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Metabolic Complications of Chronic Kidney Failure and Hemodialysis

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1. Introduction

Chronic kidney disease 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 chronic kidney disease currently affects approximately 19 million adult Americans, with an incidence that is still increasing (Snyder & 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 a further important factor.

Chronic kidney disease is characterized by progressive deterioration of kidney function, which develops eventually into a terminal stage of chronic kidney failure. Chronic kidney failure has traditionally been categorized as mild, moderate, or severe. Other poorly defined terms like uremia and end-stage renal disease have commonly been applied. During the last few years, an international consensus has emerged categorizing chronic kidney failure 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). RIFLE (from Risk, Injury, Failure, Loss, End Stage) is a modern classification of acute renal failure and it is noteworthy here (Van Biesen et al., 2006).

Stage 5 of chronic kidney failure represents the total inability of kidneys to maintain homeostasis, and this metabolic state is without treatment 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 hemodialysis, peritoneal dialysis, and other extracorporeal purifying procedures, or kidney transplantation.

Chronic kidney failure is associated with many kinds of metabolic changes caused by the kidney disease itself and also attributable to dialysis treatment. Phenomena such as accumulation or deficit of various substances and dysregulation of metabolic pathways participate and combine in the pathogenesis of these changes. 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, substances with middle molecular weight such as beta-2 microglobulin and other). 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. The deficit of some important substances in chronic kidney failure 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 or active vitamin D) in kidneys also plays an important role (Cibulka & Racek, 2007).

All of the abovementioned factors lead to many serious complications for patients with chronic kidney disease during the course of predialysis and dialysis. All markedly affect prognosis and the quality of life of these patients.

Metabolic complications of chronic kidney failure and hemodialysis include basically changes in acid-base balance and changes in metabolism of proteins, carbohydrates and lipids. Furthermore, we describe disorders typical for chronic kidney disease such as renal anemia, bone mineral disease, atherosclerosis and cardiovascular disease, oxidative stress, dialysis-related amyloidosis, hyperhomocysteinemia and endothelial dysfunction.

2. Acid–base balance

Acid-base disorder is commonly observed in the course of chronic kidney failure.

Metabolic acidosis is noted in a majority of patients when GFR decreases to less than 25% of normal. The degree of acidosis approximately correlates with the severity of chronic kidney failure and usually is more severe at a lower GFR. Metabolic acidosis can be of the high-anion-gap type, although anion gap can be normal or only moderately increased even with stages 4 or 5 of chronic kidney failure (Kraut & 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).

Metabolic acidosis resulting from advanced chronic kidney failure 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, symptomatic 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, e.g. muscle wasting, bone disease, abnormalities in growth hormone and thyroid hormone secretion, impaired insulin sensitivity, and exacerbation of beta-2 microglobulin accumulation (Kraut & 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 treated with sodium bicarbonate complain of gastric discomfort. In this case, they may use Shohl's solution (a mixture of sodium citrate and citric acid). In dialysis patients, the 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).

3. Protein metabolism

Patients with chronic kidney disease in predialysis stages have to keep a low-protein diet to protect kidneys against hyperfiltration and following progression of chronic kidney disease. On the other hand, a too-strict low-protein diet can have a negative effect on nitrogen balance. A safe low-protein diet should contain 0.6 g of protein/kg/day, minimally. Disorders in protein metabolism in hemodialysis patients 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 a further important factor that markedly contributes to negative nitrogen and total body protein balance in patients with chronic kidney failure (Kovacic et al., 2003).

It has been demonstrated that the presence of uremic malnutrition increases mortality and morbidity in chronic dialysis patients (Ikizler et al., 1999). It is very often combined with a chronic inflammation state in the syndrome known as malnutrition-inflammation complex syndrome (Kalantar-Zadeh et al., 2003). Chronic inflammation accelerates the catabolism and deepens the negative nitrogen balance. The malnutrition-inflammation score (MIS) is a number from 0 to 30 by which an outcome of a dialysis patient can be estimated. Its calculation includes seven components of subjective global assessment, body mass index, and serum albumin and transferrin concentrations. Higher value of MIS indicates worse outcome of a patient (Rambod et al., 2009).

