Renal Failure, 29:529–534, 2007

ISSN: 0886-022X print / 1525-6049 online
DOI: 10.1080/08860220701391670

informa
healthcare

REVIEW

Potential Benefits of Renal Diets on Cardiovascular Risk Factors in Chronic Kidney Disease Patients

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Dietary manipulation, including protein, phosphorus, and sodium restriction, when coupled with the vegetarian nature of the renal diet and ketoacid supplementation can potentially exert a cardiovascular protective effect in chronic renal failure patients by acting on both traditional and nontraditional cardiovascular risk factors. Blood pressure control may be favored by the reduction of sodium intake and by the vegetarian nature of the diet, which is very important also for lowering serum cholesterol and improving plasma lipid profile. The low protein and phosphorus intake has a crucial role for reducing proteinuria and preventing and reversing hyperphosphatemia and secondary hyperparathyroidism, which are major causes of the vascular calcifications, cardiac damage, and mortality risk of uremic patients. The reduction of nitrogenous waste products and lowering of serum PTH levels may also help ameliorate insulin sensitivity and metabolic control in diabetic patients, as well as increase the responsiveness to erythropoietin therapy, thus allowing greater control of anemia. Protein-restricted diets may have also anti-inflammatory and anti-oxidant properties.

Thus, putting aside the still debatable effects on the progression of renal disease and the more admitted effects on uremic signs and symptoms, it is possible that a proper nutritional treatment early in the course of renal disease may be useful also to reduce the cardiovascular risk in the renal patient. However, conclusive data cannot yet be drawn because quality studies are lacking in this field; future studies should be planned to assess the effect of renal diets on hard outcomes, as cardiovascular events or mortality.

Keywords low protein diet, chronic renal failure, cardiovascular disease, chronic kidney disease, nutrition, cardiovascular risk factors

INTRODUCTION

Cardiovascular (CV) disease is the main cause of morbidity and mortality in chronic uremic patients. In dialysis patients, CV disease accounts for about half of the deaths, with a mortality rate 65 times higher than in general population in the 45–54-year age group and up to 500 times higher in the younger cohorts.[1]

Actually, abnormal CV risk is present from the early stages of renal insufficiency and increases as the disease progresses.[2] Adjusted risk of CV event ranges from a 43% increase with a glomerular filtration rate of 45–59 mL/min, to a 343% increase when <15 mL/min. The risk of death linked to cardiovascular events has been estimated to be almost 16 times higher than that of progressing to end-stage renal disease.[2,3] Moreover, when patients reach ESRD, most of them present cardiovascular complications.

It is likely that the high prevalence of CV disease observed in chronic kidney disease (CKD) results from the addition to traditional risk factors of non-traditional factors such as inflammation, oxidative stress, and increased asymmetric dimethylarginine levels.[4] An early detection and correction of these factors should have great clinical and public health importance.[5] Unfortunately, so far, most of

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the attempts to improve survival by focusing of conventional CV risk factors or dialysis techniques have failed.

Moreover, the interpretation of some of the traditional risk factors is disturbed by the interference of malnutrition, which is not rare in CKD patients. Overweight, high blood pressure, and high serum cholesterol levels, which are deleterious in the general population, can also be considered in dialysis patients as elements of overnutrition and paradoxically are favorable factors for decreased morbidity and death.[6] To explain these paradoxical data, known as "reverse epidemiology" or "risk factor paradox," it has been advanced that in these patients malnutrition exerts a stronger influence on survival, at least in the short-term, than atherosclerosis.[7] Conversely, patients who present with low body weight, low blood pressure, and low serum cholesterol levels die faster due to the consequences of their poor general status than people who present with metabolic syndrome and hypertension, which require much more time to exert their deleterious effects.[8]

Regardless of the mechanisms responsible, traditional and/or nontraditional, effective interventions should be initiated as soon as possible in the course of the nephropathy to reduce this disproportionate CV risk. The medical strategies are associated with the pharmacological and non-pharmacological approaches. Among the latter, nutritional treatment may have a central role.[9] As a matter of fact, among the different goals of dietary prescription in CKD patients, such as the protection of residual renal function and delay of dialysis initiation time, the prevention and correction of complications of renal failure[9,10]—especially those favoring the development of CV complications—have a major importance because CV disease plays a major role in the long-term prognosis of CKD patients. Unfortunately, very few high quality studies have addressed the effect of dietary management implemented in CKD patients on the overall risk of cardiovascular events,[11,12] but some data could be extrapolated from the literature regarding the known CV risk factors

It is commonly believed that the diet for renal patients mainly consists of a restriction in protein intake. However, the nutritional management of renal patients also includes other features that may increase the benefits of the conservative treatment, especially to obtain CV protection, such as the reduction of sodium and phosphorus intake and the prevalence or exclusive plant origin of food consumed. Many of these aspects are included especially in the keto diet, which is a vegetarian diet very low in protein and phosphorus, low in sodium, and supplemented with essential amino acids and ketoacids as well as with water-soluble vitamins, calcium carbonate, and iron.[12]

The quite low mortality rate of the dialysis patients who were previously treated with the keto diet[13,14] and the improved prognosis of type 1 diabetes patients with CKD when treated by a low protein diet[15] indirectly suggests a possible beneficial effect of renal diets on CV events. However, no study has directly addressed the efficacy of dietary treatment on the cardiovascular protection of CKD patients.

In examining the literature and our personal data, we have reviewed the effects of several components of the nutritional therapy of CKD patients on some of the modifiable traditional and nontraditional CV risk factors, namely, hypertension, insulin resistance, dyslipidemia, anemia, calcium-phosphate abnormalities, proteinuria, and oxidative stress.

