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NEPHROLOGY - REVIEW

Preventing the progression of chronic kidney disease: two case reports and review of the literature

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Abstract A variety of therapeutic modalities are available to alter the abnormalities seen in patients with chronic kidney disease (CKD). A comprehensive plan can now be developed to slow the progression of CKD. Two clinical cases of delay in the need for renal replacement therapy are described. This delay was achieved by using recognized recommendations for optimal diabetes therapy (HbA1c target 7 %), goals for blood pressure levels, reduction of proteinuria, and the proper use of ACEI/ARB therapies. Recent recommendations include BP <140/90 mmHg for patients <60 years old and <150/90 mmHg for older patients unless they have CKD or diabetes. Limits on dietary sodium and protein intake and body weight reduction will decrease proteinuria. Proper treatment for elevated serum phosphorous and parathyroid hormone levels is now appreciated as well as the benefits of therapy for dyslipidemias and anemia. Concerns regarding unfavorable outcomes with excess ESA therapy have led to hemoglobin goals in the 10–12 g/dL range. Finally, new therapeutic considerations for the treatment of acidosis and hyperuricemia are presented with data available to suggest that increasing serum bicarbonate to >22 mmol/L is beneficial, while serum uric acid therapeutic goals are still uncertain. Also, two as yet insufficiently understood approaches to altering the course of CKD (FGF-23 level reduction and balancing gut microbiota) are noted.

Keywords Chronic kidney disease · Hypertension and chronic kidney disease · Proteinuria · Parathyroid hormone · Metabolic acidosis · Hyperuricemia

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Introduction

A variety of therapeutic modalities are available to pharmacologically alter the various clinical and laboratory abnormalities seen in patients with chronic kidney disease (CKD). Much has been written about the appropriate management of hypertension, and studies more than two decades ago demonstrated that angiotensin-converting enzyme inhibitors (ACEIs) can alter the clinical outcomes of patients with diabetes mellitus [1, 2]. In addition, modern therapy has also focused on control of serum glucose, reduction of nondiabetic proteinuria, treatment of lipid abnormalities, amelioration of the anemia of renal disease, and treatment of calcium–phosphorous abnormalities [2]. More recently, control of metabolic acidosis and serum uric acid concentration have been suggested as components of CKD therapy. These approaches have all developed into the comprehensive management of patients with CKD with the goal of attenuating the progressive nature of this disorder.

In this report, we briefly describe two patients with advanced CKD who demonstrated stabilization of their

kidney disease associated with control of diabetes, blood pressure, proteinuria, cholesterol, anemia, and other metabolic abnormalities. We then proceed to review the current literature on strategies to slow the progression of CKD.

Case 1

A 74-year-old female was referred to our nephrology clinic for the management of renal disease. Her past medical history was significant for hypertension and hypercholesterolemia. At the time of the initial evaluation, her blood pressure was 160/70 mmHg and she was being treated with atorvastatin 10 mg once a day, calcium carbonate one tablet with each meal and vitamin supplements. Her laboratory work revealed:

Sodium	139 mmol/L	Albumin	4.1 g/dL
Potassium	4.3 mmol/L	Uric acid	8.9 mg/dL
Chloride	104 mmol/L	Hemoglobin	9.6 g/dL
CO2	23 mmol/L	Cholesterol	166 mg/dL
BUN	61 mg/dL	24-h urine protein	487 mg
Creatinine	5.2 mg/dL	24-h creatinine clearance	12 mL/min
Calcium	8.9 mg/dL	intact PTH	203 pg/mL
Phosphorus	3.9 mg/dL		

Subsequently, the patient underwent renal biopsy which showed arterial and arteriolar nephrosclerosis. The patient's serum creatinine remained stable between 4 and 5 mg/dL in the following few months, and the patient underwent AV access creation. Thereafter, the patient was carefully managed to minimize the risk of progression of renal disease. Over 4 years later, the patient is on multiple medications to control blood pressure, cholesterol, anemia, phosphorus, parathyroid hormone (PTH), serum bicarbonate, and uric acid and her clinical course has been remarkable with creatinine clearance remaining stable at 17 mL/min and 24-h protein excretion of 461 mg. She has not yet required dialysis.

