

Optimal predialysis care

Yvo W. J. Sijpkens, Noeleen C. Berkhout-Byrne and Ton J. Rabelink

Department of Nephrology, Leiden University Medical Center, Leiden, The Netherlands

Abstract

Management of severe chronic kidney disease (CKD) involves dealing with medical, nursing and psychosocial problems and therefore warrants support from a multidisciplinary team. In the Kidney Disease Outcomes Quality Initiative (KDOQI) classification system of CKD, preparation for renal replacement therapy has been recommended in CKD stage 4, characterized by a reduction in the estimated glomerular filtration rate (GFR) of <30 ml/min. In this article we share our approach to perfecting predialysis care. Tools are given to make an estimation of the progression of kidney disease. Also the prevention and treatment of metabolic complications and cardiovascular risk management are summarized. Finally, the possibilities for dialysis but even more important, aiming for pre-emptive transplantation, are being discussed. Using a multidisciplinary integrated care approach predialysis care has come of age.

Keywords: chronic kidney disease; predialysis; pre-emptive transplantation

Introduction

Patients approaching kidney failure need optimized predialysis care to improve their dialysis and transplantation outcomes [1]. Particularly, patients with advanced chronic kidney disease (CKD) have an increased cardiovascular risk that needs to be addressed in the earlier stages. The focus of 'late CKD' care has been expanded from planning of dialysis to all themes of the CKD action plan, including estimating and retarding progressive disease, preventing and treating complications, cardiovascular risk management, and, when possible, promoting pre-emptive transplantation. Successful implementation of all aspects of the CKD action plan demands integrated care with special attention given to intensive patient education, cognitive behaviour therapy, improvement of adherence to target-driven lifestyle modifications, and pharmacotherapy. Management of severe CKD requires a well-organized patient-focused multidisciplinary team and early referral. Therefore, a nurse practitioner (NP)

led, physician supervised predialysis clinic was established at the Department of Nephrology, Leiden University Medical Center (LUMC) in 2006. The appointment of the NP was due to a joint decision made by the medical and nursing staff leadership at our department of nephrology. Incentives in this decision-making process were motivated by recognition of predialysis care as an integral part of the chain of care for patients with CKD. Preparation for renal replacement therapy (RRT) involves dealing with medical, nursing and psychosocial problems and therefore warrants support from a multidisciplinary team. The NP is a care coordinator and as such responsible for planning the course of treatment that each patient should follow. Referring physicians remain medically responsible and continue to see their patients in alternating visits with the NP. Measurement of outcome parameters has been introduced for evaluation and improvement of the management of CKD patients. In this article we share our approach to perfecting predialysis care.

Definition

The term 'predialysis' has not been officially defined in guidelines. Most renal physicians will initiate predialysis care in patients with a creatinine clearance of <15–20 ml/min, decline in renal function and an expected start of dialysis within 6–12 months. However, in the Kidney Disease Outcomes Quality Initiative (KDOQI) definition and classification system of CKD, preparation for RRT has been recommended in CKD stage 4, characterized by a reduction in the estimated glomerular filtration rate (GFR) of <30 ml/min. Because of the broad variation in decline in renal function, predialysis care in our centre has been restricted to patients with a possible need for RRT in the future. We suggest early referral to our predialysis outpatient clinic to implement the CKD action plan and in particular to promote pre-emptive transplantation, which may need more than one year of preparation. In appreciation of expanded care, some centres advocate alternative terms such as 'late CKD' or 'kidney failure' clinic instead of predialysis.

Estimating and slowing the progression of kidney disease

Preservation of renal function is an important goal of the CKD action plan, even in patients with severe renal

Correspondence and offprint requests to: Y. W. J. Sijpkens, Department of Nephrology, C3P, Leiden University Medical Center, Box 9600, 2300 RC Leiden, The Netherlands. Tel: +003-171-5262169; Fax: +003-171-5266868; E-mail: Y.W.J.Sijpkens@lumc.nl

