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Delayed Progression to Dialysis with Early and Intensive Management of Predialysis Chronic Kidney Disease: A Case-Based Approach

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Key Words
Chronic kidney disease · Estimated GFR · Comorbidities · Multifactorial treatment regimen

Abstract
In addition to hypertension and diabetes, disorders in mineral metabolism and bone disease (e.g. affecting phosphorus, calcium, parathyroid hormone, and vitamin D) are common complications of chronic kidney disease (CKD) and contribute to morbidity and mortality. Consequently, CKD requires multifactorial treatment to slow CKD progression and avoid end-stage renal disease. CKD progression and treatment outcomes are monitored by measuring the estimated glomerular filtration rate (eGFR), which decreases by 2–12 ml/min/1.73 m^2 per year depending on the stage of CKD and comorbidities, such as diabetes. This paper presents representative case studies illustrating the delay and reversal of CKD progression with comprehensive, individualized treatment regimens, including non-calcium phosphate binders, antihypertensives, lipid-lowering drugs, calcimimetics, and other drugs as required, to treat each component of CKD including CKD-mineral and bone disorder. Four patients are included, with an average age of 70–81 years and CKD stage 3 or 4 accompanied by various comorbidities, most notably diabetes and hypertension. The range of treatment and follow-up durations was 6–7 years. In each case, there was evidence of slowing or prevention of CKD progression, according to eGFR and serum creatinine, regardless of the patient's age or CKD stage. Despite a baseline eGFR of <20 ml/min/1.73 m^2 in 1 female patient, after 6 years of follow-up, her eGFR had stabilized and was maintained at >15 ml/min/1.73 m^2. These observations reinforce the value of early nephrology referral and comprehensive management of CKD and underlying conditions (hypertension and diabetes) beginning at eGFR <60 ml/min/1.73 m^2.

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Introduction

Chronic kidney disease (CKD) is an increasingly prevalent healthcare burden, affecting approximately 13% of the US population [1]. Hypertension and type 2 diabetes are the major causes of CKD and are important treatment targets. In addition, CKD is often accompanied by metabolic disturbances including hyperphosphatemia, vitamin D deficiency, and metabolic acidosis, which are therefore also important therapeutic targets. As a consequence, a multifactorial treatment approach is advocated to treat the causes and consequences of CKD, to slow CKD progression, and to avoid end-stage renal disease (ESRD) [2]. Early referral to a nephrologist is also essential to slow progression of CKD and avoid complications of ESRD [3, 4].

CKD is defined as a progressive loss of kidney function where the glomerular filtration rate (GFR) is <60 ml/min/1.73 m^2 or there is evidence of kidney damage for at least 3 months [5]; evidence of kidney damage may include abnormal proteinuria or microscopic hematuria, with additional abnormalities related to anatomy, radiology, or histopathology. Estimated GFR (eGFR) is the preferred method over change in albuminuria to assess kidney function, since changes in GFR are more consistent with progressive deterioration in renal function [6, 7]. The relationship between change in proteinuria and worsening GFR also suggests that reduced albumin excretion may not be a meaningful clinical outcome [2].

Reliable and accurate estimations of GFR using the Modification of Diet in Renal Disease (MDRD) equation [8] and, more recently, the Chronic Kidney Disease Epidemiology Collaboration equation [9] have been reported. Studies indicate that there can be a 2–12 ml/min/1.73 m^2 annual loss in eGFR on average with renal disease [10] and an annual decline in eGFR of 1–8 ml/min/1.73 m^2 in diabetic patients with micro/macroalbuminuria [11]. More recent studies indicate that eGFR declines by an average of 5.8 ml/min/1.73 m^2 per year in patients with type 2 diabetes and preserved kidney function [12], while patients with diabetes and advanced renal disease who received an angiotensin receptor blocker (ARB) showed a similar decline of approximately 5 ml/min/1.73 m^2 per year [13, 14]. The benefit of antihypertensive therapy on eGFR decline is exemplified by Murussi et al. [15] who demonstrated that patients with diabetes not receiving early antihypertensive treatment experienced an annual decline of 10–14 ml/min/1.73 m^2. Early studies comparing reciprocal serum creatinine semilogarithmic curves showed that different disease entities and specific diagnoses had different slopes: diabetic renal disease was associated with very steep curves and led to a rapid decline in GFR and dialysis dependence. As GFR declined, it was also apparent that a more rapid decline and steeper slope of the curve was associated with ESRD [10]. These concepts are useful to compare and contrast with the results presented in this case series.