Case 2

A 52–year-old male with hypertension and noninsulin-dependent diabetes mellitus was followed as an outpatient for the management of biopsy proven diabetic nephropathy. During the initial evaluation, the patient had a blood pressure of 180/65 mmHg and his laboratory work revealed:

Sodium	141 mmol/L	Albumin	3.8 g/dL
Potassium	4.1 mmol/L	Uric acid	9.8 mg/dL
Chloride	95 mmol/L	Hemoglobin	9.3 g/dL
CO2	16 mmol/L	Cholesterol	256 mg/dL
BUN	40 mg/dL	24-h urine protein	5990 mg
Creatinine	3.6 mg/dL	24-h creatinine clearance	26 mL/min
Calcium	8.7 mg/dL	intact PTH	295 pg/mL
Phosphorus	5.6 mg/dL	HbA1c	8.2 %

Following evaluation of this data, his hypertension, diabetes, cholesterol, acidosis, uric acid, proteinuria, anemia, calcium, phosphorus, and PTH levels were carefully managed. More than 6 years later, the patient has a creatinine clearance of 37 mL/min with proteinuria of 1.7 g per day. Other follow-up clinical data include serum bicarbonate 23 mmol/L, phosphorus 5.0 mg/dL, uric acid 7.0 mg/dL, cholesterol 175 mg/dL, and HbA1c 6.9 %. He has not yet required dialysis and has been placed on "inactive category" by his transplant center.

Discussion

Research has identified a number of strategies to slow the progression of CKD, such as controlling diabetes, blood pressure, proteinuria, cholesterol, anemia, mineral metabolism, metabolic acidosis, and, perhaps, uric acid (Table 1). We describe two cases of advanced CKD where the risk factors for progression of kidney disease were aggressively managed and the renal function of the patients remained stable for more than 4 years. This illustrates that dialysis may be at least temporarily avoidable for patients with advanced CKD. We will now review current literature and guidelines on strategies to delay CKD progression.

Diabetes mellitus

Diabetes mellitus is currently responsible for the largest proportion of patients with end-stage renal disease (ESRD). Approximately 25–40 % of diabetic patients develop kidney damage and CKD [3]. In a retrospective study by Altemtam et al. [3] investigating potential risk factors which may enhance the progression of diabetic kidney disease in patients with CKD, they concluded that baseline HbA1c was a strong determinant for disease progression. Thus, the

Table 1 Summary recommendations to prevent progression of CKD

Diabetes mellitus	HbA1c ~7 %
	Note: higher individualized goals are recommended based on comorbidities, life expectancy, and risk of hypoglycemia
Hypertension	Blood pressure <140/90 mmHg for age <60 years or with DM or CKD
	Low-sodium diet (<2 g/day), unless patient prone to hypotension or volume contraction
Proteinuria	Diet: low sodium (<2 g/day)
	Diet: low protein <1.3 or <0.8 g/kg/day for GFR <30 mL/min/1.73 m^2
	Weight reduction
	ACEI or ARB (not both), especially for proteinuria >300 mg/day, in both diabetic and nondiabetic patients
Dyslipidemia	Therapeutic lifestyle changes (i.e., diet, exercise, decrease alcohol intake)
	Statin therapy to moderate lipid levels especially in high-risk patients including known CAD, DM, or CVA
Anemia	Screen at least annually and up to monthly depending on stage and risk factors.
	Iron therapy if TSAT <30 % and ferritin <500 ng/mL
	For Hg <10 g/dL and adequate iron stores, ESA therapy to goal 11.5 g/dL
	Avoid red blood cell transfusions, especially in patients eligible for organ transplantation
Abnormal mineral metabolism	For GFR <45 mL/min/1.73 m^2, maintain strict control of serum phosphorous with low-phosphorous diet and phosphate binders
	Treat with vitamin D analogs (i.e., paricalcitol, doxercalciferol, calcitriol) or calcimimetics to control secondary hyperparathyroidism to goal PTH level 100–400 pg/mL
Metabolic acidosis	Maintain serum bicarbonate level >22 mmol/L
	Oral sodium bicarbonate of 1–2 g/day usually adequate to achieve level (will not affect BP)
Hyperuricemia	Consensus regarding renoprotective value of altering serum uric acid levels is lacking
	Proper diet and/or daily oral allopurinol 50–100 mg or febuxostat 40 mg are useful if desired