Table 1. Progression factors: treatment and targets

Factor	Target	Treatment
Hypertension	Systolic blood pressure <130 mmHg	Salt restriction, exercise, RAAS-blockade, diuretics, calcium entry blocker
Proteinuria	24 h protein <1 g/day	Salt and protein restriction, RAAS-blockade, diuretics
Hyperlipidaemia	LDL-cholesterol <2.5 mmol/l	Saturated and trans-fat restriction, statine, ezetrol
Obesity	Waist circumference <94 cm (♂), <80 cm (♀)	Calory and mono-disaccharide restriction, increased physical activity, increasing muscle mass
Smoking	0 cigarettes	Ask, advise, assess, assist, arrange
Hyperglycaemia	HbA _{1c} <7%	Weight reduction, pioglitazon, insulin
Hyperphosphataemia	Phosphate <1.2 mmol/l	Phosphate restriction, phosphate binders
Hyperuricaemia	Uric acid <0.35 mmol/l	Purine and fructose restriction, allopurinol

dysfunction. There is much diversity in the decline of renal function among patients with CKD stage 4, which depends primarily on the original disease and the presence of progression factors. At this stage, diabetic nephropathy, glomerular and polycystic diseases are characterized by more rapid deterioration compared to patients with nephrosclerosis. Young, male or black patients also have the tendency to lose renal function at a faster rate. Progression factors are modifiable risk factors that are related to a faster decline in renal function, independent of the background of the disease. Treatment of each independent factor should be able to prevent or retard progression. This bidirectional relationship has been demonstrated for hypertension, proteinuria, hyperlipidaemia, smoking, obesity and hyperglycaemia [2–5]. Hyperphosphataemia and hyperuricaemia are emerging progression factors that need more randomized controlled trials for confirmation [6,7]. Besides pharmacotherapy, dietary counselling for appropriate restriction in salt, protein (red meat), saturated and trans fatty acids, nicotine, advanced glycation end products, phosphate (additives), purines and fructose is an important but often underappreciated tool for renoprotection [8,9].

Table 1 summarizes the measures that we find useful to postpone or even prevent the need for dialysis. Persistent adherence might also play a role in maintaining residual renal function once on dialysis [10]. Moreover, this multifactorial strategy is good not only for the kidney but also for the cardiovascular system.

Prevention and treatment of metabolic complications

In CKD stages 4 and 5, metabolic complications are prevalent and clinically present. Severe anaemia may contribute to left ventricular failure, cerebrovascular accidents and lower quality of life. Recent studies have consistently shown that aiming for normal haemoglobin levels may have detrimental effects; therefore, haemoglobin targets are set at the narrow range of 6.8–7.5 mmol/l [11]. Chronic kidney disease–mineral bone disorder (CKD–MBD) is a significant complication during the course of CKD. CKD–MBD is a systemic disorder manifested by abnormalities in bone and mineral metabolism and extraskeletal calcification [12]. The term renal osteodystrophy is currently used to define the bone pathology associated with kidney disease. CKD–MBD can result in fractures, bone pain, vascular cal-

cification and cardiovascular disease, and, ultimately, mortality. Prevention and treatment of CKD–MBD is therefore essential in the management of patients with CKD. Low bone turnover might be the default of CKD with hyperparathyroidism as adaptation mechanism [13]. The parathyroid glands grow in response to persistent hypocalcaemia, hyperphosphataemia, high levels of FGF23 and vitamin D deficiency. Late CKD is characterized by a high prevalence of hyperphosphataemia and both calcidiol and calcitriol deficiency [14]. Early vitamin D substitution by cholecalciferol and phosphate control is important to prevent hyperparathyroidism [15]. Alfacalcidol or paricalcitol might be needed to reduce high PTH levels [16]. Cinacalcet is not a standard recommended in the predialysis patient because it inhibits phosphate excretion. Long-standing uncontrolled hyperparathyroidism may still warrant parathyroidectomy, especially if large adenomatous parathyroid glands are documented.

Patients with advanced CKD develop metabolic acidosis, which is strongly related to inflammation and low albumin levels [17]. Buffering from bone and muscle contributes to CKD–MBD and weakness. Protein restriction and use of sodium bicarbonate or calcium carbonate should maintain bicarbonate levels [18]. Potassium excretion is relatively preserved at low GFR [19]. Hyperkalaemia is the result of acidosis, use of RAAS-blockers or NSAIDs. Restriction of potassium, resonium, sodium bicarbonate and diuretics might be needed in some individuals to prevent high potassium levels.

Hyperuricaemia is often present and associated with an increased prevalence of gouty arthritis and tophi in CKD. It also acts as an independent renal progression and cardiovascular risk factor. High uric acid levels induce vasoconstriction, inflammation and intrarenal generation of angiotensin II, all of which promote hypertension [20]. Restriction of purines and fructose and allopurinol are useful means of reducing uric acid levels, and RAAS blockade may offer tissue protection to some of the detrimental effects of uric acid.