Cardiovascular Disease Risk and Mineral Metabolism in CKD

Patients with CKD are exposed to competing risks: progression of CKD to ESRD and increased cardiovascular disease (CVD) risk (compared to patients without CKD). The relative risk of CVD-related mortality is 6 times higher than the risk of progressing to ESRD [16]. CKD is also a greater risk factor than diabetes for future coronary events in high-risk patients [17]. CKD tends to aggravate traditional CVD risk factors, such as hyperlipidemia, which should be assiduously managed in renal-impaired patients [2]. Additional CKD-specific sources of CVD risk include uremic toxins, advanced glycation endproducts (AGEs),

and the mineral and endocrine derangements of CKD-mineral and bone disorder (CKD-MBD) [2].

CKD-MBD comprises metabolic abnormalities affecting phosphorus, calcium, parathyroid hormone (PTH), vitamin D, bones (e.g. affecting bone turnover, strength, and volume), and calcification of vascular or other soft tissue [18]. Not only is hyperphosphatemia itself a source of cardiovascular pathology, but the preceding elevations in PTH and fibroblast growth factor (FGF)-23 also contribute to cardiovascular and renal risk; FGF-23 elevation is associated with CKD progression [2] and causes left ventricular hypertrophy [19]. Studies on human CKD suggest that sevelamer [20] or lanthanum binders [21] lower serum FGF-23, while the use of calcium binders does not [20, 21]. Uremic animal models suggest that a positive calcium balance (from a diet, supplements, and calcium-based phosphate binders) can fuel vascular and valvular calcification in CKD/ESRD [22, 23]. In human CKD patients, a positive calcium balance may contribute to the deposition of calcium in soft tissue [24]. An excess of calcium has been associated with an increased CVD risk in the general population [25].

The current Kidney Disease Improving Global Outcomes (KDIGO) guidelines for CKD-MBD recommend evaluating serum phosphorus, calcium, and PTH every 6–12 months, if eGFR is 30–50 ml/min/1.73 m^2 (CKD stage 3), every 3–6 months, if eGFR is 15–29 ml/min/1.73 m^2 (CKD stage 4), and every 1–3 months, if eGFR is <15 ml/min/1.73 m^2 (CKD stage 5) [18].

Practice Characteristics and Treatment Rationale

CKD etiologies in patients presenting at the Hudson Essex Nephrology Clinic (Union City, N.J., USA) are mostly hypertensive nephrosclerosis and/or diabetic nephropathy. This urban practice represents a socioeconomically challenged and ethnically diverse demography, with a large Hispanic-American population. Adherence rates to prescribed treatments are generally high in this practice's patients.

Phosphate binders are important in CKD-MBD management to control hyperphosphatemia and secondary hyperparathyroidism (SHPT) [18]. There is some evidence that suggests that calcium-free binders are associated with lower CVD risk in CKD stages 3–5 [26]. The current KDIGO guidelines suggest restricting the dose of calcium-based binders in high-risk patients such as those with persistent hypercalcemia, adynamic bone disease, or known vascular calcifications [18]. Sevelamer carbonate, a calcium-free phosphate binder, is approved for hyperphosphatemic dialysis patients in the USA and for hyperphosphatemic patients with CKD stages 3–5 or on dialysis in many other countries.

In the author's practice, contrary to US labeling, almost all patients with CKD stages 3–5 receive sevelamer carbonate; calcium-based binders are not routinely used. Treatment with sevelamer carbonate is initiated at eGFR <60 ml/min/1.73 m^2 and is typically dosed at 1 tablet daily with supper. Dose escalation of sevelamer to 2 or 3 tablets per day occurs, when there is evidence of CKD progression rather than elevated phosphate levels. The decision to use off-label dosing was based on exploratory data in predialysis CKD patients and uremic animal models that suggest sevelamer may slow the progression of CKD (particularly diabetic nephropathy) and significantly reduce serum FGF-23 [20, 27, 28]. All 4 patients described in this paper were taking 1 or more sevelamer tablets with *each* meal. Predialysis sevelamer use, as well as once daily dosing, is off-label in the USA: FDA-approved labeling specifies the use in hyperphosphatemic dialysis patients and administration with all meals, whereas outside the USA, sevelamer is also indicated in patients with hyperphosphatemia in

predialysis CKD stages. Patients 3 and 4 of this paper, who presented with baseline eGFR of 20 and 24 ml/min/1.73 m^2, respectively, received lanthanum carbonate once daily (with 1 meal) in addition to sevelamer carbonate thrice daily (with each meal).

