Chronic Kidney Disease as a Metabolic Syndrome with Malnutrition—Need for Strict Control of Risk Factors

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Abstract

Patients with chronic kidney disease (CKD) have been found to have an increased risk for death from cardiovascular disease (CVD). They have multiple metabolic abnormalities that may accelerate atherosclerosis, such as hypertension, insulin resistance, and dyslipidemia, along with other CKD-related risk factors. In addition, a considerable proportion of patients with advanced stages of CKD are malnourished, presenting “metabolic syndrome with malnutrition”. The presence of malnutrition/inflammation dramatically changes the apparent relationship between CVD death risk and some risk factors. For example, in stage 5 CKD patients on hemodialysis, a higher body mass index and a higher plasma cholesterol are predictors of better survival. To understand the paradoxical epidemiology, we should recognize risk factors for occurrence of CVD events and risk factors of fatality after an event. In this article, we review the unique situation of CKD, emphasizing the need of more strict control of both types of risk factors to improve survival of CKD patients. (Internal Medicine 44: 179–187, 2005)

Key words: atherosclerosis, cardiovascular disease (CVD), risk factors, chronic kidney disease (CKD), malnutrition

Elevated Risk of Cardiovascular Disease in Chronic Renal Failure

According to the latest statistics, there are more than 230,000 patients receiving dialysis therapy in Japan. As compared with the general population, hemodialysis patients are at an increased risk of death, and cardiovascular disease (CVD) is the leading cause of death in the dialysis population. More than one half of these patients die from CVD including ischemic heart disease, stroke, peripheral arterial disease, congestive heart failure, and sudden death. The relative risk of CVD death in hemodialysis patients is in the range of 10–30. The aim of this review is to determine the basic strategies to prevent CVD and to improve the outcome of patients with chronic kidney disease (CKD) by managing metabolic alterations.

One of the major causes for the increased risk of CVD death is advanced arterial changes. Patients treated by hemodialysis have increased arterial wall thickness, measured as intima-media thickness of the carotid artery (CA-IMT) (4–7). They also have increased arterial wall stiffness, measured as aortic pulse wave velocity (PWV) (8–10). Both of the morphological (11–13) and the functional changes (14, 15) of the large arteries are shown to be significant predictors of CVD death in hemodialysis patients. Although Lindner et al (1) previously speculated that chronic hemodialysis treatment may accelerate atherosclerosis, predialysis patients with chronic renal failure have increased CA-IMT (6) and aortic PWV (10) to a degree comparable with those on maintenance hemodialysis. The existence of renal failure, rather than the hemodialysis procedure, was a significant risk factor for these arterial wall changes independent of other traditional risk factors. Interestingly, being treated by hemodialysis was not a significant factor associated with CA-IMT (6). Based on these recent findings, we should consider renal failure as an important and independent risk factor for morphological and functional changes of large arteries that are present before starting renal replacement therapy.

Concept of Chronic Kidney Disease (CKD)

Arterial wall changes are present in patients with earlier stages of renal disease. Aortic PWV is inversely correlated with the glomerular filtration rate (GFR) in hypertensive patients with moderate renal insufficiency (16). As compared to those with a normal urinary albumin excretion rate, increased aortic PWV, CA-IMT, and impaired endothelial function are documented in subjects with microalbuminuria.
(17), one of the earliest signs of kidney damage. In addition, the presence of microalbuminuria (18, 19) and reduced GFR (20) are both significant predictors of CVD. Thus, not only patients with end-stage renal disease (ESRD), but also those with very early signs of renal damage have arterial wall changes and the increased risk of CVD.

Chronic kidney disease (CKD) is a concept covering broad spectrum of kidney dysfunction from microalbuminuria or other evidence of kidney damage to ESRD proposed by the National Kidney Foundation (NKF) in 2002 (21). Stages of CKD are defined primarily by GFR standardized by body surface area (ml/min/1.73 m^2) into Stage 1 (90 or higher), Stage 2 (60–89), Stage 3 (30–5), Stage 4 (15–29), and Stage 5 (<15 or dialysis). This new staging system can be applied to a wide range of renal damage caused by any kind of underlying renal disease such as chronic glomerulonephritis, hypertensive nephrosclerosis and diabetic nephropathy. NKF has proposed the NKF K/DOQI guidelines for managing dyslipidemias (22), hypertension (23), and other complications (24) in CKD patients. Following these activities by nephrologists, the American Heart Association (AHA) has published the scientific statement that CKD is a significant risk factor of CVD (25). Clearly, CVD in CKD has gained the attention of not only nephrologists but also cardiologists and physicians in other fields of medicine.