Patients with advanced CKD have an increased risk of drug-related side effects. Dose adjustment is mandatory for some renal cleared drugs such as digoxin, metformin, sotalol and valaciclovir. Information on drug dosing is available at <http://www.kdp-baptist.louisville.edu/renalbook/>. Patients with GFR <30 ml/min, especially those with diabetic nephropathy or multiple myeloma, are at increased risk of contrast nephropathy, which should be actively prevented by sodium chloride and acetylcysteine [21].

Table 2. Metabolic complications: treatment and targets

Complication	Target	Treatment
Anaemia	Haemoglobin 6.8–7.5 mmol/l, ferritin 100–500 µg/l, transferrin saturation (20–50%)	Darbepoëtime/epoëtime β, ferrofumarate/sulfate, vitamin C
Hypovitaminosis D	25(OH)D >75 nmol/l	Cholecalciferol
Hypocalcaemia	Calcium 2.1–2.4 mmol/l	Calcium carbonate/acetate, alfacalcidol, phosphate reduction
Hyperphosphataemia	Phosphate <1.2 mmol/l	Phosphate restriction, phosphate binders
Hyperparathyroidism	PTH 7–12 pmol/l	Phosphate reduction, cholecalciferol, alfacalcidol, paricalcitol
Metabolic acidosis	Bicarbonate >22 mmol/l	Protein restriction, sodium bicarbonate
Hyperkalaemia	Potassium 3.5–5.5 mmol/l	Potassium restriction, diuretics, resonium
Hyperuricaemia, gout	Uric acid <0.35 mmol/l	Fructose and purine restriction, allopurinol
Cardiovascular disease	LDL-cholesterol <2.5 mmol/l	Statin, aspirin

Magnetic resonance imaging using linear gadolinium contrast agents has been associated with severe nephrogenic systemic fibrosis and should be avoided in (pre)dialysis patients [22].

The uraemic syndrome consists of pruritis, polyneuropathy, restless legs, anorexia, nausea and pericarditis. These complaints could be partially prevented by a protein-restricted diet but are usually signs to start dialysis.

For successful prevention and treatment of the metabolic complications of severe CKD, we have implemented a systematic, target driven approach (Table 2).

Cardiovascular risk management

Mortality and morbidity due to cardiovascular disease are substantial in CKD stage 4 and 5 patients, even before starting dialysis [23]. Patients have a high prevalence of cardiovascular comorbidity or subclinical damage such as left ventricular hypertrophy and calcifications at initiation of dialysis. Traditional risk factors including older age, male gender, family history, hypertension, diabetes mellitus, dyslipidaemia and physical inactivity are common among CKD patients. Moreover, blood pressure, cholesterol and glucose control are often suboptimal. In addition, many factors related to the uraemic state contribute to the high risk of cardiovascular disease. These include anaemia, vitamin D deficiency, positive salt balance, acidosis, hyperphosphataemia, hyperparathyroidism, hyperuricaemia, accumulation of asymmetrical dimethyl arginine (ADMA), advanced glycation end products (AGEs) and triglycerides, and mononuclear infiltration of the diseased kidney itself. All these factors culminate in a syndrome of chronic systemic inflammation due to oxidative stress and endothelial dysfunction, which might be recognized by high (hs)CRP levels, high fasting glucose and triglyceride levels, and anorexia, weight loss and hypoalbuminaemia in more advanced stages [24]. Inflammation may contribute to atherosclerosis, arteriosclerosis, vascular calcifications, insulin resistance and low turnover bone disease [25]. Therefore, to prevent cardiovascular disease in CKD patients, all input factors of inflammation should be addressed in order to achieve predefined target levels. Inhibitors of the renin angiotensin aldosterone system, statins and aspirin are advocated to reduce the

inflammatory response to injury. Independent of blood pressure, LDL cholesterol, and glucose control, exercise and a diet restricted in salt, trans- and saturated fatty acids, phosphate, fructose and AGEs are recommended with the aid of a dietician. We have adopted this multifactorial approach to improve the cardiovascular prognosis awaiting confirmation in prospective studies [26].