role of blood glucose control in the progression to ESRD is highly relevant.

The data supporting glucose control in patients with type 1 diabetes mellitus are compelling. In the landmark study, the Diabetes Control and Complications Trial, patients with type 1 diabetes mellitus were randomized to intensive glucose control and conventional therapy [4]. The intensive therapy group achieved a HbA1c level of ~7 %, and the conventional therapy group maintained a level of 9 %. When the effects of the two interventions on the prevention of de novo disease and reduction in progression of established disease were evaluated, the results were unambiguous. After an average follow-up of 6.5 years, intensive therapy reduced the risk for developing microalbuminuria by 34 % in the primary prevention group (i.e., no retinopathy at baseline). This indicates the importance of controlling HbA1c levels since microalbuminuria is a known marker for early glomerular and vascular damage [3]. In the secondary intervention group (i.e., very mild-to-moderate nonproliferative retinopathy at baseline), intensive therapy reduced the risk for both microalbuminuria and albuminuria by 43 and 56 %, respectively.

KDIGO recommendations regarding HbA1c levels in patients with CKD suggest a target level of approximately 7 %. Further recommendations include not treating patients to a level <7 % if he or she is at risk for hypoglycemia and targeting a level of >7 % in those individuals with significant comorbidities or limited life expectancy who have a risk of developing hypoglycemia [5]. Achievement of appropriate HbA1c levels will require involvement of physicians with extensive training in the management of patients with hyperglycemia.

Hypertension

It has been well established that hypertension is one of the key contributing factors to progression for CKD. It is the second leading cause of ESRD due to its adverse effects on blood vessels. Thus, control of blood pressure is a cornerstone of treatment for CKD patients. However, the degree of blood pressure reduction needed to optimize renoprotection remains unclear.

In an analysis of multiple clinical trials, Bakris et al. [6] showed that in both diabetic and nondiabetic kidney disease, lower blood pressure was associated with slower progression of CKD. The Modification of Diet in Renal Disease Study demonstrated that in patients with nondiabetic proteinuric renal disease, a target mean arterial pressure (MAP) of 92 mmHg or less reduced GFR declines more effectively than a target of <107 mmHg [7]. However, in the African American Study of Kidney Disease and Hypertension (AASK), the group of patients who had a target MAP of 92 mmHg (mean achieved BP 128/78 mmHg) did not have a significantly different change in GFR over 4 years than those with a target MAP of 102–107 mmHg (mean achieved BP 141/85 mmHg), illustrating the difficulty of establishing treatment goals for different patient groups [8].

Current recommendations of the Eighth Joint National Committee (JNC 8) have suggested goals of <150/90 mmHg for persons aged ≥60 years, unless they have diabetes or CKD, and <140/90 mmHg for younger patients or those with diabetes and CKD. Various therapies can be

initiated for the nonblack population, but a calcium channel blocker or thiazide diuretic is recommended for black hypertensives [9].

