

Metabolic disorders in patients with chronic kidney failure

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Summary

This review article summarizes the problems of metabolic disorders and nutrition imbalances that often occur in chronic kidney failure or following regular dialysis treatment. In this paper, we cover the pathogenesis of these disorders, their clinical consequences, and their association with the most severe complications of chronic kidney failure and dialysis treatment. These complications are primarily atherosclerosis, malnutrition, anemia, hyperparathyroidism, and other serious problems that markedly and negatively affect prognosis and the quality of life of uremic patients. Risk factors for cardiovascular disease are discussed in-depth because cardiovascular disease is the leading cause of death in patients with chronic kidney failure. It is important to give attention to the development of these complications because early diagnosis and therapy can improve prognosis for these patients and reduce treatment costs.

Key words: metabolic disorders, chronic kidney failure, dialysis, cardiovascular disease

Introduction

Chronic kidney disease (CKD) is a very real and growing problem, as indicated by demographic trends. The total number of treated patients has markedly increased during the last 30 years, and CKD currently affects approximately 19 million adult Americans, with an incidence that is increasing rapidly (Snyder and Pendergraph 2005). This trend is caused by a growing percentage of elderly people in the population as well as by technical progress and broader availability of dialysis therapy. An increasing number of diabetic patients is also an important factor.

CKD is characterized by progressive deterioration of kidney function, which develops eventually into a terminal stage of chronic kidney failure (CKF). CKF has traditionally been categorized as mild, moderate, or severe. Other poorly defined terms like uremia and end-stage renal disease (ESRD) have commonly been applied. During the last few years, an international consensus has emerged categorizing CKF into 5 stages according to the glomerular filtration rate (GFR) and presence of signs of kidney damage: stage 1: GFR > 90 ml/min and signs of kidney damage; stage 2: GFR = 60–89 ml/min and signs of kidney damage; stage 3: GFR = 30–59 ml/min; stage 4: GFR = 15–29 ml/min; and stage 5: GFR < 15 ml/min (Levey *et al.* 2005).

Stage 5 represents the total inability of kidneys to maintain homeostasis, and this metabolic state is incompatible with life. Thus, at this stage, it is necessary to use methods that substitute for kidney function to ensure patient survival; these methods include peritoneal dialysis, hemodialysis, and other extracorporeal purifying procedures, or kidney transplantation.

CKF is associated with many kinds of metabolic changes caused by the kidney disease and also attributable to dialysis treatment. Phenomena such as accumulation or deficit of various substances and dysregulation of metabolic pathways combine in the pathogenesis of these changes (Cibulka *et al.* 2005). In the process of accumulation, decreased urinary excretion plays a crucial role and leads to retention of metabolites in the organism (e.g., creatinine, urea, electrolytes, water). The increased formation of metabolites through catabolic processes and alternative metabolic

pathways also wields an influence. Regular dialysis treatment partly decreases this accumulation but cannot avert the overall deficit.

This deficit of some important substances in CKF can be caused by deficient intake in diet, impaired intestinal absorption, or increased losses during dialysis sessions. Disturbed synthesis of some crucial metabolic regulators (e.g., erythropoietin, active vitamin D) in kidneys also plays an important role.

All of the abovementioned factors lead to many serious complications for CKD patients during the course of predialysis and dialysis. All accelerate development of atherosclerosis, malnutrition-inflammation complex syndrome (MICS), anemia, hyperparathyroidism, and other serious problems that markedly affect prognosis and the quality of life of patients with CKF (Cibulka *et al.* 2005, Lindner *et al.* 1974, Durak *et al.* 1994, Silver 2000).

Metabolic disorders in CKF

Acid–base balance

Acid–base disorder is commonly observed in the course of CKF. Metabolic acidosis is noted in a majority of patients when GFR decreases to less than 20% to 25% of normal. The degree of acidosis approximately correlates with the severity of CKF and usually is more severe at a lower GFR. Metabolic acidosis can be of the high-anion-gap variety, although anion gap can be normal or only moderately increased even with stage 4 or 5 CKF (Kraut and Kurtz 2005). In mild chronic renal insufficiency, metabolic acidosis is the result of a reduced ability to reabsorb bicarbonate, to excrete ammonia, and to eliminate titratable acid excretion (hyperchloremic, normal anion gap acidosis). In more severe renal insufficiency, organic and other conjugate anions of acids (nonvolatile acids) cannot be sufficiently excreted, and elevated anion gap acidosis appears (Kovacic *et al.* 2003). Acidosis resulting from advanced renal insufficiency is called uremic acidosis. The level of GFR at which uremic acidosis develops varies depending on a multiplicity of factors. Endogenous acid production is an important factor, which in turn depends on the diet. Ingestion of vegetables and fruits results in net production of alkali, and therefore increased