Aiming for pre-emptive transplantation

Restoring normal renal function is the best way to contain the metabolic and cardiovascular burden of CKD and should be given the highest priority in predialysis care. Long waiting lists for cadaver kidney transplantation and the success of the living-related donation kidney transplant programme have been motivators to establish pre-emptive living (un)related donation programmes. So far, the avoidance of a period on dialysis has a significantly positive impact on the morbidity and mortality of patients with kidney failure [27]. With the cost of dialysis treatment per annum at €60 000 and the cost of transplantation after the first year at €14 000, establishing pre-emptive transplantation in a large number of patients is very cost-effective. Improvement in quality of life for patients following transplantation is more important. This is due to an overall improvement in a feeling of well being, more energy, improved bone metabolism and neuropathy, return of fertility and sexual function, and reduction of dietary and fluid restrictions. During the initial NP predialysis consultation at the LUMC, the possibility of pre-emptive transplantation is considered. Patients are encouraged to discuss this option with family members and friends. Many patients find this difficult and they feel inhibited about asking someone, however close, to donate. Strategies and tips are given on how to broach the subject without actually *asking* for a kidney. Booklets about transplantation are supplied and the transplant coordinator's telephone number is given. Frequently, tentative suggestions lead to actual donation. Once a prospective donor has intimated interest in donation, appointments are set up to explain in detail the donation procedure. Coordination of this procedure is performed by the transplant coordinator while the preparation of the receiver is in the hands of the NP and nephrologist. Early referral to the predialysis clinic is important to complete the procedure before

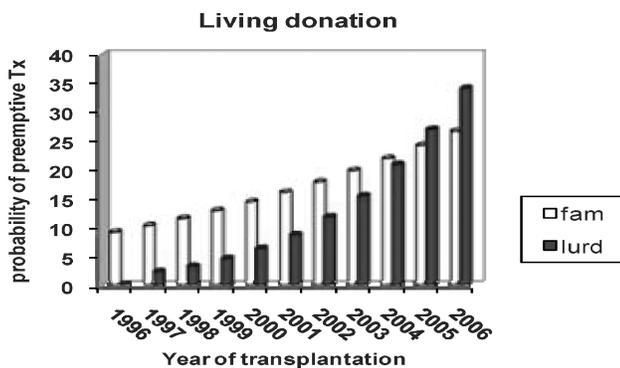


Fig. 1. Sharp increase in the probability of achieving pre-emptive transplantation at the Leiden University Medical Center (fam: living related transplantation; LURD: living unrelated renal donation).

dialysis is required. We achieved a sharp increase in pre-emptive (un)related donor transplantation (Figure 1).

Preparation for dialysis modalities

When pre-emptive transplantation is not an option, preparation for dialysis is started. Visits to the nephrology department are alternated between the NP and the nephrologists, with the frequency of visits depending on the symptoms of CKD, results of blood and urine tests, education and psychosocial requirements of patients, and at the discretion of the NP. The initial NP consultation is characterized by its counselling and structured education-orientated content. The NP assesses the level of kidney disease-related knowledge and, with this in mind, tailors the education programme to suit the needs of the individual patient. Depending on the reaction and emotional state of well-being of the patient, choices of RRT are introduced (Figure 2). Using a picture flap-over, haemodialysis (HD) and peritoneal dialysis (PD) are broadly explained. An information booklet (Zorgmap, Dutch National kidney foundation) is given to each patient. In collaboration with other members of the multidisciplinary team an education programme is initiated. Experienced dialysis nurses explain in detail each modality, the dialysis unit is visited and the patient is given the opportunity to speak to a dialysis patient. The social worker is consulted when necessary. During each visit, time is allocated to answer specific questions and to check that information has been understood. Education is furthered through thematic group sessions with other patients, including those already on dialysis.

Where there is a preference for HD, vessel mapping is performed so that timely access can be created. Venous preservation in the upper extremities is explained and from this point on patients are instructed to use the nondominant arm only for blood sampling. Timely access creation and maturation is of particular importance, as it is well known that vascular access complications are one of the leading causes for hospitalization and morbidity in patients with renal failure [28].

Managing each individual's care collaboratively, the multidisciplinary meeting discusses the best suitable option for each patient, with attention focused on medical and psy-

chosocial contraindications to a given therapy. Patient preference for a particular modality is considered and patient involvement in the decision-making process is considered essential as this will influence the quality of life on dialysis.

Integrated predialysis care

Many patients experience the initiation into the predialysis phase as stressful. Illness and coping strategies, which have currently been successful, are no longer effective for most patients. The long foreseen implications of kidney disease become immediate and many patients experience feelings of helplessness and hopelessness. It is at this stage that integrated care becomes essential if the patient is going to meet the challenges of CKD (Figure 3).