Angiotensin-converting enzyme inhibitors (ACEIs) and ARBs are the antihypertensive agents of choice in CKD, targeting both blood pressure (<130/80 mm Hg for CKD patients) and kidney function via inhibition of the renin-angiotensin-aldosterone system (RAAS), which reduces proteinuria and slows progression of CKD [2]. Additional classes of antihypertensive agents (e.g. doxazosin, metoprolol, hydrochlorothiazide, amlodipine, or hydralazine) are also commonly used to further ameliorate CVD risk and delay CKD progression.

Diabetes is commonly associated with CKD, and poor glycemic control contributes further to CKD progression [18]. Guidelines recommend a glycosylated hemoglobin (HbA_{1c}) level not exceeding 6.5–7.0% to delay CKD progression [29]. In type 2 diabetic subjects with early CKD, all hypoglycemic agents are applicable. In advanced CKD, some drugs are contraindicated or require dose reduction because of reduced renal clearance and a resulting increased risk of hypoglycemia.

Vitamin D deficiency affects most CKD and ESRD patients. Low levels of calcidiol [25 $(OH)_2$-vitamin D_2] are associated with a more rapid progression of CKD [2]. Current guidelines recommend supplementation with vitamin D, once calcidiol levels drop below 30 ng/ml using nutritional sources and/or active vitamin D analogs [5]. Active vitamin D analogs are also used to treat SHPT and high-turnover bone disease in early CKD [5]. SHPT is also treated with calcimimetics, such as cinacalcet, to increase the sensitivity of parathyroid calcium-sensing receptors.

Metabolic acidosis occurs as a result of reduced renal ammoniagenesis, leading to decreased serum bicarbonate [2]. As CKD progresses, acidosis stimulates renal ammoniagenesis and progressive tubulointerstitial injury, an effect initiated by the activation of the complement cascade [2]. Sodium bicarbonate is commonly used to restore serum bicarbonate and has been shown to significantly slow the rate of GFR decline and CKD progression [2]. A typical starting dose is 650 mg once to thrice daily, aiming for a total blood CO_2 of 19–28 mEq/l. Hyperuricemia, blood uric acid exceeding 7 mg/dl, appears as GFR declines and renal uric acid excretion deteriorates; it is associated with CVD and may contribute to CKD progression. Allopurinol inhibits uric acid production and is commonly prescribed as part of the CKD treatment regimen [2]. Other drugs with uricosuric properties that are commonly used in CKD patients include fenofibrate, atorvastatin, and amlodipine.

Hyperlipidemia, most notably triglyceridemia, increases glomerular atherogenesis and contributes to CKD progression. Lipid-lowering treatment usually includes statins, omega-3 fatty acids, and fibrates to control low-density lipoprotein cholesterol (LDL-C, which should remain <100 mg/dl) and triglycerides (which should remain <150 mg/dl) [2].

Anemia affects almost all patients with CKD stages 3–5. Hypoxia and oxidative stress associated with anemia contribute to glomerulosclerosis, tubulointerstitial damage, and, ultimately, CKD progression. Anemia treatment includes erythropoiesis-stimulating agents (e.g. epoetin alfa or darbepoetin alfa), iron supplements (e.g. ferrous sulfate), and occasionally folic acid or vitamin B_{12}. Current guidelines recommend hemoglobin levels of 10–12 g/dl in ESRD, which can also be applied to predialysis CKD patients [2].

Additional therapeutic interventions common to this practice include multivitamins (e.g. Centrum® Silver® or Renax) to correct for mineral deficiencies related to CKD-MBD and antidepressants (e.g. venlafaxine) to combat this common comorbidity of chronic disease. Table 1 summarizes the author's main renoprotective strategies and treatment targets for each component related to CKD progression.