Due to the effects of increased salt intake on increasing blood pressure, proteinuria, and albuminuria and the limited ability of CKD patients to excrete sodium, a low-salt diet is recommended for CKD patients [10]. A systematic review and meta-analysis of 56 cohort and randomized-controlled studies revealed that a low-sodium diet (<2 g/day) resulted in significant reductions in blood pressure and cardiovascular death, with no adverse effects on blood lipids, catecholamine levels, or renal function ($p < 0.05$) [11]. As per current KDIGO recommendations, a diet consisting of <2 grams sodium per day is advised, unless contraindicated as in those patients prone to hypotension or volume contraction [5].

Proteinuria and ACEIs/ARBs

Proteinuria has been one of the major predictors of poor renal outcomes for patients with diabetic or nondiabetic nephropathy. Various studies have shown that the degree of proteinuria is directly associated with loss of renal function. One such study, the Irbesartan Diabetic Nephropathy Trial (IDNT), evaluated 1,715 patients with type 2 diabetes with hypertension and proteinuria and demonstrated that the risk for kidney failure doubled for each doubling of level of proteinuria [12]. Similarly, for each halving of proteinuria level between baseline and 12 months of treatment, the risk for kidney failure decreased by more than half. Another study, the Ramipril Efficacy in Nephropathy (REIN) trial, found that in patients with nondiabetic renal disease, the percentage of decrease in proteinuria correlated inversely with decrease in GFR [13].

Among CKD patients with proteinuria of >300 mg per day, antihypertensive therapies inhibiting the renin–angiotensin system axis are considered superior to other classes of antihypertensives for slowing the progression of CKD [14]. ACEIs and ARBs have become drugs of choice for reducing proteinuria in both diabetic and nondiabetic kidney disease. In an early study by Lewis et al. [1], 407 patients with insulin-dependent diabetes mellitus were randomly assigned to administration of captopril or placebo. Patients assigned to captopril administration not only had risk reduction in progression to ESRD or death, but had a decrease in microalbuminuria independent of the effect on systemic blood pressure. A more recent study by Brenner et al. [15] showed similar results. A total of 1,513 patients with type 2 diabetes and nephropathy were randomized to a group receiving either losartan or placebo. This study showed that losartan reduced the incidence of a doubling of the serum creatinine (RR 25 %; $p = 0.006$) and ESRD (RR 28 %; $p = 0.002$). This renal benefit conferred by losartan still remained significant after differences in blood pressure were corrected.

It is necessary for clinicians to keep in mind that the combination of an ACEI with an ARB can lead to unfavorable effects. Adverse events including hyperkalemia and acute kidney injury led to the termination of a recent ACEI/ARB study by Fried et al. [16]. Further, the use of ACEIs or ARBs alone but in excessive doses, with or without diuretics, may result in rapid deterioration of renal function, and this effect should be ruled out by dose adjustment whenever such changes occur.

With ever increasing evidence that decreasing proteinuria improves renal outcomes, it is also essential for patients to be advised on appropriate dietary intake. KDIGO recommends that dietary protein intake of >1.3 g/kg per day should be avoided in adults with CKD. If a patient's GFR is <30 mL/min/1.73 m^2, then a lower protein intake of <0.8 g/kg per day is advised [5].

Recent interest in the possibility of obesity-related renal damage suggests that attention to control of BMI may prove beneficial to at-risk patients. Several population-based studies have linked obesity with proteinuria and microalbuminuria. The pathogenic mechanisms linking obesity and renal damage include insulin resistance, sodium retention, inappropriate activation of the renin–angiotensin and aldosterone system, oxidative stress, leptinemia, and adiponectin deficiency [17]. More recently, studies have also shown that weight reduction, including after bariatric surgery, has led to reduction in proteinuria [18].

Lipid abnormalities

Dyslipidemia is commonly associated with CKD and has significant effects on CKD progression and associated morbidity through mechanisms involving oxidative stress-induced systemic inflammation and direct injury to the glomerular basement membrane [19]. Toxic lipid components such as LDL may incite inflammatory responses, which result in vascular damage. HDL, on the other hand, is an antiatherogenic lipoprotein with anti-inflammatory and antioxidant properties which has been shown to increase following therapy with erythropoiesis-stimulating agents (ESAs) [20]. Statins may have beneficial renal hemodynamic effects by improving endothelial function [19].

