such as cardiovascular complications and malnutrition are to some extent preventable. The prevention of cardiovascular disease and the associated LVH can be undertaken by paying attention to the early correction of some of its precipitating factors including volume overload, hypertension, anaemia and hyperparathyroidism. Preliminary evidence suggest that the correction of anaemia can reverse the left ventricular hypertrophy of patients with CRF (33). In these high risk patients the control of hyperlipidaemia would also be advantageous, with lower target cholesterol levels (4.8 mmol/l). Similarly, low dose aspirin prophylaxis would be justifiable on the assumption that many of these patients have coronary heart disease by the time they reach ESRF.

Malnutrition is another major determinant of survival in RRT. Patients with low serum albumin levels have significantly higher mortality compared, to others (33). This is why special attention should be paid to the prevention of malnutrition in patients with CRF. This is another reason why overzealous dietary protein restriction should be avoided. When moderate protein restriction is imposed on patients with CRF it should be associated with a high calorie intake (>35 kcal/kg/day). Furthermore, the nutritional status of these patients should be carefully monitored by experienced dietitians.

6. Optimal referral and initiation of renal replacement therapy (RRT)

Delay in the initiation of RRT is associated with shortened survival (37). It is therefore imperative that patients with CRF are started on RRT at an optimal time. Different recommendations have been made suggesting that RRT should be initiated around a creatinine clearance ranging from 10 to 14 ml/min and a GFR between 6 to 10 ml/min (38). For this a close monitoring of patients with advanced renal insufficiency is necessary, with a careful

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preparation of patients both physically (access formation) and psychologically. Here again, a multidisciplinary approach has to be implemented with the involvement of access surgeons, nurse counsellors, social workers and doctors. It is important that the patients' carers and family are involved in their preparation for RRT.

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