Case Presentations

The 4 cases presented herein were selected retrospectively to illustrate the author's experience of successful management of severe CKD using a multifactorial treatment approach. The 4 patients described were 70–81 years old with CKD stage 3 or 4, accompanied by several comorbidities, most notably diabetes and hypertension. One patient had severe CKD stage 4 with a baseline eGFR <20 ml/min/1.73 m^2. Treatment and follow-up durations were 6–7 years. Clinical characteristics and comorbidities are presented along with treatment regimens and final outcomes with respect to CKD progression (eGFR and/or serum creatinine plus other on-treatment renal chemistry parameters) in table 2 and figure 1 and figure 2. The patients provided written informed consent for the anonymous publication of their clinical data.

Discussion

In each case presented, there was evidence of slowing or prevention of CKD progression regardless of the patient's age or CKD stage. After 6 or 7 years of follow-up, eGFR was maintained at or above the levels indicative of ESRD and the need for dialysis, despite advanced CKD and comorbidities. For instance, in the case of the 70-year-old woman with CKD stage 4 and diabetes, despite a baseline eGFR <20 ml/min/1.73 m^2, after 6 years of follow-up her eGFR had stabilized and was maintained >15 ml/min/1.73 m^2. This preservation of remaining renal function represents a clinically meaningful delay in the requirement of renal replacement therapy. In each case, the majority of metabolic parameters related to CKD-MBD progression was within, or close to, recommended target ranges.

Hyperphosphatemia is usually associated with a rapid decline in eGFR; it also contributes to SHPT, renal osteodystrophy, and cardiovascular calcifications. Treatment of hyperphosphatemia was central to the observed benefit in these patients and was achieved using the calcium-free phosphate binders sevelamer and lanthanum carbonate either as monotherapy (n = 2; sevelamer) or concomitantly (n = 2). Both binders have demonstrated significant reductions in serum phosphorus and progression of SHPT in predialysis patients [30]. There are also reports suggesting that sevelamer may be associated with additional benefits beyond its effects on serum phosphorus and PTH. For instance, sevelamer binds dietary-derived AGEs in the intestines and reduces systemic exposure to AGEs which elicit a broad range of cellular responses leading to kidney injury. This dose-dependent effect may reduce the AGE burden and the rate of AGE-induced kidney damage in diabetic patients [28]. Sevelamer can also lower LDL-C and inflammatory markers with potentially useful antiatherogenic effects [31], and increase the clearance of uremic toxins [32]. Sevelamer reduces circulating FGF-23, which has been shown to cause left ventricular hypertrophy in animal models [19], predicts CKD progression [33] and mortality [34] in humans, and is regarded as a new target in CKD-MBD therapy. Although FGF-23 data were not collected in our representative cases, it is conceivable that FGF-23 lowering contributed to the delay in CKD progression. Furthermore, the availability of novel dosage forms with sevelamer (as powder or tablets) allows greater flexibility that may translate into increased compliance and improved phosphate control.

All of these patients had hypertension, which is independently associated with CKD progression. Potential mechanisms linking high blood pressure and kidney disease include salt retention and volume overload, increased sympathetic nervous system activity, increased RAAS activity, and increased PTH [35]. Most patients received a combination of

RAAS inhibitors (ACEI/ARBs) and other antihypertensive classes. Reducing RAAS activity decreases proteinuria, which otherwise has direct toxic effects on the kidney and facilitates CKD progression [2]. However, ACEIs and ARBs only partially suppress the RAAS due to an up-regulation of renin activity [36]. Reduced GFR and hyperkalemia are common side effects of RAAS inhibition requiring regular monitoring. Blood pressure control without RAAS inhibition appears to be less effective in CKD patients unless there is pronounced proteinuria evident, in which case achieving a blood pressure goal does show a benefit in renal outcomes [2].

As with hypertension, hyperglycemia contributes to glomerular damage and CKD progression. Of the 2 cases with diabetes, strict glycemic control (HbA_{1c} <7%) was evident in 1 patient; at final assessment, HbA_{1c} was slightly elevated (7.5%) in the other patient. Although the benefits of glycemic control in diabetic CKD with GFR <60 ml/min/1.73 m^2 or macroalbuminuria have not been confirmed, glycemic control apparently benefits CKD patients with microalbuminuria [2].

Metabolic acidosis associated with low serum bicarbonate levels contributes to CKD progression and increased mortality [2]. Total CO_2 levels, indicative of acidosis, were well controlled in all patients following sodium bicarbonate treatment, which has been shown to slow the rate of progression to ESRD and improve nutritional status [2]. The use of sevelamer carbonate, which has been shown to generate serum bicarbonate and improve acid-base status, may also have contributed [37].