ingestion of these foods will tend to delay the appearance of metabolic acidosis in chronic renal failure. Diuretic therapy and hypokalemia, which tend to stimulate ammonia production, may delay the development of acidosis. The etiology of the renal disease also plays a role. In predominantly tubulointerstitial renal diseases, acidosis tends to develop earlier in the course of renal insufficiency than in predominantly glomerular diseases. In general, metabolic acidosis is rare when the GFR is greater than 25–20 ml/min (Oh *et al.* 2004).

Several adverse consequences have been associated with uremic acidosis, including muscle wasting, bone disease, abnormalities in growth hormone and thyroid hormone secretion, impaired insulin sensitivity, and exacerbation of beta-2 microglobulin accumulation (Kraut and Kurtz 2005). Other complications include negative nitrogen balance, anorexia, fatigue, impaired function of the cardiovascular system, hyperkalemia, and altered gluconeogenesis and triglyceride metabolism (Kovacic *et al.* 2003).

Therapy of uremic acidosis should aim to obtain a serum bicarbonate level as close to normal as possible (i.e., 22–26 mmol/l). The best way to initiate therapy is with oral sodium bicarbonate (1 tablet three times a day) and to increase the dosage as necessary. The usual tablet of 650 mg of sodium bicarbonate contains 7.5 mmol of alkali (HCO_3^- ions). Occasionally patients experience gastric discomfort with sodium bicarbonate may use Shohl's solution (a mixture of sodium citrate and citric acid). In dialysis patients, treatment of acidosis relies on the gain of alkali from the dialysate either as bicarbonate in hemodialysis or as lactate in peritoneal dialysis (Oh *et al.* 2004).

Protein metabolism

A too-strict low-protein diet can have a negative effect on nitrogen balance in the predialysis period. A safe low-protein diet should contain 0.6 g of protein/kg/day, minimally. Disorders in protein metabolism in the dialysis period are usually caused by combined (protein and energy) malnutrition that can be termed uremic malnutrition. It is present in approximately 20%–50% of patients on dialysis and is characterized by insidious loss of somatic protein stores (reflected in lean body mass and serum creatinine) and visceral protein concentrations (reflected in serum albumin

and prealbumin concentrations) (Ikizler 2004). Urinary losses of protein and losses of amino acids during a dialysis session may play a role as well. Metabolic acidosis is an important factor that markedly contributes to negative nitrogen and total body protein balance in CKF (Kovacic *et al.* 2003, Mehrotra *et al.* 2003). It has been demonstrated that the presence of uremic malnutrition increases mortality and morbidity in chronic dialysis patients (Kopple 1994, Ikizler *et al.* 1999). It is very often combined with a chronic inflammation state in the syndrome known as MICS (Kalantar-Zadeh *et al.* 2003).

Carbohydrate metabolism

Disorders of carbohydrate metabolism are also very frequent in CKD. Diabetics represent about 35% of all patients on dialysis therapy. Generally, non-diabetic CKD patients often also have glucose intolerance, probably because of peripheral insulin resistance (Alvestrand 1997). Insulin resistance is primarily detectable when the GFR is below 50 ml/min. Reduced insulin-mediated non-oxidative glucose disposal is the most evident defect of glucose metabolism, but impairments of glucose oxidation, the defective suppression of endogenous glucose production, and abnormal insulin secretion also contribute to uremic glucose intolerance (Rigalleau and Gin 2005). Accumulating nitrogenous uremic toxins seem to be the dominant cause of a specific defect in insulin action, and identification of these toxins is progressing, particularly in the field of carbamoylated amino acids. The consequences of CKF, such as exercise intolerance, anemia, metabolic acidosis, secondary hyperparathyroidism, or vitamin D deficiency, also indirectly play a role (Rigalleau and Gin 2005, Rasic-Milutinovic *et al.* 2000). It has been reported that insulin resistance may be related to arterial hypertension (Ferrannini *et al.* 1987) and may contribute to high cardiovascular morbidity and mortality in patients with CKF (Shoji *et al.* 2001, Shinohara *et al.* 2002). The underlying mechanism can be an impaired synthesis of nitric oxide (NO) in endothelium of patients with CKD. It was reported that appropriately functioning endothelial NO synthase (eNOS) is important for the control not only of arterial pressure but also of glucose and lipid homeostasis (Duplain *et al.* 2001).