Several studies have shown that hyperlipidemia increases the risk for worsening CKD. In a prospective, controlled, open-label study, Bianchi et al. [21] showed that when patients with CKD and proteinuria were treated with atorvastatin in addition to ACEIs or ARBs, the rate of progression of kidney disease was significantly reduced. The group treated with atorvastatin had a slight but not

significant reduction of creatinine clearance from 51 ± 1.8 mL/min to 49.8 ± 1.7 mL/min after 1 year of treatment. In contrast, the group not treated with atorvastatin had a statistically significant decrease in creatinine clearance from 50 ± 1.9 mL/min to 44.2 ± 1.6 mL/min ($p < 0.01$).

More recent studies also suggest that statins may reduce the rate of kidney function loss in CKD patients, although it is unclear if this is due to lowering cholesterol or other multi-dimensional effects of statin therapy (i.e., anti-inflammatory effect). The Study of Heart and Renal Protection (SHARP) was a large randomized control trial of over 4,000 CKD patients that evaluated the effects of simvastatin and ezetimibe combination therapy versus placebo [22]. It concluded that a reduction of LDL cholesterol was associated with a significant decrease in major atherosclerotic events in CKD patients. It also found correlations between patients treated with cholesterol lowering therapy and prespecified measures of renal disease progression (i.e., doubling creatinine or ESRD), although these were not statistically significant (RR 0.93; 95 % CI 0.86–1.01; $p = 0.09$). Future therapies aimed at reducing inflammation and limiting progression of CKD and associated cardiovascular disease by balancing gut microbiota are currently being explored [23]. At present, it would seem prudent in regard to both cardiovascular and renal outcomes, and in accord with KDIGO guidelines [5], to moderate lipid levels in those patients who demonstrate excessive elevations of various components of the lipid profile.

Anemia

Anemia is a very common occurrence in CKD, largely due to relative erythropoietin (EPO) deficiency but also influenced by other metabolic and mechanical factors. Anemia in CKD patients can have a significant impact on morbidity, as hypoxia and oxidative stress can contribute to worsening progression of CKD through tubulointerstitial damage, glomerulosclerosis, and interstitial fibrosis [24].

Several studies have produced data regarding the safety and efficacy of iron therapy and ESAs, while investigating optimal targets for treatment goals of decreased hemoglobin (Hg) levels [25]. In a prospective control trial, Gouva et al. [26] randomized patients with a serum creatinine of 2–6 mg/dL and a hemoglobin of 9–11.6 g/dL to receive erythropoietin immediately (early treatment arm) or when hemoglobin decreased to <9 g/dL (deferred treatment arm). During a median follow-up of 22.5 months, the early treatment arm had a delay in the initiation of renal replacement therapy and a relative hazard of 0.42 for doubling of creatinine, renal replacement, or death ($p = 0.012$). Another study by Siamopoulos et al. [20] demonstrated that EPO administration significantly increased serum HDL levels in the CKD population, indicating the various ways in which ESAs may have an impact in slowing the progression of CKD. Most experts agree that Hg targets should lie between 10 and 12 g/dL for CKD patients, since several large-scale studies have raised concerns that ESA therapy targeting a higher Hg concentration goal of 13 g/dL may be associated with increased cardiovascular risk for stroke [27].

Current KDIGO guidelines published in 2012 suggest that all CKD patients should be screened for anemia (Hg concentration <13.0 g/dL in males and <12 g/dL in females). Treatment with iron is recommended as long as transferrin saturation (TSAT) is <30 % and ferritin level is <500 ng/mL. Oral iron therapy may be effective in some patients. For nonresponders, intravenous iron therapy would be appropriate. For patients with Hg concentration <10 g/dL and adequate iron stores, initiation of intravenous or subcutaneous ESA therapy should be utilized with treatment to a maintenance goal of 11.5 g/dL and without using excessive dosing in patients who demonstrate ESA hyporesponsiveness. The use of red blood cell transfusion should be avoided, especially in patients eligible for organ transplantation [25].