An integrated care model seeks to reverse, halt or at least minimize the underlying pathophysiological processes of the disease (restorative care) while maximizing disease control and quality of life (supportive care and palliative care). CKD and kidney failure are well suited to this approach. Dialysis and transplantation do not cure patients. Both therapies can be considered as life-extending therapies whereby life is prolonged and the symptoms of kidney failure are reduced enabling patients to live longer despite their disease [29].

Working in a multidisciplinary team, integrated care draws on the expertise of each professional. Complementary to each other and concomitantly, they combat the onerous effects of kidney disease. Shared responsibility and synergy within the team are fundamental. Working from this synergy the boundaries between the disciplines fade allowing engagement not only within the team but also most importantly with the patient.

The objectives of the predialysis team include promotion of self-management and management of stress. By provision of comprehensive information and education, patients learn to understand their illness enabling them to make well-considered decisions about their therapy. In our multicultural society, acknowledgement of cultural influences and social support systems is important. To accomplish better results, supportive care must be given just as much priority as diagnostics and treatment. The measure of kidney function determines the intensity of multidisciplinary care. During visits to the dietician, the importance of salt, protein and phosphate restriction is discussed. Patients are instructed in the use of phosphate binders and a cookery book is issued. Visits to the social worker are planned when requested or deemed necessary. Information about health insurance coverage, social security benefits and possible changes within the home to facilitate dialysis is given. During consultations with the nephrologist and the NP, attention is focused on combating the symptoms of uraemia, results of blood and urine tests and medication. Independent of kidney function, each patient, in conjunction with diagnostics and treatment, is screened and treated for risk factors in order to achieve a reduction in comorbidity and mortality. In addition, the NP discusses the importance of adherence to prescribed medication, a healthy diet, daily exercise and encourages patients to stop smoking. Preparation for kidney transplantation is completed ensuring inclusion of patients

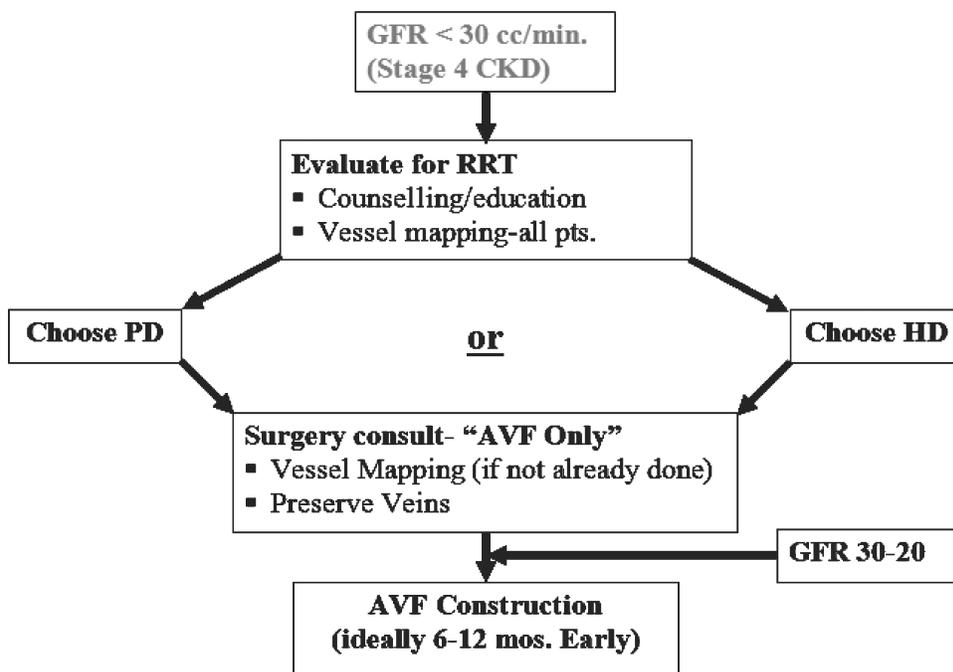


Fig. 2. Early preparation for dialysis. AVF: arteriovenous fistula.

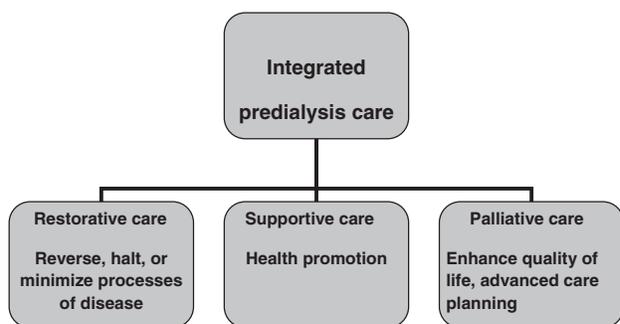


Fig. 3. Integrated predialysis care concept: administration of care that promotes self-management. By utilization of the intrinsic strengths of each individual, patients are empowered to face the challenges of their illness.

on the (cadaver) waiting list from the first day of dialysis. Care is focused on supporting the CKD patient in coping with existential psychological and spiritual stress, and in finding a renewed balance in life.

