Recent advances

General management of end stage renal disease

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The criteria for accepting patients for renal replacement therapy have been widened over the past decade. Morbidity and mortality, however, remain high in people with end stage renal disease, and the medical, social, and economic repercussions of this condition are widespread. This review aims to identify the ways in which primary care physicians or non-specialists can reduce morbidity and mortality in people with end stage renal failure. It will look at recent developments in our understanding and management of the factors that contribute to the increased mortality and morbidity in patients with end stage renal failure. Dialysis and transplant registries around the world report that cardiovascular diseases and infection remain the major causes of death. However, detailed review of the provision and technical aspects of dialysis and transplantation, and the ethical issues associated with selection criteria or withdrawal from renal replacement therapy, are outside the scope of this article.

Summary points

- Cardiovascular disease is the major cause of death in patients with end stage renal disease
- Hypertension, anaemia, dyslipidaemia, hyperparathyroidism, and hyperphosphataemia contribute to the increased mortality and morbidity in end stage renal disease and should be managed appropriately
- Early dietary review is necessary to maintain a good nutritional status
- Adequate dialysis is vital for a favourable outcome; long, slow dialysis is associated with improved survival
- Good management calls for the timely referral of patients to nephrology services (creatinine concentration >250 µmol/l) and close collaboration between these and primary care

Methods

Recent articles (1990-6) on cardiovascular disorders, anaemia, hyperparathyroidism, and nutrition related to end stage renal disease were identified from a search of Medline. Key words used included chronic renal disease, anaemia, erythropoietin, ischaemic heart disease, cardiac disease, lipids and lipoproteins, hyperparathyroidism, calcium, phosphate, and nutrition. Because few large clinical trials on the treatment of end stage renal disease were found, this review is also based on observational studies and on review articles covering pathophysiology, clinical management, and reported best clinical practice from leading nephrologists.

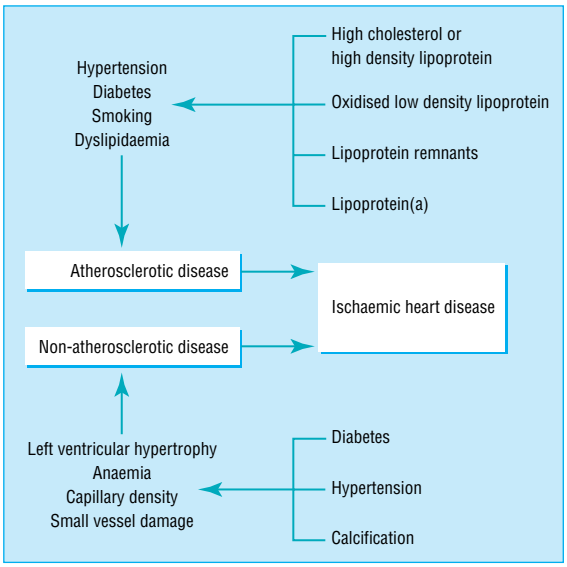
Cardiovascular disease

Cardiac disease is the major cause of death in patients with end stage renal disease. It accounts for about 40% of deaths in most large registries, and the high mortality persists after renal transplantation.[1 2] In patients receiving any form of renal replacement therapy, the relative risk of death from myocardial ischaemia is five times greater than in the normal population.[3] Several factors contribute to the development of ischaemic heart disease and congestive heart failure in chronic renal failure: volume overload (anaemia); pressure overload (hypertension); arteriovenous fistulas; dyslipoproteinaemia; lipid abnormalities; myocardial cell injury related to uraemia (impaired energy production, hyperparathyroidism, metastatic calcification); and endothelial cell dysfunction (figure).[4]

Echocardiographic abnormalities including left ventricular hypertrophy, left ventricular dilation, and systolic dysfunction are common in patients with end stage renal disease and are associated with increased mortality from cardiovascular diseases even in patients with no symptoms.[5 6] In a large prospective study, Foley and colleagues found that left ventricular cavity volume and left ventricular mass were predictive of death from cardiovascular causes in patients with renal failure.[6]

Patients without serious coronary atherosclerosis may develop symptoms of ischaemia related to a reduction in coronary vasodilatory reserve, altered myocardial oxygen utilisation, and uraemic intramyocardial fibrosis (reviewed in Parfrey et al[4]). Anaemia creates a hyperdynamic circulatory state and reduces the oxygen delivered to the myocardium. This situation is worsened if the patient has an arteriovenous fistula.