Lipid metabolism

Serum triglycerides (TG) are elevated in CKF because of enhanced production of TG-rich lipoproteins such as very-low-density lipoproteins (VLDL) in the liver (Attman *et al.* 1993) and also because of dysfunction of TG degradation resulting from insufficient mitochondrial beta-oxidation of fatty acids. It can be caused by a deficit of *L*-carnitine, which is frequently present, especially in hemodialysis (HD) patients (Cibulka *et al.* 2005, Guarnieri *et al.* 1992).

Hyperinsulinemia is the main factor increasing synthesis of TG and also directly decreases activity of lipoprotein lipase. The following changes in lipid metabolism are also found in many patients with CKF. The most prominent are increased serum TG levels and low levels of high-density lipoprotein (HDL) cholesterol. Low-density lipoprotein (LDL) cholesterol levels are often normal, but the cholesterol may originate from the atherogenic small and dense LDL subclass. The apolipoprotein B-containing part of the lipoprotein may undergo modifications (peptide modification of the enzymatic and advanced glycation end-product, oxidation, or glycation). Modifications contribute to impaired LDL receptor-mediated clearance from plasma and promote prolonged circulation. HDL particles are structurally altered during states of inflammation. The contribution of this complex and the atherogenic form of dyslipidemia to cardiovascular disease (CVD) in patients with renal disease is at present unclear.

Some studies report negative results regarding the predictive power of serum lipids for the development of CVD (Wanner and Krane 2002). Recent findings have suggested that the development of MICS is responsible for this phenomenon. Because MICS leads to a low body mass index, hypocholesterolemia, hypocreatinemia, hypohomocysteinemia, and other manifestations, a reverse epidemiology of traditional cardiovascular risk factors occurs in CKF. Therefore, hypercholesterolemia, obesity, and increased blood levels of creatinine and homocysteine appear to be protective and paradoxically associated with a better outcome in patients with CKF (Kalantar-Zadeh *et al.* 2003, Kalantar-Zadeh *et al.* 2005).

It is well known that HDL cholesterol levels are inversely correlated with the risk of atherosclerosis. In addition to its role in reverse cholesterol transport, HDL has the ability to protect LDL particles against oxidation. The underlying mechanism by which HDL inhibits LDL oxidation is partly enzymatic. There is increasing evidence that paraoxonase 1 (PON1) could be involved in this process (Mackness *et al.* 1993). It was proved that serum PON1 activity is reduced in CKF patients. The possible causes can include reduced HDL levels, altered HDL subfraction distribution, reduced PON1 concentration and different PON1 phenotype distributions. Another possible explanation could be that PON1 activity is inhibited in the uremic environment. Generally, reduced serum PON1 activity could also contribute to the accelerated development of atherosclerosis in CKF patients (Dirican *et al.* 2004).

Lipoprotein(a) [Lp(a)] has been identified as an independent risk factor for atherosclerotic CVD. It was found to be consistently elevated in a considerable proportion of CKD patients. Plasma concentrations of Lp(a) are highly heritable and mainly determined by a size polymorphism of apolipoprotein(a) [Apo(a)]. It has been demonstrated that the low-molecular-weight Apo(a) phenotype independently predicted coronary artery disease occurrence in a cohort of 440 unselected HD patients in a prospective study over five years (Kronenberg *et al.* 1999). It has been suggested that the Apo(a) size and the Lp(a) plasma concentration may play a synergistic role in advanced atherosclerosis.

Because kidneys perform important hormonal functions, there are also some serious complications associated with a lack of important metabolic hormonal regulators in the course of CKF. The major problems are primarily renal anemia and renal bone disease (renal osteodystrophy).

Renal anemia

Renal anemia, which is often associated with fatigue and cognitive and sexual dysfunction, has a significant impact on the quality of life of patients with CKF. Anemia has also been identified as an important etiologic factor in the development of left ventricular hypertrophy, an independent risk factor for heart failure and a predictor of mortality in HD patients (Golper *et al.* 2003). The

major cause of renal anemia in CKF is an inadequate production of the glycoprotein hormone erythropoietin (EPO) because of a reduction in functional kidney parenchyma (Santoro 2002). Furthermore, free radicals elicited from leucocytes by their contact with the dialysis membrane cause hemolysis with consecutive anemia in CKF patients on extracorporeal renal replacement therapy (Eiselt *et al.* 1999).