Early referral

To implement all the aspects of the CKD action plan timely referral is mandatory. Therefore, patients with signs and symptoms of kidney disease must be recognized and should be sent to an internist/nephrologist at an early stage of the disease. Referral to our specialized predialysis clinic is indicated in patients with a clearance of <30 ml/min, progressive decline in renal function and an anticipated need for RRT. Predialysis nephrological care duration can be defined as the period between specialized nephrological care

and the first day of dialysis. Long duration nephrological care can significantly reduce the prevalence of cardiovascular morbidity in kidney failure and the survival rate on dialysis can be positively influenced [30]. The definition of ‘late referral’ varies in the medical literature but in general referral <1–4 months prior to the initiation of RRT is accepted. Unfortunately, one-third of the patients are referred to the nephrologist too late—a figure that has not improved in recent years [31]. Timely referral is necessary to treat progression factors and the related comorbidities [32]. It has been demonstrated that among patients referred late significantly fewer patients undergo transplantation in the second and following years on dialysis and that there is a significant increase in mortality during the first year of dialysis. Early referral to a nephrologist influences the progression of CKD to kidney failure. Moreover, nephrological care possibly influences the reduction of early mortality. The detrimental effects of late referral develop within the first few months of RRT. Late referral is an independent risk factor for early mortality on dialysis [33]. With mounting evidence in favour of early referral, nurse-driven predialysis clinics could improve patient outcomes. The objectives of an early referral strategy are not merely to prepare patients for RRT but to continue to treat the complications and risk factors associated with CKD and to halt progression of the disease. Therefore, we recommend referral to our predialysis clinic at least 1 year prior to the need for RRT.

Outcome parameters

Following the implementation of the predialysis clinic in LUMC, objective assessment was desired. Parameters such as GFR on initiation of predialysis care, choice of RRT

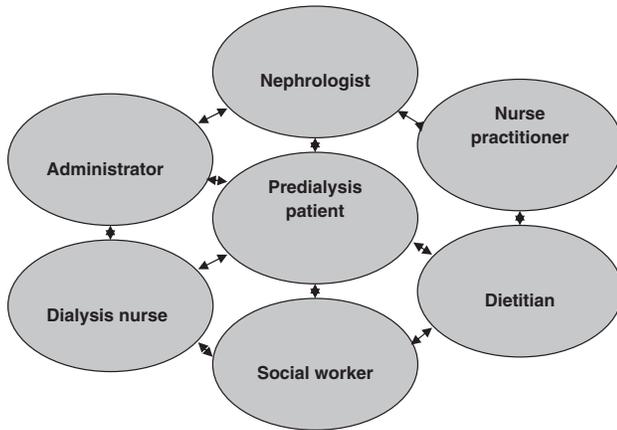


Fig. 4. Multidisciplinary approach. Our patient is central to all our actions. Psychological, social and spiritual guidance goes hand in hand with medical care. The multidisciplinary team supports the patient on his road to acceptance and at all times endeavours to promote self-management.

and blood test results were recorded. In 2006, 69 patients were referred to the multidisciplinary predialysis clinic. Patient characteristics were as follows: 49 (71.0%) male and 20 female (29.0%); age ranged from 56.3 ± 15.9 years; the MDRD clearance was 15.8 ± 6.3 ml/min (average \pm SD). Within 1 year of predialysis care, 28% of the patients chose pre-emptive transplantation, 38% PD and 10% haemodialysis. In the others, 7% had not decided yet, 7% refused further RRT, 3% died and 7% was referred to a hospital in their region.

We recorded lab results twice a year at prespecified dates to evaluate the achievement of KDOQI targets (Figure 5). In 82.9% of the patients, haemoglobin was >6.8 mmol/l. Calcium and phosphate levels were at target in 61.4% and 78.1%, respectively. However, optimal PTH levels were difficult to maintain within the target range. This was reached in only 15.7% of the patients.