4. Carbohydrate metabolism

Disorders of carbohydrate metabolism are very frequent in patients with chronic kidney failure. On the one hand, diabetes mellitus is the most common cause of kidney failure. Diabetics represent about 35% of all dialyzed patients. In these cases, the causality seems to be relatively clear.

On the other hand, a majority of dialyzed patients are not diabetics. But also non-diabetics patients with chronic kidney disease have often disorders of carbohydrate metabolism. Impaired glucose tolerance occurs together with the loss of kidney function (Alvestrand, 1997). Insulin resistance is primarily detectable when 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 & 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

chronic kidney failure, such as exercise intolerance, anemia, metabolic acidosis, secondary hyperparathyroidism, or insufficient activation of vitamin D, also indirectly play a role (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 chronic kidney failure (Shinohara et al., 2002). The underlying mechanism can be an impaired synthesis of nitric oxide (NO) in endothelium of patients with chronic kidney disease. It was proved that appropriately functioning endothelial NO synthase is important for the control not only of arterial pressure but also of glucose and lipid homeostasis (Duplain et al., 2001).

Disturbance in synthesis of adipocytokines may contribute to the insulin resistance and related metabolic disorders in patients with chronic kidney failure. Patients with metabolic syndrome have lower levels of adiponectin and, on the contrary, higher levels of leptin than patients without metabolic syndrome (Vostry et al., 2008).

5. Lipid metabolism

Lipid metabolism appears to be substantially influenced by the severity of renal dysfunction.

Patients with chronic kidney disease have elevated levels of triglycerides mainly because of enhanced production of triglyceride-rich lipoproteins such as very-low-density lipoproteins (VLDL) in the liver (Attman et al., 1993). Further reasons are decreased activities of hepatic lipase and peripheral lipoprotein lipase. These abnormalities in turn may be due to an inhibitory effect of hyperparathyroidism, calcium accumulation in islet cells resulting in impaired insulin action, elevated level of apolipoprotein C-III which acts as a direct lipase inhibitor, or a putative circulating inhibitor detected in uremic plasma (Shurraw & Tonelli, 2006). Hyperinsulinemia is, however, probably the main factor increasing synthesis of triglycerides and directly decreases activity of lipoprotein lipase.

Insufficient mitochondrial beta-oxidation, due to a deficit of L-carnitine, is an important factor for the development of disorder in lipid metabolism in hemodialysis patients. L-carnitine is an essential substance for transport of long chain fatty acids across the inner mitochondrial membrane into mitochondrial matrix where beta-oxidation proceeds (Cibulka et al., 2005).

Following changes in lipid metabolism are also found in many patients with chronic kidney failure. The most prominent are increased serum triglyceride levels mentioned above 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 lipoprotein particles 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 (Cibulka & Racek, 2007).

The contribution of this complex atherogenic form of dyslipidemia to cardiovascular disease in patients with chronic renal disease is not absolutely clear. Some studies reported negative results regarding the predictive power of serum lipids for the development of cardiovascular disease in these patients (Wanner & Krane, 2002). Recent findings have suggested that the development of malnutrition-inflammation complex syndrome is

responsible for this phenomenon. Because malnutrition-inflammation complex syndrome leads to a low body mass index, hypocholesterolemia, hypohomocysteinemia, and other manifestations, a reverse epidemiology of traditional cardiovascular risk factors occurs in patients with chronic kidney failure (Kalantar-Zadeh et al., 2003). It means that for example hypercholesterolemia, obesity or hyperhomocysteinemia appear to be protective and paradoxically associated with a better outcome.