Abnormal mineral metabolism

While much has been published on the association of calcium–phosphorous disorders and cardiovascular mortality in CKD patients, the effect of abnormalities in mineral metabolism on CKD progression remains yet to be fully elucidated. There are some data which suggest that the use of active vitamin D agents or calcimimetics to control hyperparathyroidism in CKD may be renoprotective [28]. A recent prospective cohort study of 985 US veterans showed that higher calcium–phosphorous products are associated with higher risk of CKD progression [29]. It has been suggested that elevated serum calcium–phosphorous products induce inflammatory responses which may subsequently be a factor in renal disease progression [30].

In patients with eGFR <45 mL/min/1.73 m^2, it is recommended to maintain the serum phosphorous concentration within normal limits [5]. A daily dietary restriction of protein to 0.8 g/kg should suffice to limit dietary phosphorous exposure. Products available to help control serum phosphorous levels include aluminum hydroxide, magnesium salts, calcium-based phosphate binders (i.e., calcium carbonate, calcium acetate), and other noncalcium-based phosphate binders, which include lanthanum and sevelamer. A recent meta-analysis suggested that noncalcium-based phosphate binders, in comparison with calcium-based phosphate binders, are associated with a decreased risk of all-cause mortality [30]. Aluminum-containing

antacids are no longer recommended because they incur the risk of aluminum toxicity and magnesium salts have fallen out of favor due to adverse risks such as hypermagnesemia and diarrhea. Typical dosing regimens for phosphate binders in routine clinical practice to control serum phosphorous levels include 2–4 g per day of calcium containing binders and/or 1.5–3 g per day of lanthanum carbonate and/or 2.4–4.8 g per day of sevelamer, all of which are given in divided doses with meals [5].

Parathyroid abnormalities in CKD include parathyroid gland hyperplasia, decreased expression of vitamin D receptors, and an increased set point of serum calcium in regard to suppression of PTH secretion. To help control elevated PTH levels, there are advanced vitamin D preparations available, including paricalcitol, doxercalciferol, and calcitriol. It is imperative for clinicians to monitor the doses of these medications and avoid oversuppression of PTH to prevent adynamic bone disease. Since the optimal level of PTH is not known for CKD patients, recent guidelines suggest the use of these vitamin D preparations when PTH is progressively rising and remains persistently above the upper limit of normal for the assay with a goal in the range of 100–400 pg/mL [5, 31].

Recent studies further suggest that 1,25 $(OH)_2$ vitamin D may also have renoprotective effects in patients with diabetic nephropathy. A study by Zhang et al. [32] demonstrated that combined treatment with losartan and paricalcitol had profound renal effects in diabetic mice. These effects included the prevention of albuminuria, restored glomerular filtration barrier structure, and markedly reduced glomerulosclerosis. Vitamin D analogs are also able to directly inhibit renin biosynthesis by suppressing renin gene transcription, thereby promoting renoprotective effects. Furthermore, a very recent study demonstrated that treatment with cholecalciferol can decrease albuminuria in patients with low vitamin D_3 and high PTH levels [33].

One of the body's innate responses to hyperphosphatemia is osteocytic and osteoblastic release of fibroblast-growth-factor-23 (FGF-23), which has been found to be associated with endothelial dysfunction and cardiac hypertrophy in CKD when levels are elevated [34]. Despite the known early rise of FGF-23 levels in the earliest stages of CKD and its well-studied toxic effects including vascular calcification, we still lack an adequate approach, other than normalizing serum phosphorous levels, to combat rising FGF-23 levels in CKD patients.