Chronic hyperuricemia stimulates the RAAS and inhibits the release of endothelial nitric oxide, contributing to renal vasoconstriction, hypertension, and progression of renal disease [38]. Allopurinol has been shown to improve eGFR significantly over 2 years [39] and may have contributed to the delayed CKD progression observed in these cases.

Vitamin D levels were maintained >20 ng/ml as recommended through the use of nutritional and active vitamin D analogs. In cases in which hypercalcemia developed, doses were adjusted. In addition to improving PTH, vitamin D is also associated with anti-inflammatory effects, the inhibition of mesangial and podocyte proliferation, the downregulation of RAAS by inhibiting renin production, the prevention of glomerular hypertrophy, and reduced proteinuria in different animal models of CKD [40].

Hyperlipidemia, most commonly hypertriglyceridemia, can also contribute to CKD progression by promoting atherogenesis, glomerulosclerosis, and renal fibrosis. LDL-C and triglycerides also directly stimulate mesangial cell proliferation in the glomerulus [2]. Statins were prescribed in 2 of the 4 cases to control components of dyslipidemia, and omega-3 fatty acids to control triglycerides in 1 case. Statins have previously demonstrated a small but significant decline in annual eGFR (1.22 ml/min/1.73 m^2) and an increase in creatinine clearance compared with placebo [41]. However, uncertainty still exists whether lipid-lowering medication delays CKD progression in predialysis CKD patients [2].

Conclusion

Contrary to many nephrologists' dogma, this case series highlights a subset of CKD patients who exhibited minimal disease progression according to changes in eGFR and/or serum creatinine for many years, when treated proactively with a multiple-drug regimen. These observations reinforce the value of early nephrology referral and comprehensive management of CKD and underlying hypertension and diabetes beginning at eGFR <60 ml/min/1.73 m^2, and invite further research into the effects and mechanisms of CKD-MBD interventions on progression of CKD of different etiologies.

Disclosure Statement

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Table 1. Renoprotective strategies for slowing CKD progression

Parameter	Goal	Intervention
eGFR	KDIGO classification: stage 1: eGFR ≥90 ml/min/1.73 m^2 stage 2: eGFR 60–89 ml/min/1.73 m^2 stage 3: eGFR 30–59 ml/min/1.73 m^2 stage 4: eGFR 15–29 ml/min/1.73 m^2 stage 5: eGFR <15 ml/min/1.73 m^2	Phosphate binders, RAAS inhibitors (ACEIs/ARBs)
Blood pressure control	<130/80 mm Hg, if proteinuria <1 g/day <125/75 mm Hg, if proteinuria >1 g/day	ACEIs/ARBs, sodium restriction, diuretics
Reduction in proteinuria	<0.5 g/day	ACEIs/ARBs
Glycemic control	HbA_{1c} <7%	Dietary counseling, oral hypoglycemic agents, insulin
Dietary protein restriction	0.6–0.8 g/kg/day	Dietary counseling
Lipid lowering	LDL <100 mg/dl Triglycerides <150 mg/dl	Dietary counseling, statins, omega-3 fatty acids, fibrates
Lifestyle modifications	Smoking cessation, achieving ideal body weight, regular exercise	Counseling, exercise program
PTH control	KDIGO goals[a]: stage 3: 35–70 pg/ml stage 4: 70–110 pg/ml stage 5: 150–300 pg/ml	Active vitamin D, calcimimetics (e.g. cinacalcet), phosphate binders
Phosphorus control	Target range: stages 3 and 4: 2.7–4.6 mg/dl stage 5 or ESRD: 3.5–5.5 mg/dl	Phosphate binders
Hypercalcemia control	8.5–10.2 mg/dl calcium-phosphorus product <55 mg^2/dl^2	Non-calcium phosphate binders, dietary counseling, calcimimetics
Anemia control	Target hemoglobin 11–12 g/dl	Erythropoiesis-stimulating agents, ferrous sulfate
Hyperuricemia control	Serum uric acid <7 mg/dl	Allopurinol
Vitamin D	Serum $25(OH)D_2$ ≥20 ng/ml	Nutritional and active vitamin D
Metabolic acidosis	Bicarbonate (or total CO_2) 19–28 mEq/l	Sodium bicarbonate

[a] In the author's practice, PTH management is individualized, and PTH goals are dependent on PTH history. For instance, a patient who has PTH 70 pg/ml in CKD stage 3 is managed to remain at 70 pg/ml in subsequent stages 4 and 5 if possible; a patient who starts treatment with 300 pg/ml is managed to keep within 150–300 pg/ml.