**Dyslipidemias in Patients with CKD**

Patients with advanced stages of CKD often have hypertriglyceridermia and a lowered high-density lipoprotein (HDL) cholesterol level. Low-density lipoprotein (LDL) cholesterol is usually within the normal range (26). Elevated serum triglycerides (TG) reflect the accumulation of TG-rich lipoproteins such as very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). The mean level of IDL-cholesterol is 2–3 times higher in non-diabetic hemodialysis patients than the healthy subjects (27), and the level is further elevated in hemodialysis patients with diabetes mellitus (28). The increased levels of TG-rich lipoproteins are explained by catabolic defects caused by suppressed activity of hepatic triglyceride lipase (HTGL, HL). Post-heparin plasma lipoprotein lipase (LPL) levels are reported to be normal (29, 30) or decreased (31), but the decrease in the apolipoprotein C-II/C-III ratio (32) may contribute to the impaired co-activator function for LPL, making uremic VLDL resistant to LPL. LDL size is smaller in diabetic nephropathy (33), but the LDL size returns to normal in patients on maintenance hemodialysis (34), presumably because the reduced HL activity in dialysis patients fails to convert large LDL into small dense LDL.

Patients with stage 5 CKD on hemodialysis or peritoneal dialysis have markedly lowered HDL-cholesterol (35), particularly cholesterol of the HDL2 subfraction. An in vivo kinetics study (36) of apolipoprotein A-I, the major protein of HDL, revealed that the apolipoprotein A-I catabolic rate is increased in hemodialysis patients. Hypertriglycerideremia and impaired enzymatic activities of LPL, HL, and lecithin-cholesterol acyltransferase (LCAT) (37) are factors responsible for the lowered HDL-cholesterol and abnormal HDL subfraction distribution (30). Although the precise mechanisms are unknown for the altered enzyme levels, some of the enzymatic changes are shown to be associated with altered calcium homeostasis (30).

Arterial wall changes are associated with some of these lipoprotein abnormalities in CKD. In our previous analysis of hemodialysis patients, aortic PWV was found to be significantly correlated with VLDL-, IDL-, and LDL-cholesterol levels, independent of age, gender, blood pressure, and dialysis duration (9). Therefore, the sum of cholesterol of these non-HDL lipoproteins, namely non-HDL-cholesterol, serves as an integrated marker of atherogenic lipoproteins (38). Non-HDL-cholesterol is also positively correlated with CA-IMT in predialysis (6) and maintenance hemodialysis patients (5). Increased anti-oxidized LDL antibody titer is inversely correlated with IMT in hemodialysis patients (39), as well as in the general population (40). Thus, the direction of correlation between plasma lipids and arterial wall changes in renal failure patients is the same as that of the general population.

CVD events in hemodialysis patients are also associated with plasma lipids and lipoprotein parameters. Koch et al (41) reported that a history of myocardial infarction is associated with higher levels of total cholesterol, LDL-cholesterol, apolipoprotein B, and low molecular weight isoforms of apolipoprotein (a) compared to those without myocardial infarction. According to a report of the Japanese Society for Dialysis Therapy (42), the risk of new myocardial infarction in one year is higher in those with higher plasma cholesterol levels regardless of the presence of diabetes mellitus. These data indicate that the atherogenic lipoprotein changes known for the general population also increase the risk of CVD events in the hemodialysis population.

The relationship between plasma lipids and mortality risk in observational cohort studies among CKD patients on dialysis is confusing. Previous studies in hemodialysis patients (43) have shown that those with a higher plasma total cholesterol had a lower risk of overall mortality. This was true for deaths from cardiovascular diseases (43). Iseki et al (44) confirmed the inverse correlation between cholesterol and mortality risk in Japanese hemodialysis patients, but they carefully found that an adverse impact of hypercholesterolemia was present in a subset of hemodialysis patients having serum albumin of 4.5 g/dl or higher. A recent study by Liu et al (45) showed that mortality risk was inversely related to plasma cholesterol in the total cohort of their hemodialysis patients, as previously shown in other studies. When the subjects were divided into two subgroups based on the presence and absence of inflammation/malnutrition status, the association between mortality risk and cholesterol remained significant and negative in the subgroup with inflammation/malnutrition. However, the relationship between cholesterol and mortality risk was significant and positive in those without
signs of inflammation/malnutrition. The risk of cardiovascular death was surprisingly low in hemodialysis patients with low plasma cholesterol levels in the subgroup without inflammation/malnutrition.