There are a number of other metabolic derangements associated with uremia that can affect the production and survival of red blood cells (e.g., some uremic toxins, parathormone, protein malnutrition) (Golper *et al.* 2003, Eschbach and Adamson 1985). The introduction of recombinant human EPO (rHuEPO) has revolutionized the treatment of anemia in CKF. The vast majority of patients respond very well to treatment, but 5%–10% of patients show some resistance to rHuEPO, the most common causes of which are considered iron deficiency (Santoro 2002) and the development of MICS (Kalantar-Zadeh *et al.* 2003). The EPO hyporesponsiveness can further worsen symptoms that decrease the quality of life, such as an intolerance of physical work, deterioration of cognitive functions, anorexia, insomnia, or depression. These problems are partly related to the deficit of *L*-carnitine in HD patients (dialysis-related carnitine disorder). This disorder is a functional metabolic deficiency common in chronic HD patients and can have a negative impact on erythrocyte production and survival. Laboratory studies examining the influence of carnitine on red blood cell function and clinical trials in HD patients support the use of *L*-carnitine in the setting of rHuEPO hyporesponsiveness (Golper *et al.* 2003).

Renal osteodystrophy

Renal osteodystrophy, which is the term used to describe the skeletal abnormalities of many CKD patients, is a multifactorial disorder of bone remodeling. It encompasses a heterogeneous group of disorders from states of high bone turnover to states of low bone turnover. High-turnover bone disease or osteitis fibrosa represents the manifestations of secondary hyperparathyroidism (SHPT) on bone. Low bone turnover syndromes are represented by the increasingly prevalent adynamic bone or less commonly, by osteomalacia. These disorders may occur in combination or

alternately, each may predominate in any given patient (Gonzalez and Martin 2001). The most important factor, which is probably responsible for SHPT development, is a deficit of active vitamin D (calcitriol). Diseased kidneys cannot sufficiently hydroxylate 25-hydroxycholecalciferol, which is a precursor of calcitriol. The deficit of calcitriol causes an inadequate absorption of calcium in the small intestine, with resulting hypocalcemia. Retention of inorganic phosphate may deteriorate this situation because phosphates impair the activity of 1- α -hydroxylase even more. Long-lasting hypocalcemia and coincidental hyperphosphatemia lead to the stimulation of parathyroid glands and subsequent SHPT, which causes decalcification of bones. Chronic metabolic acidosis intensifies this harmful process (Kraut and Kurtz 2005). All of these factors are closely interrelated, and while one or more of them may predominate in a particular patient during the course of CKF, much overlap occurs (Gonzalez and Martin 2001). Moreover, hyperphosphatemia has been recognized as an important risk factor for CVD mortality in patients with CKF. It is a direct cause of vascular calcification, the cardio-bone connection (Giachelli *et al.* 2005, Lund *et al.* 2006).

The treatment of vitamin D deficiency when present in CKD patients is warranted since such therapy may reduce or prevent SHPT in the early stages of CKD. In patients with CKD and GFR of 20 to 60 ml/min, nutritional vitamin D deficiency and insufficiency can both be prevented by supplementation with vitamin D₂ (ergocalciferol) or vitamin D₃ (cholecalciferol). The recommended daily allowance in individuals over 60 years is 800 IU, and for younger adults 400 IU. In patients in stage 5 of CKF and in those on dialysis, the value of supplementation is less certain; although in dialysis-dependent patients, high doses of ergocalciferol or 25-hydroxycholecalciferol can raise the serum levels of calcitriol. Calcitriol or other 1- α -hydroxylated vitamin D sterols should not be used to treat vitamin D deficiency (National Kidney Foundation 2004).