It is well known that HDL cholesterol level is 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 could be involved in this process (Mackness et al., 1993). It was proved that serum paraoxonase 1 activity is reduced in patients with chronic kidney failure. The possible causes can include reduced HDL level, altered HDL subfraction distribution, reduced paraoxonase 1 concentration and its different phenotype distribution. Another possible explanation could be that paraoxonase 1 activity is inhibited in the uremic environment. Generally, reduced serum paraononase 1 activity could also contribute to the accelerated development of atherosclerosis in patients with chronic kidney failure (Dirican et al., 2004).

Lipoprotein (a) has been identified as an independent risk factor for atherosclerotic cardiovascular disease. It was found to be consistently elevated in a considerable proportion of patients with chronic kidney disease. Plasma concentration of lipoprotein (a) is highly heritable and mainly determined by a size polymorphism of apolipoprotein (a). It has been demonstrated that the low-molecular-weight apolipoprotein (a) phenotype independently predicted coronary artery disease occurrence (Kronenberg et al., 1999). It has been suggested that the apolipoprotein (a) size and the lipoprotein (a) plasma concentration may play a synergistic role in advanced atherosclerosis.

Patients treated with peritoneal dialysis have a similar but more severe dyslipidemia compared to hemodialysis patients due to stimulation of hepatic lipoprotein synthesis by glucose absorption from dialysate, increased insulin levels, and selective protein loss in dialysate analogous to the nephrotic syndrome (Shurraw & Tonelli, 2006).

6. 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 chronic kidney failure. Anemia has 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 hemodialysis patients (Cibulka & Racek, 2007).

The major cause of renal anemia in patients with chronic kidney disease is an inadequate production of the glycoprotein hormone erythropoietin 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 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., uremic toxins, parathormone, protein malnutrition) (Cibulka & Racek, 2007).

The introduction of recombinant human erythropoietin has revolutionized the treatment of anemia in patients with chronic kidney failure. The majority of patients respond very well,

however, about 10% of patients show some resistance to this therapy. The most common causes of that are considered iron deficiency (Santoro, 2002) and the development of malnutrition-inflammation complex syndrome (Kalantar-Zadeh et al., 2003). The erythropoietin 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 mentioned above. In hemodialysis patients, a complex of complications related to the deficit of this important substance is marked as dialysis-related carnitine disorder. This disorder is a functional metabolic deficiency which can have a negative impact on erythrocyte production and survival. Laboratory studies examining the influence of L-carnitine on red blood cell function and clinical trials in hemodialysis patients support the use of L-carnitine in the setting of erythropoietin hyporesponsiveness (Golper et al., 2003).

The supplementation with iron in patients with chronic kidney disease might obviate or delay the need for treatment with erythropoietin. Oral iron is inferior to intravenous iron in patients on hemodialysis, in part because elevated serum levels of hepcidin prevent intestinal absorption of iron. Increased levels of hepcidin, a peptide hormone produced by the liver, also impair the normal recycling of iron through the reticuloendothelial system (Besarab & Coyne, 2010).

7. Bone mineral disease

Bone mineral disease or renal osteodystrophy are terms which are used to describe the skeletal abnormalities of many patients with chronic kidney disease.

Bone mineral disease is basically 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 on bone. Low bone turnover syndromes are represented by the increasingly prevalent adynamic bone disease or less commonly, by osteomalacia. These disorders may occur in combination or alternately, each may predominate in any given patient (Gonzalez & Martin, 2001).

The most important factor which is responsible for the development of secondary hyperparathyroidism is a deficit of active vitamin D (calcitriol). Diseased kidneys cannot sufficiently hydroxylate 25-hydroxycholecalciferol, which is a precursor of calcitriol (1,25-dihydroxycholecalciferol). 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-alpha-hydroxylase even more. Long-lasting hypocalcemia and coincidental hyperphosphatemia lead to the stimulation of parathyroid glands with subsequent secondary hyperparathyroidism which causes decalcification of bones (Cibulka et al., 2007). 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 chronic kidney failure, much overlap occurs (Gonzalez and Martin, 2001).