Table 2. Summary of the clinical characteristics, treatment regimen and CKD outcome

Case		Clinical characteristics and comorbidities	Treatment regimen[a]	Outcome at final assessment
1	78-year-old woman with moderate CKD stage 3	Hypertensive arteriolar nephrosclerosis and 7-year history of psoriasis; adrenal adenoma; anemia; homocystinemia; hyperlipidemia; hypertension; hyperuricemia; iron deficiency; macular degeneration; rheumatoid arthritis; SHPT; vitamin D deficiency	Treatment consisted of aldactazide 25 mg; allopurinol 100 mg; aspirin 81 mg; cardizem CD 120 mg; rosuvastatin 5 mg; Feosol 45 mg; Folbee Plus 5/1.5/25 mg; methotrexate 2.5 mg (3 tablets once a week), and etanercept 50 mg/ml (once a week) to treat psoriasis and rheumatoid arthritis; Ocuvite (eye vitamins); sevelamer 800 mg (thrice a day with meals); cinacalcet 30 mg, and paricalcitol 1 μg	After 7 years of therapy, serum creatinine declined from 1.5 mg/dl and remained stable at approx. 1.3 mg/dl and the MDRD creatinine clearance increased from 37 to 42 ml/min. This was accompanied by stabilized eGFR >35 ml/min/1.73 m^2 and, despite a sharp decline after 5 years, was maintained >40 ml/min/1.73 m^2 at the final assessment. KDIGO-recommended targets were achieved for key parameters (initial and final values): serum calcium (10. 5 and 10.1 mg/dl); phosphorus (3.4 and 3.2 mg/dl); PTH (95 and 75 pg/ml); vitamin D (10.7 and 26.5 ng/ml). Other parameters at goal included total CO_2 (29 mEq/l) and uric acid, which was reduced from an initial value of 7.4 to 5.4 mg/dl.
2	78-year-old diabetic man with moderate CKD stage 3	Hypertension; type 2 diabetes; atrial fibrillation; benign prostatic hypertrophy; homocystinemia; hyperlipidemia; hyperuricemia; SHPT; vitamin D deficiency; Alzheimer's disease; metabolic acidosis; MBD	Pioglitazone 15 mg (1/2 tablet daily) for glycemic control; allopurinol 100 mg (twice daily); amlodipine 5 mg; ezetimibe 10 mg; rosuvastatin 10 mg, and carvedilol 12.5 mg (twice daily); multivitamins (Cerefolin 6/5/50/1 mg and Diatx Zn 5/1.5/25 mg; warfarin 5 mg; ergocalciferol (vitamin D_2) 50,000 units (once every other week), and paricalcitol 1 μg (once every other day); rivastigmine transdermal 4.6 mg (as directed) for Alzheimer's disease, and memantine 5 mg to treat dementia associated with Alzheimer's disease; sertraline 50 mg (antidepressant); finasteride 5 mg, and alfuzosin 10 mg for benign prostatic hyperplasia; sevelamer 800 mg (thrice a day with meals)	After 7 years, serum creatinine declined from 1.9 to 1.46 mg/dl and GFR was stabilized at >40 ml/min/1.73 m^2 (maintained at stage 3). Important parameters (with initial and final values) were maintained within range: serum calcium (9.6 and 9.3 mg/dl); serum phosphorus (2.8 and 3.1 mg/dl); intact PTH (50.4 and 47 pg/ml); HbA_{1c} (5.9% and 6.1%). Other parameters at goal included triglycerides (86 mg/dl); total CO_2 (21 mEq/l); hemoglobin (12.2 g/dl), and uric acid (reduced from 7.7 to 4.3 mg/dl).
3	70-year-old hypertensive diabetic woman with severe CKD stage 4	Hypertension; type 2 diabetes; hyperlipidemia; hyperuricemia; iron deficiency; knee replacement; metabolic acidosis; MBD; osteoarthritis; vitamin D deficiency	Allopurinol 300 mg; glimepiride 4 mg; insulin glulisine 100 U/ml (8 units in the morning and 8 units at night), and insulin glargine 100 U/ml (8–10 units daily); diltiazem 180 mg (2 capsules daily); valsartan/hydrochlorothiazide 160/12.5 mg (twice daily); furosemide 80 mg (1 tablet every other morning), and atorvastatin 80 mg; multivitamins (Centrum Silver and Folbee Plus 5/1.5/25 mg, vitamin C 600 mg, vitamin E); Pro-Stat 64 (30 ml twice daily) liquid protein formula; ergocalciferol (vitamin D_2) 50,000 units (one every other week); raloxifene 60 mg (for her osteoporosis); ferrous sulfate 325 mg (twice daily on empty stomach); lanthanum carbonate 1,000 mg (twice daily with meals), and sevelamer 800 mg (thrice daily with meals); sodium bicarbonate 650 mg (twice daily)	After 6 years of follow-up, eGFR remained stable (20 ml/min/1.73 m^2 at presentation and 17 ml/min/1.73 m^2 at final assessment). Despite a peak in serum creatinine to almost 4 mg/dl, the final level after 6 years was similar to the baseline level (2.5 mg/dl). Initial and final values for serum phosphorus (4.7 and 3.6 mg/dl); calcium (8.9 and 9.5 mg/dl); iPTH (76.6 and 36.7 pg/ml) were all within range. Other parameters at goal included total CO_2 (24 mEq/l) and uric acid (3.1 mg/dl). HbA_{1c} (7.5%) levels were slightly elevated above the recommended target at final assessment.