Cardiovascular disease

CVD is the leading cause of death in patients with CKF. For every registry reporting national dialysis data in Europe, the U.S., Japan, and elsewhere, about 50% of deaths are attributed to CVD

(Foley *et al.* 1998). In comparison with the general population, dialysis patients have a greater than 20-fold increased risk of a cardiovascular death (Levey and Eknoyan 1999). A majority of these deaths are related to vascular occlusive disease with associated myocardial infarction, cerebrovascular accidents (strokes), and ischemic events of the limbs. Additionally, patients with CKD exhibit evidence of early and exaggerated vascular and cardiac remodeling (arteriosclerosis and left ventricular hypertrophy). The risk of CVD and associated mortality increases in proportion to the decrease in GFR. It is significantly higher if GFR has fallen below approximately 75 ml/min. The evidence suggests that the damage is already far progressed when patients reach ESRD; thus, effective intervention must be started much earlier (Diaz-Buxo and Woods 2006). Patients with albuminuria and normal GFR also are at increased risk (Go *et al.* 2004). Evaluation for traditional risk factors, including high lipid levels, hypertension, smoking, and sedentary lifestyle, is essential (Snyder and Pendergraph 2005). The KDOQI (Kidney Disease Outcomes Quality Initiative) recommended a blood pressure goal of 130/80 mmHg in patients with normal urinary albumin concentrations, and a blood pressure goal of 125/75 mmHg in patients with excretion of more than 1 g of protein/24 hours (National Kidney Foundation 2002).

The KDOQI guidelines on managing dyslipidemias in CKD patients recommend an LDL cholesterol goal of less than 100 mg/dl (2.60 mmol/l) (National Kidney Foundation 2006). However, as mentioned above, some CKD patients with the lowest cholesterol levels are the most likely to die of CVD because low levels of cholesterol are associated with nontraditional cardiac risk factors of malnutrition and are markers of MICS (Kalantar-Zadeh *et al.* 2005, Liu *et al.* 2004). Additional cardiac risk factors specific to CKF include volume overload, hyperparathyroidism, uremia, anemia, endothelial dysfunction, and, especially in HD patients, oxidative stress (Eiselt *et al.* 1999).

Oxidative stress

Oxidative stress is the state in which the production of reactive oxygen species (ROS) exceeds the capacity of the antioxidant defense system in cells and tissues. ROS are free radicals, highly

reactive substances with an unpaired electron in the outer orbital, and other related reactive compounds (such as hydrogen peroxide and hypochlorous acid) that can attack lipids, proteins, and nucleic acids and alter the structure and function of these macromolecules (Klaunig *et al.* 1998, Eiselt *et al.* 1999). Specifically, LDL particles are damaged by excessive oxidation and consequently are not recognized by cell LDL receptors. They are subsequently accumulated in the blood in higher amounts and penetrate the vascular walls. This mechanism is probably the basis of atherosclerotic lesions. Oxidative stress threatens HD patients with serious clinical complications (e.g., accelerated atherosclerosis, amyloidosis, hemolysis, and the development of the state of chronic inflammation). Free radicals originate from leucocytes, which are activated during the contact with the dialysis membrane, and also from erythrocyte iron released as a consequence of hemolysis (Eiselt *et al.* 1999). Intravenous administration of iron often used as a supplement of EPO treatment can also contribute to oxidative stress, increasing free radical production by the so-called Fenton reaction (Lim *et al.* 1999). Co-administration of ascorbic acid with the goal of mobilizing iron stores further stimulates free radical formation, possibly by reduction of Fe(III) ions to more dangerous Fe(II) compounds (Eiselt *et al.* 2006).

Dialysis-related amyloidosis

Dialysis-related amyloidosis (DRA) is a frequent complication of CKF and long-term renal replacement therapy. Beta-2 microglobulin is a major constituent of amyloid fibrils in DRA. Amyloid deposition mainly involves bone and joint structures, presenting as carpal tunnel syndrome, destructive arthropathy, and subchondral bone erosions and cysts. The molecular pathogenesis of this complication remains unknown. Recent studies, however, have suggested a pathogenic role of a new modification of beta-2 microglobulin in amyloid fibrils. Increased carbonyl compounds derived from autoxidation of both carbohydrates and lipids modify proteins in uremia, leading to augmentation of advanced glycation end-products and advanced lipoxidation end-product production. Thus, uremia might be a state of carbonyl overload with potentially damaging proteins (carbonyl stress) (Miyata *et al.* 1999).