Secondary hyperparathyroidism is important in the development of impaired energy production and



The pathogenesis of ischaemic heart disease in chronic uraemia. Reprinted with permission from Silberg et al[5]

utilisation in the myocardium, and it affects myocardial contractility. Raised concentrations of calcium phosphate product may cause vascular calcification, which contributes to the myocardial ischaemia.[7]

Management

Correction of the pressure overload (hypertension) and volume overload (anaemia, together with excess salt and water retention) are most important in management. Adequate dialysis is essential. Long, slow (8 hours per session) haemodialysis to maintain an appropriate "dry" weight (no fluid retention) and a normal blood pressure without the need for antihypertensive treatment was associated with a reduction in mortality of a half to a third.[8 9]

Treatment of anaemia with recombinant human erythropoietin reduces the heart rate, cardiac contractility, and left ventricular hypertrophy.[10 11] These effects may delay the progression of cardiac disease in patients with end stage renal disease, but the outcome of long term studies is awaited. The efficacy of drug treatment for heart failure or ischaemic heart disease in patients with renal failure has not been clearly defined in any large prospective studies. Studies to date have used surrogate end points. However, it is probably appropriate to extrapolate results from clinical trials of angiotensin converting enzyme inhibiting drugs in patients with impaired cardiac function but no renal failure.[4] Caution is required in titrating the appropriate dose of cardiac drugs in patients with end stage renal failure.

Cardiovascular disease in renal failure—key points

- Cardiovascular disease is a major cause of death
- Its causes are multifactorial—volume and pressure overload, lipid abnormalities, anaemia, myocardial dysfunction
- Echocardiographic abnormalities of left ventricular function predict outcome
- Control of hypertension, anaemia, lipids, and hyperparathyroidism is essential
- Long slow haemodialysis is associated with better survival

Lipid and lipoprotein abnormalities

Lipoprotein metabolism is altered in most patients with renal insufficiency, but this does not always lead to hyperlipidaemia. Dyslipidaemia develops early in renal failure. It becomes more pronounced as the renal disease progresses because of an imbalance between lipoprotein synthesis and degradation.[12 13] Clinical evidence suggests that reduced catabolism of lipoproteins rich in triglycerides is an early fundamental disturbance of lipoprotein metabolism in renal disease that is not necessarily linked to increased plasma concentrations of triglycerides.[14]

After renal transplantation, hypercholesterolaemia is the major lipid abnormality. It responds to treatment with hydroxymethyl glutaryl coenzyme A reductase inhibiting drugs, but caution is required as there may be an adverse interaction between these drugs and cyclosporin.

Management

Changing the diet is difficult and has little success. Studies of lipid lowering treatment in patients with end stage renal disease have been small, and the efficacy of treatment has been determined in relation to surrogate end points. A recent meta-analysis of lipid lowering treatments in renal disease showed that only hydroxymethyl glutaryl coenzyme A reductase inhibiting drugs and fibrates had a consistent and substantial effect in renal failure.[14 15] Fibrates are associated with an increased risk of myositis and rhabdomyolysis in renal failure, and dose reduction is essential. Hydroxymethyl glutaryl coenzyme A reductase inhibiting drugs may therefore be better in these patients, particularly if cholesterol is raised. To date there are no long term studies which show that the development of cardiovascular disease in end stage renal disease is delayed or prevented by treatment to lower lipids.