4	81-year-old hypertensive man with CKD stage 4	Hypertension; anemia, benign prostatic hyperplasia; hyperlipidemia; hyperuricemia; metabolic acidosis; MBD; SHPT; vitamin D deficiency	Multivitamins and natural health products including Folbee Plus 5/1.5/25 mg, benefiber (guar gum) 1 g (3 tablets twice a day), Centrum Silver, fish oil omega 3-6-9 capsule Delayed Release 300–1,000 mg (twice daily), Ginkgo Biloba 40 mg (an antioxidant to treat dementia), niacinamide 250 mg (thrice daily) and Joint Support (glucosamine, etc.) 375/300/50/2 mg (3 capsules twice a day). Medications included allopurinol 300 mg; darbepoetin alfa (60–100 units every 2 weeks, if hemoglobin levels warranted); atenolol 25 mg; aspirin 325 mg; valsartan 80 mg, and furosemide 80 mg (every other day); ergocalciferol (vitamin D_2) 50,000 units (one capsule a week), and doxercalciferol 0.5 μg (every other day); lanthanum carbonate 1,000 mg (once daily with supper), and sevelamer 800 mg (2 tablets thrice a day with meals); polyethylene glycol 17 g (1 capsule with water once to twice daily) to alleviate constipation; sodium bicarbonate 650 mg (2 tablets four times daily); terazosin 5 mg (for benign prostatic hyperplasia)	After 6 years of treatment, eGFR remained stable, changing from an initial value of 24 to 17 ml/min/1.73 m^2 (eGFR has been <20 ml/min since 2009). Serum creatinine gradually increased, though considering that this patient was advanced CKD stage 5, these changes are relatively stable. Serum phosphorus (3.9–3.4 mg/dl), calcium (8.7–9.2 mg/dl); iPTH (55–46 pg/ml), and vitamin D (50.3–37.3 ng/ml) were all in range. In addition, HbA_{1c} (5.6%); total CO_2 (21 mEq/l); triglycerides (109 mg/dl); uric acid (2.9 mg/dl), and hemoglobin (10.2 g/dl) were maintained in range.

[a] All doses are once daily unless indicated otherwise; in some cases, multivitamins (e.g. Centrum Silver) and vitamins such as vitamin E were over-the-counter and used on the patients' own initiative, and as such doses are not provided.