Conclusions

Predialysis care has come of age. The predialysis period has been broadened to embrace CKD stage 4 and should be started in patients showing an MDRD clearance of >30 ml/min, decline in renal function and a foreseeable need for renal replacement therapy. In these patients, all parts of the CKD action plan need to be addressed. Renoprotection is achieved by strict treatment of progression factors, directed to prespecified target levels. Besides reduction in blood pressure, proteinuria and HbA1c, other measures include weight loss in the presence of obesity, quitting smoking and statins to control LDL-cholesterol. Lowering uric acid and phosphate levels may also provide better results. In advanced CKD, treatment of complications is likely to be intensified and is directed at achieving target levels of haemoglobin, calcidiol, calcium, phosphate and PTH. Potassium and bicarbonate levels should be routinely checked and normalized by additional measures. Patients with severe CKD are at risk of premature death before reaching the dialysis phase [34]. Use of statins, aspirin

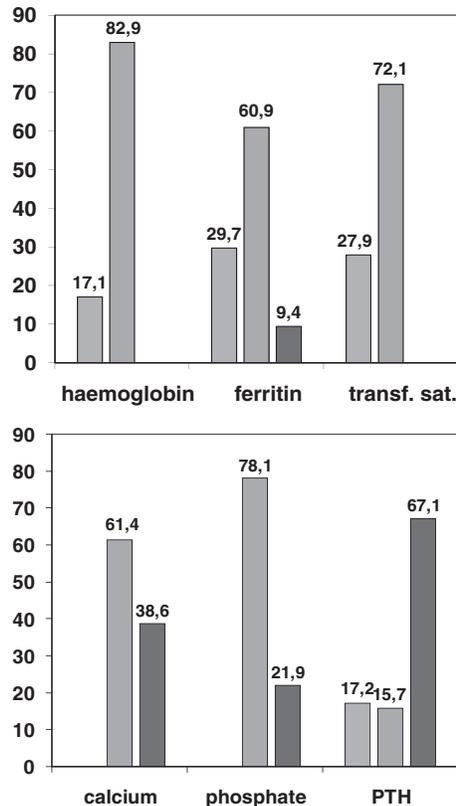


Fig. 5. KDOQI targets a: haemoglobin: >6.8 mmol/l; ferritin: 100–500 μ g/l; transferrin saturation: $>20\%$; b: calcium: <2.4 mmol/l; phosphate: <1.5 mmol/l; PTH: 7–12 pmol/l.

and more exercise is likely to decrease cardiovascular risk. Restoration of renal function by pre-emptive transplantation is the best way to combat the metabolic and cardiovascular burden of CKD. Preparation for transplantation can be time-consuming and warrants starting predialysis care at an earlier phase. In the absence of a living donor, preparation for dialysis includes counselling on modalities and measures to create an arteriovenous fistula before starting haemodialysis. Intensive patient education is needed to improve adherence to better lifestyle and extensive pharmacotherapy. Integrated care provided by a multidisciplinary team (Figure 4) of professionals and coordinated by the NP can be effective in supporting the patient during predialysis. An NP is equipped to manage the predialysis clinic. The MASTERPLAN study is currently undertaken in the Netherlands to study superior treatment efficacy in renal patients with the aid of nurse practitioners [26]. Alternating visits between NP guarantees medical supervision. Use of outcome parameters and patient surveys are important stimuli to improve practice continuously. Early referral is necessary to implement the CKD action plan in predialysis patients in order to improve outcomes. By referring our patients early to the NP-driven predialysis clinics, we hope to achieve improved quality of care and, in the long term, positively influence patient survival.

Conflict of interest statement. None declared.