Hyperhomocysteinemia and endothelial dysfunction

Hyperhomocysteinemia is present in the majority of CKF patients. They have a plasma concentration of homocysteine (Hcy) elevated 3 to 4 times above normal (Suliman *et al.* 2001). The causes are still not clear, but the possibilities include defective renal or extrarenal metabolism as a result of uremic toxicity (Perna *et al.* 2004). In the general population, hyperhomocysteinemia is considered to be an independent risk factor for the development of CVD. As mentioned above, reverse epidemiology of traditional cardiovascular risk factors can occur in CKF, so that increased Hcy levels appear to be paradoxically associated with a better clinical outcome. The development of MICS is responsible for this phenomenon (Kalantar-Zadeh *et al.* 2005). Plasma Hcy concentration is higher in CRF patients with normal nutritional status than in malnourished patients. Plasma Hcy was inversely correlated with subjective global nutritional assessment and positively correlated with serum albumin and protein intake. Thus, serum albumin concentration is a strong determinant of plasma Hcy in patients with CRF, which may contribute to the lower Hcy levels in malnourished patients (Suliman *et al.* 2001).

On the other hand, the toxicity of Hcy results from the structural modification of proteins and DNA. Disruption of DNA methylation has been demonstrated to occur as a result of hyperhomocysteinemia and is associated with vascular damage (Perna *et al.* 2005). Hcy could be a principal candidate for endothelial dysfunction in patients with CRF. Hyperhomocysteinemia may impair endothelial function by the generation of oxygen species and decreased NO bioavailability. Normal endothelium is characterized by an intact and appropriately functioning eNOS–NO system in which eNOS is constitutively active and constantly generates small amounts of NO (Nedeljkovic *et al.* 2003). NO mediates normal endothelial and vessel wall functions including antithrombosis, endothelial permselectivity, and vasomotor tone. In addition, NO suppresses cellular proliferation (e.g., of vascular smooth muscle cells) and has a quenching effect on inflammation. The function of the eNOS–NO system is impaired in patients with CKD (Kone 1997). However, the precise mechanisms underlying the link between hyperhomocysteinemia and impaired endothelial function

in CRF remain unclear (Takamitsu and Nakanishi 2001). Some authors propose that accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, is the missing connecting link. Hcy is produced during ADMA synthesis and can alter ADMA catabolism mainly by inhibiting dimethylarginine dimethylaminohydrolase (Dayal and Lentz 2005). ADMA levels are elevated in CKD patients, and ADMA is a candidate as a new uremic toxin (De Deyn *et al.* 2003). In some studies, an increased level of ADMA has been identified as an independent predictor of mortality in patients with CKD (Ravani *et al.* 2005). In any case, modulation of endothelial function in CRF may offer a novel strategy to reduce CVD.

Thus, it is necessary to emphasize the necessity of searching actively for CKD. Unfortunately, it is often overlooked in its earliest, most treatable stages. Guidelines from the National Kidney Foundation's KDOQI recommend estimating GFR and screening for albuminuria in patients with risk factors for CKD, including diabetes, hypertension, systemic illnesses, age greater than 60 years, and family history of CKD. When CKD is detected, an attempt should be made to identify and treat the underlying conditions as well as the secondary abnormalities. These goals include slowing disease progression, detecting and treating complications, and managing cardiovascular risk factors. Suitable treatment also includes attention to the influence of elevated blood pressure, malnutrition, anemia, hyperparathyroidism, insulin resistance, disorders of lipid metabolism, and acid–base balance. At the same time, it is necessary to continue research projects focused on other areas that may uncover new aspects of cardiometabolic risk and its influence in CKD patients. These areas include the development of MICS, management of oxidative stress, and endothelium protection. Clearly, progress in management of CVD in patients with CKD will require collaboration with experts in the research and treatment of vascular disease.

Conclusion

CKD leading to CKF is an urgent medical problem in the context of demographic trends. In addition to the basic kidney disease, many metabolic disorders develop in the course of CKF. Particularly, patients in the terminal stage of CKF are endangered. Regular dialysis treatment

decreases the accumulation of metabolites; however, it contributes to a deficit of some important metabolic regulators and to the development of a chronic inflammation state. These factors can lead to serious secondary complications in CKF, including atherosclerosis and related cardiovascular disease, malnutrition, anemia, renal bone disease, and other problems. These complications markedly and negatively affect the prognosis and quality of life of patients with CKF and increase costs for their treatment. The prognosis of CKD patients can be improved if kidney disease is diagnosed early and properly cured, inclusive of the secondary complications. Appropriate treatment encompasses consistent control of blood pressure, prevention of malnutrition, anemia, and hyperparathyroidism, and treatment of metabolic disorders. It is necessary to search actively for kidney disease and to develop new therapeutic methods to improve the quality of life of CKD patients. At the same time, we must try to reduce economic costs connected with treatment.

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