Moreover, hyperphosphatemia has been recognized as an important risk factor for cardiovascular disease mortality in patients with chronic kidney failure. It is a direct cause of vascular calcification, the cardio-bone connection (Lund et al., 2006).

The treatment of vitamin D deficiency when present in patients with chronic kidney disease is warranted since such therapy may reduce or prevent secondary hyperparathyroidism in

the early stages. In patients with chronic kidney disease and GFR of 20 to 60 ml/min, nutritional vitamin D deficiency and insufficiency can both be prevented by supplementation with vitamin D_2 (ergocalciferol) or vitamin D_3 (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 chronic kidney failure 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 (National Kidney Foundation, 2004). Calcitriol himself and 1-alpha-hydroxylated derivate of calcitriol (alphacalcidiol) are also commonly used for supplementation in clinical practice.

In hemodialysis patients, the administration of L-carnitine may also have some positive effects on bone metabolism. It probably increases production of osteoprotegerin which is one of the most important regulators of osteoclastogenesis. Osteoprotegerin is a tumor necrosis factor-related cytokine which is produced by osteoblasts. It suppresses bone resorption and increases the density, area and strength of bone (Cibulka et al., 2007).

8. Atherosclerosis and cardiovascular disease

Cardiovascular disease is the leading cause of death in patients with chronic kidney failure. For every registry reporting national dialysis data in Europe, the U.S., Japan, and elsewhere, about 50% of deaths are attributed to cardiovascular disease. In comparison with the general population, dialysis patients have a greater than 20-fold increased risk of a cardiovascular death (Levey & Eknoyan, 1999). A majority of these deaths are related to atherosclerosis with subsequent myocardial infarction, cerebrovascular accidents (strokes), and ischemic events of the limbs. Additionally, patients with chronic kidney disease exhibit evidence of early and exaggerated vascular and cardiac remodeling (arteriosclerosis and left ventricular hypertrophy). The risk of cardiovascular disease and associated mortality increases in proportion to the decrease of 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 end-stage renal disease; thus, effective intervention must be started much earlier (Diaz-Buxo & Woods, 2006). Patients with albuminuria and normal GFR also are at increased risk (Go et al., 2004).

Evaluation of traditional risk factors, including lipid levels, blood pressure, smoking, and sedentary lifestyle, is essential (Snyder & 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 patients with chronic kidney disease recommended an LDL cholesterol goal of less than 100 mg/dl (2.60 mmol/l) (National Kidney Foundation, 2006). We use statins at moderate doses for reduction of LDL cholesterol levels.

However, as mentioned above, some patients with chronic kidney disease with the lowest cholesterol levels are the most likely to die of cardiovascular disease because low levels of cholesterol are associated with nontraditional cardiac risk factors of malnutrition and inflammation (Liu et al., 2004). Additional cardiac risk factors specific to chronic kidney failure may also play an important role in the development of atherosclerosis. Among these factors we include for example volume overload, hyperparathyroidism, uremia, anemia, endothelial dysfunction, and, especially in hemodialysis patients, oxidative stress (Cibulka & Racek, 2007).

Statins probably influence, except the LDL cholesterol levels, still other cardiovascular risk factors, namely the chronic inflammation state. It is manifested as a decrease of C-reactive protein level. Large observational studies demonstrate that statin treatment is associated with a significant reduction of mortality in dialysis patients (Shurraw & Tonelli, 2006).

9. Oxidative stress

Oxidative stress is a state in which the production of reactive oxygen species exceeds the capacity of the antioxidant defense system in cells and tissues. Reactive oxygen species 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). 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 hemodialysis 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 can also contribute to oxidative stress, increasing free radical production by the so-called Fenton reaction. 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).

10. Dialysis-related amyloidosis

Dialysis-related amyloidosis is a frequent complication of chronic kidney failure and long-term renal replacement therapy. Beta-2 microglobulin is a major constituent of amyloid fibrils. 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).