Patients whose risk of vascular disease is high may be considered for empirical treatment to lower lipids, modified for altered drug handling in renal failure.[16] Treatment should be considered when the patient's glomerular filtration rate is less than 50 ml/min, depending on their risk profile.

Anaemia

Anaemia causes many of the symptoms experienced by patients with end stage renal disease. Recombinant human erythropoietin has been the major advance in

Lipid abnormalities in renal failure—key points

- Dyslipidaemia occurs early in renal failure
- Reduced catabolism of lipoproteins rich in triglycerides and increased apolipoprotein B increase the atherogenic potential
- Empirical treatment to lower lipids is probably indicated in high risk patients
- Risk of myositis and rhabdomyolysis is increased if fibrate treatment is given

Anaemia in renal failure—key points

- Anaemia is a major cause of uraemic symptoms
- Recombinant human erythropoietin treatment is a major advance which has produced substantial improvements in clinical wellbeing, myocardial function, and lipid profiles
- Unrecognised iron deficiency reduces considerably the effectiveness of recombinant human erythropoietin: avoid unnecessary blood tests

treatment in the past decade. It has improved patients' quality of life by increasing their energy and exercise tolerance, reducing fatigue, increasing the appetite, and reducing needs for blood transfusion.[16] Direct improvement in myocardial function has been well documented, and a better lipid profile, with appreciable reductions in total serum cholesterol, triglycerides, and apolipoprotein B100, has been shown.[10 11 17] Treatment with recombinant human erythropoietin may lead to a reduction in cardiovascular mortality associated with end stage renal disease.

Management

Early recognition of the correctable causes of treatment failure is needed to prevent hyporesponsiveness to recombinant human erythropoietin.[18] Unrecognised mild to moderate iron deficiency, either at the start of treatment or secondary to better utilisation of body iron stores, is common. Depletion of iron stores may be caused by blood loss resulting from too many blood tests, haemodialysis, or occult gastrointestinal bleeding.

The diagnosis of iron deficiency can be difficult as serum ferritin and transferrin saturation may not reflect the availability of marrow iron. The percentage of hypochromic cells (>10%) and the concentration of transferrin receptors in the blood may be more reliable markers.[19] Oral or, more often, parental iron supplementation is usually necessary to restore the response to recombinant human erythropoietin. Infection or inflammation is associated with increased cytokine production, which suppresses erythrocyte stem cell proliferation.[19] In addition, iron stores may be less available because ferritin concentrations are high as a result of the acute inflammatory response.[20] Correction of hyperparathyroidism is often followed by an improvement in the responsiveness to recombinant human erythropoietin.[20]

Nutrition

Protein energy malnutrition is associated with increased morbidity and mortality in end stage renal disease. Malnutrition is not limited to a specific stage of renal failure. There is good evidence that the nutritional status of patients before dialysis affects their long term outcome after renal replacement therapy has started. A low serum albumin concentration along with a reduced muscle mass, low transferrin concentration, and decreased cholesterol at the start of renal replacement therapy correlate with a poor outcome.[20 21] Contributory factors include the anorexia of renal failure, metabolic acidosis, insulin resistance, hyperparathyroidism, and resistance to the anabolic effects of growth hormone (reviewed in Ikrizler and Hakim[21]) as well as associated comorbidity such as diabetes.

Dialysis is a catabolic process and contributes to the malnutrition. Increasing the length of dialysis leads to a substantial improvement in the rate at which protein is catabolised and a reduction in the standardised mortality rate.[21 22] In patients undergoing continuous ambulatory peritoneal dialysis, the loss of protein and water soluble vitamins in the dialysis effluent can be high and may contribute to their impaired nutritional status.