These studies indicate that dyslipidemia is bad for the morphologic and functional properties of large arteries, and increases the risk of CVD events in dialysis patients. The adverse effect of dyslipidemia on mortality is also significant in hemodialysis patients without inflammation/malnutrition. However, the relationship between plasma cholesterol and mortality risk is strongly modified by the presence of inflammation/malnutrition status, presumably through interaction between inflammation/malnutrition and plasma lipids (reduced lipid levels in ill conditions).

**Underweight Rather Than Overweight as a Risk Factor of Death**

Although racial difference is known for the BMI-survival relationship among dialysis patients (46, 47), underweight has been recognized as an important predictor of poor survival in hemodialysis patients. This is in sharp contrast to the situation in the general population where overweight or obesity is an established risk factor of CVD. In hemodialysis patients, a higher BMI is associated with a lower risk of death from all causes (43, 48, 49), CVD (43) and other causes (43). This is true in a wide range of BMI in a recent cohort study (47) including more than 418,000 patients starting hemodialysis. Because high BMI remained a significant and independent predictor of better survival even after adjustment for other nutritional parameters (50), the survival advantage associated with high BMI suggests some undefined mechanisms other than better nutrition.

In addition to dialysis patients, high BMI is associated with better survival in elderly individuals (51–54). Also, in patients with congestive heart failure, better survival was predicted by high BMI and high cholesterol (55). Based on these observational studies, it may be that increased body fat and/or muscle mass have protective effects on survival when the subjects are ill. Further data on the relative importance of body fat and lean mass on outcome is necessary.

**Other Risk Factors**

Other risk factors for CVD include blood pressure, homocysteine, inflammation markers, pro-inflammatory cytokines, insulin resistance, glycemic control in diabetics, adiponectin, oxidized LDL, and other CKD-related risk factors.

Blood pressure has a positive correlation with arterial wall thickness and stiffness in hemodialysis and predialysis patients with renal failure. However, blood pressure-mortality curves show a U-shaped relationship in dialysis patients (56). Increased mortality risk at low blood pressure may indicate pre-existence of impaired cardiac function. In fact, among patients with congestive heart failure, high blood pressure is a predictor of better survival (55). In a recent study (57), hemodialysis-associated hypotension was shown to be an independent predictor of 2-year mortality in hemodialysis patients. It is conceivable that hypertension is bad for atherosclerosis and heart failure, but once cardiac function is impaired, low blood pressure is a sign of poor outcome.

Hyperhomocysteinemia is associated with atherosclerotic arterial wall changes (13) and an increased risk of CVD events (58), whereas it is associated with a reduced risk for mortality in hemodialysis patients (59), presenting another example of the risk factor paradox. This can also be explained by the close interaction between malnutrition and a lowered homocysteine concentration (59).

C-reactive protein (CRP) is positively associated with CA-IMT (6). CVD mortality is predicted by increased CRP (60) and elevated interleukin-6 (61), one of the pro-inflammatory cytokines. There is an inverse correlation between creatinine clearance and the plasma levels of CRP and interleukin-6 (62). Since at least some pro-inflammatory cytokines are excreted through the kidneys, CKD may directly increase plasma cytokines and induce inflammation. Also, the genotype of interleukin-10, an anti-inflammatory cytokine, is a predictor of cardiovascular events: The -1082A* allele of interleukin-10 gene, which is associated with a low production of interleukin-10 and elevated inflammation markers such as CRP, was predictive for a higher cardiovascular morbidity compared to the –1082G* genotype (63).

Insulin resistance develops in uremic patients as evidenced by decreased glucose disposal in response to insulin infusion during glucose clamp test (64). The insulin resistance index derived from homeostasis model assessment (HOMA-IR) correlates well with the result of glucose clamp test in patients with and without renal failure (65). High HOMA-IR (insulin resistance) was an independent predictor of death from CVD in non-diabetic hemodialysis patients (66). In diabetic patients starting hemodialysis, a high level of glycohemoglobin (HbA1c) is a predictor of poor survival (67).