Metabolic acidosis

Another common complication in patients with CKD is metabolic acidosis. This mainly results from a decrease in ammoniagenesis secondary to a reduction in functioning nephrons [35]. Other processes include a decrease in proton secretion and hyperkalemia which suppresses ammoniagenesis. Multiple consequences may ensue from a state of chronic metabolic acidosis, including increased protein catabolism, uremic bone disease, muscle wasting, inflammation, and impaired glucose homeostasis and cardiac function [36]. Furthermore, it has been proposed that acidosis may also lead to vasoconstriction and fibrosis by upregulating the endothelin gene [37]. It would therefore be reasonable to conclude that the correction of metabolic acidosis would yield favorable effects.

Shah et al. [38] performed a large retrospective study in 2009 analyzing the progression of kidney disease, defined as a decrease in estimated GFR by 50 % or reaching an estimated GFR <15 mL/min/1.73 m^2, in relation to serum bicarbonate levels. After stratifying the patients into four different quartiles based on their bicarbonate levels, they concluded that the lowest quartile ($\leq$22 mEq/L) was associated with a 54 % increased hazard of progression of CKD when compared to patients with a serum bicarbonate level of 25–26 mEq/L ($p = 0.006$).

Susantitaphong et al. [37] performed a meta-analysis of trials examining the short- and long-term effects of alkali therapy in patients with CKD. With the use of alkali therapy, they noted that there was a significant net improvement in GFR of 3.2 ml/min/1.73 m^2 ($p < 0.001$) in 3 long-duration trials and a 79 % risk reduction in the incidence of dialysis requirement in an analysis of 2 long-term studies ($p = 0.001$). This suggests that alkali therapy can lead to GFR preservation and a decrease in dialysis requirement.

The studies mentioned illustrate the importance of paying close attention to reversing the metabolic acidosis in patients with CKD. Current guidelines by KDIGO recommend correcting the serum bicarbonate level to >22 mEq/L in order to prevent the possibility of adverse effects related to metabolic acidosis [5, 37]. It has also been noted that the use of bicarbonate does not adversely affect blood pressure control [37]. Doses of sodium bicarbonate in the range of 1–2 g per day are usually adequate to normalize serum bicarbonate levels.

Hyperuricemia

Recent studies have suggested that uric acid may be an independent risk factor for the deterioration of GFR in patients with CKD. A large epidemiologic study involving a prospective cohort of 28,117 subjects showed that hyperuricemia >6.3 mg/dL promoted the development of CKD over 12 years of follow-up [39]. In a randomized-controlled trial, Siu et al. showed that when the serum uric acid was lowered with allopurinol from 9.75 to

5.88 mg/dL, the progression of CKD was significantly delayed over 12 months [40].

Of late, more data have been accumulated which describe benefits and proposed mechanisms by which lowering of uric acid may protect renal function and result in improvement in outcomes in patients with renal disease. Studies by Hsu et al. [41] suggested an association between increased serum uric acid and loss of renal function, while data from Goicoechea et al. [42] demonstrated a decrease in renal function loss in patients treated with allopurinol.

Endothelial dysfunction has been proposed as an effect of increased uric acid levels, and Kanbay et al. [43] have data which revealed that patients who received allopurinol had improved endothelial function. Finally, data from a recent renal outcome study have demonstrated the unexpected finding that losartan can decrease serum uric acid levels and the changes are associated with enhanced renal protection [44]. Despite these findings, limitations of design and sample size in some of the studies cited have resulted in a lack of consensus regarding the efficacy of altering serum uric acid levels. Clinical experience has demonstrated that daily doses of allopurinol in the range of 50 to 100 mg or febuxostat 40 mg, with a proper diet, are usually sufficient to decrease serum uric acid levels if desired.

Conclusion

In conclusion, the information provided in this review outlines the various approaches to, and evidence which supports, the systematic management of the various abnormalities seen in patients with CKD with the suggestion that this comprehensive plan will attain the goal of delaying the inception of renal replacement therapy.

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