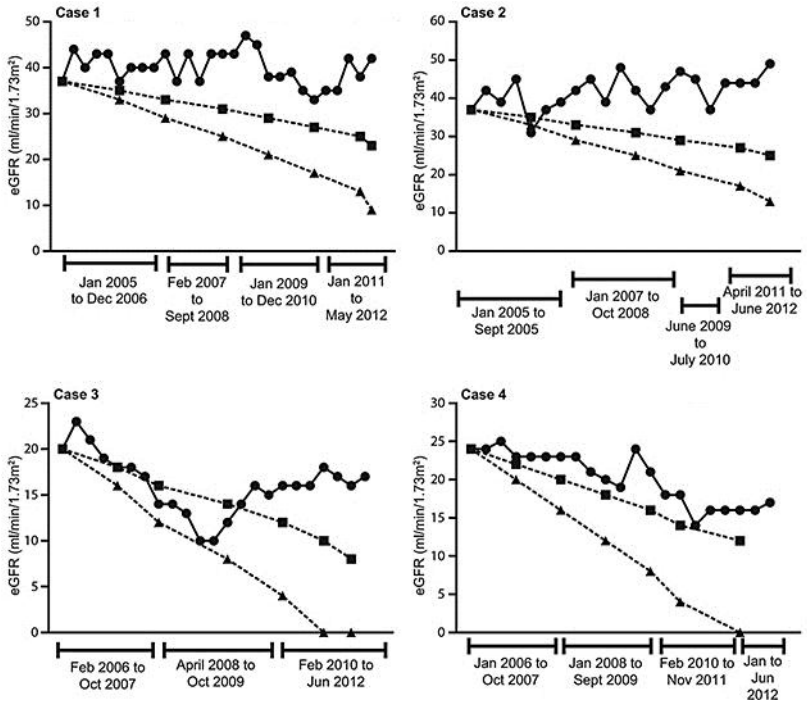

Fig. 1. Temporal changes in eGFR after treatment (●) and the expected decline in eGFR based on annual decreases of 2 (■) and 4 ml/min/1.73 m² (▲). Case 1: 78-year-old woman with moderate CKD stage 3; Case 2: 78-year-old diabetic man with moderate CKD stage 3; Case 3: 70-year-old hypertensive diabetic woman with severe CKD stage 4; Case 4: 81-year-old hypertensive man with CKD stage 4.

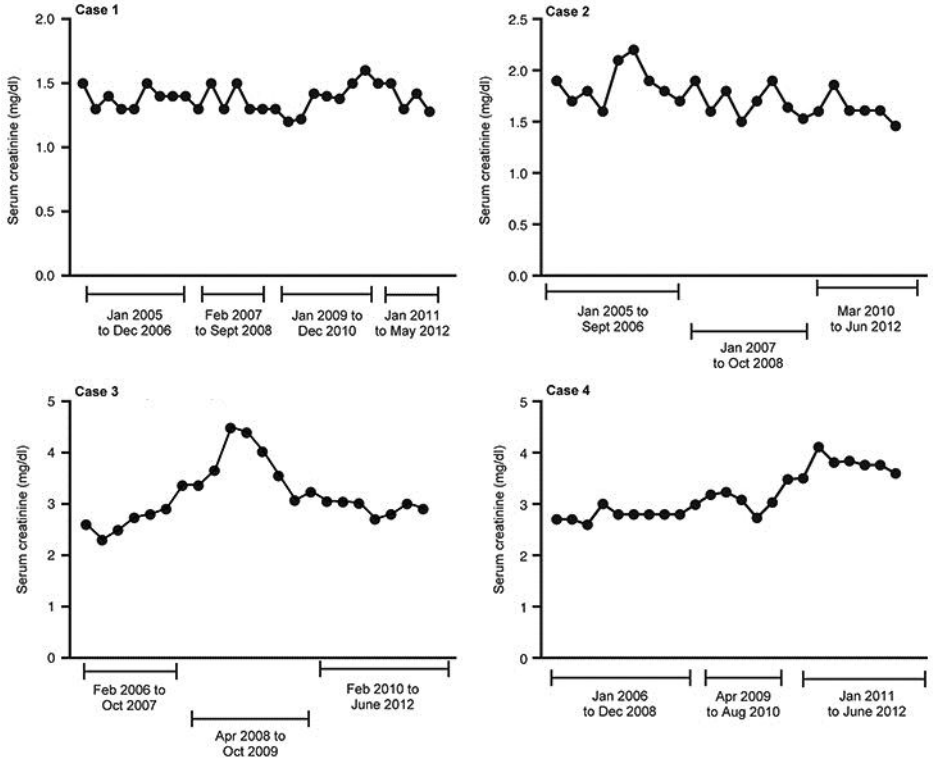

Fig. 2. Temporal changes in serum creatinine. Case 1: 78-year-old woman with moderate CKD stage 3; Case 2: 78-year-old diabetic man with moderate CKD stage 3; Case 3: 70-year-old hypertensive diabetic woman with severe CKD stage 4; Case 4: 81-year-old hypertensive man with CKD stage 4.