Oxidative stress and lipoprotein oxidation are believed to exert important roles in atherosclerosis and CVD. In dialysis patients, the lag phase during in vitro oxidation of plasma LDL is reported to be shorter than normal (68), suggesting that the oxidizability of uremic LDL is increased. A high titer of serum anti-oxidized LDL antibody (69) may be another indirect support for elevated oxidized LDL levels in these patients. Direct measurement of plasma oxidized LDL is needed to conclude whether or not oxidized LDL is increased in CKD. An increased serum titer of anti-oxidized LDL antibody inversely correlated with arterial wall thickness (IMT) among hemodialysis patients (39), as well as in the general population (40). Also, an increased serum anti-oxidized LDL antibody is an independent predictor of the reduced risk of CVD mortality (70). These studies indirectly indicate that oxidized LDL is involved in atherosclerosis and CVD of CKD patients.

There are CKD-related risk factors for mortality, such as underlying renal disease, renal anemia (71), delivered dose
of dialysis (Kt/V) (72), increased serum phosphate (73), high and low levels of parathyroid hormone (PTH) (74, 75), and presumably vitamin D deficiency (76, 77). The repeat dialysis procedure itself may have some impact on inflammation and outcome. Arterial calcification is also a predictor of CVD mortality in hemodialysis patients (78). These CKD-related risk factors, combined with the deterioration of the common risk factors, are presumably responsible for the elevated risk of death in CKD patients.

**Understanding of Reverse Epidemiology**

Theoretically, mortality risk is the product of the risk of event occurrence and the risk of fatality (79). Some patients who have had a heart attack may die due to the event, but others may survive despite the dangerous event. Therefore, some risk factors for mortality may increase the risk of event occurrence, whereas others may raise the risk of fatality. As discussed above, reverse epidemiology is known for BMI in dialysis patients, elderly people, and patients with congestive heart failure. Based on these findings, increased BMI may be protective when the patients are ill. In other words, low BMI or poor nutritional status could fall into the latter category of risk factors influencing the fatality risk after having a serious event, although direct evidence is needed. Although the mechanism for the protective effect of increased BMI is unknown at present, it may be a low likelihood of energy depletion in obese patients. Following an event, they could survive for a certain period of time that is needed to recover from the event, without food intake or instead of increased energy requirement. Otherwise, muscle and/or other protein storage may be used for gluconeogenesis for survival.

Another possibility is that adipocyte function is altered in ill conditions. We recently found that the negative effects of male gender and increased body fat mass on adiponectin, an anti-atherogenic adipocytokine (80), were insignificant in hemodialysis patients (81). This suggests that the adverse impact of fat mass is severely attenuated and the protective effect of fat mass becomes dominant in this condition.

The reverse epidemiology for plasma cholesterol may be explained by the interaction between malnutrition and plasma lipids at the level of fatality risk. As reviewed above, dyslipidemia is associated with advanced arterial wall changes and an increased risk of CVD event in dialysis patients. Adverse effect of dyslipidemia on mortality is also significant in dialysis patients without inflammation/malnutrition. However, the relationship between plasma cholesterol and mortality risk is reversed in the presence of inflammation/malnutrition. We speculate that dyslipidemia itself increases the risk of CVD event occurrence, whereas malnutrition raises the risk of fatality.

**Lipid Reduction to Prevent CVD Events**

CKD patients have multiple risk factors for CVD and malnutrition. Some risk factors may increase the risk of CVD event occurrence, and others may increase the risk of fatality following the event. Probably, some risk factors are acting both ways. For example, diabetes mellitus is a predictor of CVD event occurrence (82), and also a predictor of poor survival after ischemic heart attack and congestive heart failure (82). To reduce the risk of death from CVD, we should aim at the prevention of CVD events, and also the reduction of fatality risk.

Lipid reduction without worsening nutritional state will decrease the risk of CVD event occurrence. In a primary prevention trial with pravastatin in the general population (WOSCOPS) (83), the treatment reduced the occurrence of myocardial infarction by 31%, and the death due to myocardial infarction by 28%, suggesting that fatality risk was not changed by this treatment. High cholesterol level was associated with increased risk of CVD death in dialysis patients without malnutrition (45). Malnutrition presumably is a key factor for increased fatality and low cholesterol. If so, it would be a logical conclusion that dyslipidemia and other risk factors for event occurrence should be controlled in CKD patients as in the general population, but that nutritional condition and body weight should be kept or rather increased in this unique patient group presenting “metabolic syndrome with malnutrition”.