Dialysis-related amyloidosis is one of the most harmful osteoarticular complications with regard to the maintenance of daily activities and quality of life in patients undergoing long-term dialysis therapy (Yamamoto et al., 2009).

11. Hyperhomocysteinemia and endothelial dysfunction

Hyperhomocysteinemia is present in the majority of patients with chronic kidney failure. They have a plasma concentration of homocysteine 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 cardiovascular disease. As mentioned above, reverse epidemiology of traditional cardiovascular risk factors occurs in patients with chronic kidney failure, so that increased homocysteine levels appear to be paradoxically associated with a better clinical outcome. The development of malnutrition-inflammation complex syndrome is responsible for this phenomenon. Plasma homocysteine concentration is higher in patients with normal nutritional status than in malnourished patients. Plasma homocysteine 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 homocysteine concentration in patients with chronic kidney failure.

On the other hand, the toxicity of homocysteine results from the structural modification of proteins and deoxyribonucleic acid (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). Homocysteine could be a principal candidate for endothelial dysfunction in patients with chronic kidney failure. Hyperhomocysteinemia may impair endothelial function by the generation of oxygen species and decreased NO bioavailability. NO is produced by endothelial NO synthase and it has many positive vascular effects. It 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 endothelial NO synthase is impaired in patients with chronic kidney disease (Kone, 1997). However, the precise mechanisms underlying the link between hyperhomocysteinemia and impaired endothelial function in chronic kidney failure is not quite clear. Some authors propose that accumulation of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, could be the missing connecting link. Homocysteine is produced during ADMA synthesis and can alter ADMA catabolism mainly by inhibiting dimethylarginine dimethylaminohydrolase (Dayal & Lentz, 2005). ADMA levels are elevated in patients with chronic kidney disease, and ADMA should be considered to be a futher uremic toxin. In some studies, an increased level of ADMA has been identified as an independent predictor of mortality in patients with chronic kidney disease (Ravani et al., 2005; Cibulka et al., 2007).

In any case, influence the endothelial function in chronic kidney failure may offer a novel strategy to reduce risk for cardiovascular disease.

12. Conclusion

In conclusion, it is necessary to emphasize the importance of searching actively for chronic kidney disease. 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 chronic kidney disease, including diabetes, hypertension, systemic illnesses, age greater than 60 years, and family history of chronic kidney disease. When chronic kidney disease 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 patients with chronic kidney disease. These areas include the development of malnutrition-inflammation complex syndrome, management of oxidative stress, and endothelium protection. Clearly, progress in management of cardiovascular disease in patients with chronic kidney disease will require collaboration with experts in the research and treatment of vascular disease.

13. Acknowledgement

14. References

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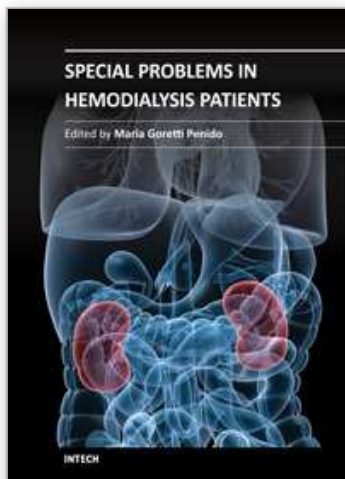
Special Problems in Hemodialysis Patients

Edited by Prof. Maria Goretti Penido

This book provides an overview of special cases in hemodialysis patients. Authors have contributed their most interesting findings in dealing with patients suffering of other diseases simultaneously, such as diabetes, cardiovascular disease and other health problems. Each chapter has been thoroughly revised and updated so the readers are acquainted with the latest data and observations in these complex cases, where several aspects are to be considered. The book is comprehensive and not limited to a partial discussion of hemodialysis. To accomplish this we are pleased to have been able to summarize state of the art knowledge in each chapter of the book.

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