Management

It is important to recognise malnutrition early on. An adequate intake of calories is essential since declining renal function is usually associated with a spontaneous reduction in dietary protein and energy intake. The patient should be referred to the renal service at an early stage and continuing collaboration between the general practitioner and the service is important. Timely renal replacement therapy may reduce malnutrition and improve the patient's long term outcome.[23]

To meet the increased demands of dialysis, patients should have an adequate energy intake with modification of protein intake. The patient's dietary status must be reviewed regularly. Any changes advised should take account of the patients' cultural and socioeconomic background as this is an important determinant of their eating habits. Control of lipids and carbohydrate is as important as control of protein, fluids, and electrolytes.

Nutrition in renal failure—key points

- A progressive decline in renal function is accompanied by a spontaneous reduction of appetite
- Early dietary review is important in maintaining an adequate intake of energy
- Adequate dialysis is essential for good nutrition
- Protein energy malnutrition is associated with a poor outcome
- Dietary regulation of phosphate is essential

Hyperparathyroidism and hyperphosphataemia

The kidneys play an important part in the metabolism of parathyroid hormone and vitamin D_3. Hyperplasia of the parathyroid glands, which occurs early in end stage renal disease, results in increased concentrations of parathyroid hormone. Reduced production of vitamin D_3 and retention of phosphate make a major contribution to the development of secondary hyperparathyroidism. Parathyroid hormone and vitamin D_3 affect calcium homeostasis directly, and each has regulatory effects on the other (reviewed in references 24-26).

Management

Good control of the concentration of serum phosphate is essential and should be part of dietary management. Controlled dietary intake of protein (0.8-1.0 g/kg/day) should be combined with oral calcium carbonate or calcium acetate (1.5 g taken with

Hyperparathyroidism in renal failure

- Hyperparathyroidism occurs early in renal failure
- Hyperphosphataemia has a direct regulatory effect on the parathyroid hormone concentration; treatment to control this is essential and should start when the glomerular filtration rate is below 50 ml/min
- Intestinal absorption of phosphate from the diet can be reduced by oral calcium carbonate or calcium acetate
- Once the phosphate concentration has been controlled, parathyroid hormone synthesis may be suppressed by treatment with intermittent high dose vitamin D_3

meals), which bind to phosphate and regulate its absorption from the intestine. Control of hyperphosphataemia should be introduced early in end stage renal disease, when the glomerular filtration rate is below 50 ml/min. Adequate dialysis treatment will reduce hyperphosphataemia and lower the concentration of parathyroid hormone. Once the phosphate concentration is controlled, inhibition of parathyroid hormone synthesis and release will be improved by giving vitamin D_3.[25 26] Caution is necessary where vitamin D_3 is given to patients with hyperphosphataemia as raised concentrations of calcium phosphate product will lead to metastatic calcification. There is good evidence that intermittent high dose vitamin D_3 is more effective in suppressing synthesis of parathyroid hormone, but whether it should be given orally or intravenously is uncertain.[25 26]

Management of the progression of renal failure

Integrated care by the primary care physician and nephrologist from an early stage is vital as the management of patients with renal failure is a dynamic process and does not just involve monitoring plasma concentrations of creatinine and urea.[27] The important points to be remembered in the management of these patients are listed below.

Patients with end stage renal disease—points to consider

- The rate of progression of renal failure is variable.
- Patients should not be selected for renal replacement therapy on the basis of age alone.
- Important coexistent disorders mean that patients should be reviewed early, before uraemia occurs.
- High risk patients (creatine concentration <300 µmol/l) must be assessed early.
- Delayed referral and emergency dialysis result in considerable morbidity and mortality, with increased social and financial costs to the patient and the community.[27 28]
- Early referral enables the nephrology service and primary care physician to discuss fully the management of the patient with renal failure and to define the goals of conservative management and the appropriateness of renal replacement therapy as the renal failure progresses.

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Endpiece

Badly needed

Statistics are like old medical journals or like revolvers in a newly opened mining district. Most men rarely use them and find it troublesome to preserve them for easy access. However, when they do want them, they want them badly.

John Shaw Billings, medical bibliographer, 1889, quoted in *The Best of Medical Humour* (Howard J Bennett, ed. Philadelphia: Hanley and Belfus, 1997)