The NKF K/DOQI has published the Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease in 2003 (22). Based on the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Panel III (ATP III) (84) and the fact that CKD patients are at the highest risk for CVD, the K/DOQI guidelines recommend the target LDL cholesterol level <100 mg/dl (Table 1). In patients with increased fasting triglycerides ≥200 mg/dl, non-HDL cholesterol <130 mg/dl is another target for prevention of CVD. Also, very high fasting triglycerides ≥500 mg/dl should be reduced to avoid pancreatitis. To achieve these targets, the guidelines recommend therapeutic lifestyle changes (TLC) and drug therapies using a statin, bile acid sequestrant, fibrate, or niacin.

Although a fibrate is an appropriate choice to normalize triglyceride-rich lipoprotein metabolism (85), most of the drugs in this class are not recommended for use in patients with renal failure, because of the renal excretion of these fibrates. Drug accumulation in plasma would increase the risk of rhabdomyolysis. However, only a few fibrate drugs may be used safely in patients with CKD. Clinofibrate (32) is excreted by the liver in experimental animals and human subjects, and was well tolerated by renal failure patients treated by peritoneal- or hemodialysis. To date, no outcome study with this fibric acid derivative has been reported for CKD patients or other patient groups. Recently, Tonelli et al (86) reported the subanalysis of the Veterans’ Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) study, a secondary intervention trial with gemfibrozil, that originally excluded subjects with increased serum creatinine (>2.0 mg/dl). Among the 2,531 original male subjects with
established coronary artery disease having an HDL cholesterol level of 40 mg/dl or less, an LDL cholesterol level of 140 mg/dl or less, and a triglyceride level of 300 mg/dl or lower, 1,046 men had decreased creatinine clearance of 75 ml/min or less by the Cockcroft-Gault equation. Of the subjects, 638, 406, and 2 had creatinine clearance of 60–75 ml/min, 30–59.9 ml/min, and <30 ml/min, respectively. During the median follow-up period of 5.3 years, the gemfibrozil recipients had a significantly lower risk of the primary outcome (coronary death or nonfatal myocardial infarction) with a hazards ratio of 0.73 (95% confidence interval 0.56–0.96, p=0.02). Although the overall incidence of adverse effects was similar between the gemfibrozil and placebo groups, the risk of sustained increase of serum creatinine was higher in individuals receiving gemfibrozil (5.9 vs 2.8%, p=0.02). It is unknown whether a fibrate drug can be safe and effective in reducing the risk of CVD in patients with more advanced stages of CKD. In an observational study by Seliger et al (87), the use of fibrate was not associated with better survival in patients starting dialysis.

Statins can be safely used in patients with CKD when monitored carefully. All statins available today are excreted through bile. Effective and safe use in Japanese dialysis patients has been reported for pravastatin (88), simvastatin (89), fluvastatin (90), and atorvastatin (91). These statins reduce plasma LDL cholesterol by approximately 25–40%. According to Seliger et al (87), the use of statin was significantly associated with better survival in patients starting dialysis, although this analysis was not controlled for plasma cholesterol level. Those on statin therapy were more likely to have a high cholesterol level, a predictor of better survival. The 4D trial (Die Deutsche Diabetes Dialyse Studie) (92, 93) is a randomized, placebo-controlled trial with atorvastatin in approximately 1,200 dialysis patients with type 2 diabetes mellitus. The final results are to be presented at the American Society of Nephrology meeting in October, 2004. There is another plan to conduct a randomized controlled intervention trial with rosuvastatin (the AURORA study) that will include close to 3,000 male and female patients on hemodialysis (94).

In our opinion, casual blood sampling may be useful enough to estimate the CVD risk, although the K/DOQI guidelines call for measurements after an overnight fast. The standard fasting blood is quite difficult to obtain in CKD patients particularly those on hemodialysis in the afternoon or evening sessions. Because total and HDL cholesterol levels do not change following oral fat load, non-HDL cholesterol is not affected by eating. Because non-HDL cholesterol is the sum of cholesterol of LDL, triglyceride-rich lipoproteins and remnant particles, it serves as an integrated marker of atherogenic lipoproteins. We (38) showed that non-HDL cholesterol by casual blood sampling was an independent predictor of CVD death in an observational cohort of hemodialysis patients (Fig. 1). Therefore, we propose that non-HDL cholesterol of <130 mg/dl in casual blood sample can be used as the target lipid level in hemodialysis patients (stage 5 CKD) regardless of the fasting plasma triglyceride level. With a statin that reduces non-HDL cholesterol by 40%, we can achieve the target non-HDL cholesterol of <130 mg/dl in patients with a pretreatment non-HDL cholesterol of <216 mg/dl. Therefore, we have sufficient tools to