References

1. Pereira BJ. Optimization of pre-ESRD care: the key to improved dialysis outcomes. *Kidney Int* 2000; 57: 351–365
2. Jafar TH, Stark PC, Schmid CH *et al.* Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; 139: 244–252
3. Ozsoy RC, Van Der Steeg WA, Kastelein JJ *et al.* Dyslipidaemia as predictor of progressive renal failure and the impact of treatment with atorvastatin. *Nephrol Dial Transplant* 2007; 22: 1578–1586
4. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients absence of evidence or evidence of absence? *Clin J Am Soc Nephrol* 2008; 3: 226–236
5. Kambham N, Markowitz GS, Valeri AM *et al.* Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001; 59: 1498–1509
6. Voormolen N, Noordzij M, Grootendorst DC *et al.* High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrol Dial Transplant* 2007; 22: 2909–2916
7. Siu YP, Leung KT, Tong MK *et al.* Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis* 2006; 47: 51–59
8. Bellizzi V, Di Iorio BR, De Nicola L *et al.* Very low protein diet supplemented with ketoanalogues improves blood pressure control in chronic kidney disease. *Kidney Int* 2007; 71: 245–251
9. Uribarri J, Tuttle KR. Advanced glycation end products and nephrotoxicity of high-protein diets. *Clin J Am Soc Nephrol* 2006; 1: 1293–1299
10. Krediet RT. How to preserve residual renal function in patients with chronic kidney disease and on dialysis? *Nephrol Dial Transplant* 2006; 21(Suppl 2): ii42–ii46
11. Drueke TB, Locatelli F, Clyne N *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; 355: 2071–2084
12. Moe S, Drueke T, Cunningham J *et al.* Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 69: 1945–1953
13. Hruska KA, Saab G, Mathew S *et al.* Renal osteodystrophy, phosphate homeostasis, and vascular calcification. *Semin Dial* 2007; 20: 309–315
14. Levin A, Bakris GL, Molitch M *et al.* Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 2007; 71: 31–38
15. Al Aly Z, Qazi RA, Gonzalez EA *et al.* Changes in serum 25-hydroxyvitamin D and plasma intact PTH levels following treatment with ergocalciferol in patients with CKD. *Am J Kidney Dis* 2007; 50: 59–68
16. Coyne D, Acharya M, Qiu P *et al.* Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. *Am J Kidney Dis* 2006; 47: 263–276
17. Kalantar-Zadeh K, Mehrotra R, Fouque D *et al.* Metabolic acidosis and malnutrition-inflammation complex syndrome in chronic renal failure. *Semin Dial* 2004; 17: 455–465
18. Roderick P, Willis NS, Blakeley S *et al.* Correction of chronic metabolic acidosis for chronic kidney disease patients. *Cochrane Database Syst Rev* 2007; 1CD001890
19. Gennari FJ, Segal AS. Hyperkalemia: an adaptive response in chronic renal insufficiency. *Kidney Int* 2002; 62: 1–9
20. Johnson RJ, Segal MS, Srinivas T *et al.* Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? *J Am Soc Nephrol* 2005; 16: 1909–1919
21. Van Praet JT, De Vriese AS. Prevention of contrast-induced nephropathy: a critical review. *Curr Opin Nephrol Hypertens* 2007; 16: 336–347
22. Penfield JG, Reilly RF Jr. What nephrologists need to know about gadolinium. *Nat Clin Pract Nephrol* 2007; 3: 654–668
23. Go AS, Chertow GM, Fan D *et al.* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305
24. Yilmaz MI, Carrero JJ, Axelsson J *et al.* Low-grade inflammation in chronic kidney disease patients before the start of renal replacement therapy: sources and consequences. *Clin Nephrol* 2007; 68: 1–9
25. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. *Circulation* 2007; 116: 85–97
26. Van Zuilen AD, Wetzels JF, Blankestijn PJ *et al.* Rationale and design of the MASTERPLAN study: multifactorial approach and superior treatment efficacy in renal patients with the aid of nurse practitioners. *J Nephrol* 2005; 18: 30–34
27. Meier-Kriesche HU, Schold JD. The impact of pretransplant dialysis on outcomes in renal transplantation. *Semin Dial* 2005; 18: 499–504
28. Lok CE, Oliver MJ. Overcoming barriers to arteriovenous fistula creation and use. *Semin Dial* 2003; 16: 189–196
29. Chambers J, Germain M, Brown E. 2004. *Supportive Care for the Renal Patient*. Oxford: Oxford University Press
30. Jungers P, Massy ZA, Nguyen-Khoa T *et al.* Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients. *Nephrol Dial Transplant* 2001; 16: 2357–2364
31. Jungers P, Joly D, Nguyen-Khoa T *et al.* Continued late referral of patients with chronic kidney disease. Causes, consequences, and approaches to improvement. *Presse Med* 2006; 35: 17–22
32. Roderick P, Jones C, Tomson C *et al.* Late referral for dialysis: improving the management of chronic renal disease. *QJM* 2002; 95: 363–370
33. Winkelmayr WC, Owen WF Jr, Levin R *et al.* A propensity analysis of late versus early nephrologist referral and mortality on dialysis. *J Am Soc Nephrol* 2003; 14: 486–492
34. Keith DS, Nichols GA, Gullion CM *et al.* Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; 164: 659–663

Received for publication: 6.3.08

Accepted in revised form: 1.7.08