**Table 1. The Management of Dyslipidemias in Adults with Chronic Kidney Disease Proposed by the NKF K/DOQI Clinical Practice Guidelines (2003)**

<table>
<thead>
<tr>
<th>Dyslipidemia</th>
<th>Goal</th>
<th>Initiate</th>
<th>Increase</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG ≥500 mg/dl</td>
<td>TG &lt;500 mg/dl</td>
<td>TLC</td>
<td>TLC+Fibrate or Niacin</td>
<td>Fibrate or Niacin</td>
</tr>
<tr>
<td>LDL 100–129 mg/dl</td>
<td>LDL &lt;100 mg/dl</td>
<td>TLC</td>
<td>TLC+low dose Statin</td>
<td>Bile acid seq. or Niacin</td>
</tr>
<tr>
<td>LDL ≥130 mg/dl</td>
<td>LDL &lt;100 mg/dl</td>
<td>TLC+low dose Statin</td>
<td>TLC+max. dose Statin</td>
<td>Bile acid seq. or Niacin</td>
</tr>
<tr>
<td>TG ≥200 mg/dl and Non-HDL ≥130 mg/dl</td>
<td>Non-HDL &lt;130 mg/dl</td>
<td>TLC+low dose Statin</td>
<td>TLC+max. dose Statin</td>
<td>Fibrate or Niacin</td>
</tr>
</tbody>
</table>

TG: triglycerides, LDL: low-density lipoprotein cholesterol, TLC: therapeutic lifestyle changes.
Figure 2. Distribution of Non-HDL cholesterol levels in hemodialysis patients. Serum lipid levels were measured in casual blood samples taken before a dialysis session in 525 patients on maintenance hemodialysis.

Figure 3. Chronic kidney disease (CKD) as a metabolic syndrome with malnutrition. CKD is a metabolic syndrome with malnutrition. To reduce the unacceptably high risk of CVD mortality in CKD, we should lower the incidence of CVD events, and also decrease the risk of fatality after an event. In this unique disease condition, nutritional improvement and maintenance of body mass appear to be of particular importance. Lipid-lowering medication with careful monitoring is justified when initiated with appropriate lifestyle changes. Treatment for the CKD-related risk factors may have additional benefit.
control non-HDL cholesterol for 98% of all hemodialysis patients based on our patient data (Fig. 2).

Control of Other Risk Factors

The mechanisms for protein-energy malnutrition in CKD are not well understood. However, decreased intake and increased catabolism are both contributory. Decreased intake may partly derive from the dietary advice to restrict water, salt, potassium, and phosphate, in addition to anorexia associated with uremia. Increased catabolism may be associated with co-morbidity and the presence of inflammation. In addition, there are losses of glucose, amino acids, and other small molecules into dialysate. The provision of calories and amino acids with intradialytic parenteral nutrition reverses the net negative whole-body and forearm muscle protein balances, but only acutely (95).

The use of vitamin E-coated dialyzer membranes may be effective in lowering oxidized LDL (96) and other oxidant markers (97), and in preventing endothelial dysfunction (98), and arterial calcification (96). Other approaches to CKD-related risk factors include reduction of serum phosphate, use of active forms of vitamin D (77), and improvement of insulin resistance by exercise or by use of thiazolidinediones. Well-designed trials are needed to obtain direct and more solid evidence.

Conclusions

Impaired renal function can lead to deteriorations both in classical risk factors for atherosclerosis and in CKD-related risk factors. In addition, many patients suffer malnutrition. Thus, CKD is a metabolic syndrome with malnutrition (Fig. 3). To reduce the unacceptably high risk of CVD mortality in CKD, we should lower the incidence of CVD events, and also decrease the risk of mortality after an event. In such an attempt, lipid-lowering medication with careful monitoring is justified when initiated with appropriate lifestyle changes. Treatment for the CKD-related risk factors may have additional benefit. Unlike in the general population, to maintain or even increase body weight appears to be beneficial in advanced stages of CKD. Clearly, we need more information about the actual impact of such interventions on outcome of CKD patients.

References

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CKD as a Metabolic Syndrome