EFFECT OF RENAL DIETS ON CV RISK FACTORS

Hypertension

Salt and fluid overload play an important role in the pathogenesis of hypertension in patients with end-stage renal disease. Recent studies suggest that hypertension causes such target organ damage as left ventricular hypertrophy, microalbuminuria, progression of renal damage, increased aortic stiffness, and increased oxidative stress.[16,17] Moreover, it is well known that sodium restriction, which leads to a reduction in volume expansion, is a key factor for improving the response to anti-hypertensive treatment in renal failure patients.[18] Last, it has been shown that the vegetarian nature of the diet contributes to a reduction of blood pressure values in both healthy and hypertensive individuals.[19] In a recent prospective, non-randomized study in which 110 consecutive patients with stages 4 and 5 CKD were followed for six months, Bellizzi et al. compared the effects of three different types of diet on blood pressure levels.[10] The authors have shown that the keto diet (0.35 g protein/kg b.w. per day) induced a significant decrease of blood pressure (14 mm Hg on average in systolic values) associated with the reduction of antihypertensive drugs. It is noteworthy that, at the same time, no reduction in sodium intake and in blood pressure was observed in the group of patients on a conventional low-protein diet (0.60 g protein/kg b.w. per day), confirming the findings of a previous study from the same group.[20] In fact, it seems that, more than total protein intake, the ratio of vegetable to animal proteins played an important role in the control of blood pressure level, as reported in several studies concerning normal persons and hypertensive patients without renal impairment.[19,21] Blood pressure levels were also related to keto diet prescription: the mixture of keto analogs and amino acids could have a vasodilatory effect in relation to the increased plasma concentration of the branched-chain amino acids.

Diabetes and Insulin Resistance

Insulin resistance is a powerful independent predictor of CV events that has been documented in patients with the metabolic syndrome. It is all the more likely that such a link also exists in renal diseases, and that the impairment of insulin sensitivity is already present in renal patients with glomerular filtration rate within the normal range.[22,23] The keto diet has a favorable effect on the progression of the diabetic nephropathy and is also able to reduce hyperglycemia and correct insulin resistance and hyperinsulinemia.[24] Despite the increased energy intake derived from carbohydrates, insulin requirement is reduced in diabetic patients on a keto diet, suggesting an improvement in insulin sensitivity, which is confirmed by clamp studies.[25,26]

The increased energy expenditure observed in patients on the keto diet is related to the increase of both carbohydrate and lipid oxidation.[27] The lowering of insulin resistance, reduction in hyperinsulinemia, and increase in energy production rate in patients on the keto diet make it a therapeutic strategy arm theoretically well adapted for the prevention of CV morbidity, particularly in the growing group of obese non-insulin-dependent diabetics with CKD.

Anemia

Low hemoglobin has been identified as an independent risk factor for left ventricular growth, suggesting that there is a direct link between anemia and adverse CV outcomes. On the other hand, it appears that the early correction of anemia in CKD patients is associated with a reduced risk of developing CV disease. In a recent randomized and controlled study, the effects of keto diet on the responsiveness to EPO therapy were assessed in 20 patients followed for two years. The mean achieved protein intake was 0.49 g /kg/day (10 patients) and 0.79 g./kg/day (10 patients) in the low protein and control group, respectively. The improvement EPO responsiveness observed in the keto diet group was found to be inversely related to the PTH level.[28] This effect appears to be dependent on the reduced phosphorus intake and increased calcium intake provided by the calcium salts of keto analogs. It is likely that lower production of waste metabolites deriving from dietary protein catabolism may also play a role.

Calcium-Phosphate Abnormalities

The disturbances of calcium-phosphate metabolism of chronic renal failure, namely hyperphosphatemia, increased calcium-phosphate product, and high serum PTH levels, are very important uremia-related risk factors for vascular calcification, cardiac damage, and mortality. Increased serum level of phosphate, with increased calcium-phosphate product, has a central role. A positive phosphate balance is the basis for hyperphosphatemia and calcium-phosphate tissue precipitation. Of consequence, the implementation of a diet reduced in phosphate represents the basis for the prevention and treatment of secondary hyperparathyroidism and hyperphosphatemia in the pre-dialysis management of renal patients.[29] A proper dietary phosphate restriction adapted to residual renal function allows for better results of phosphate binder therapy and safer and easier use of vitamin D derivatives.

Low phosphate is systematically associated with protein restriction, as the dietary phosphate parallels the dietary protein content of a mixed diet, provided the exclusion of dairy products.

The most successful results in terms of phosphate control and the prevention or correction of secondary hyperparathyroidism are obtained with the use of a keto diet.[30,31] The correction of serum phosphorus and PTH levels is only observed in patients complying to the keto diet, and not in non-complying patients, confirming that a strict low-phosphorus intake, such as that provided by keto diet, is needed to control hyperphosphatemia.[32]

Moreover, the presence of calcium in AlfaKappa® or Ketosteril® tablets (keto analogs given as calcium salts) has additional beneficial effects on calcium-phosphate metabolism and secondary hyperparathyroidism. Actually, calcium-salt ketoacids have an undeniable hypophosphatemic effect due to the anti-absorbent action on the phosphates as a result of the formation of insoluble calcium phosphate in the intestine.[33]

Dyslipidemia

In the absence of inflammation and malnutrition, renal failure is commonly associated with abnormalities of lipoprotein metabolism, which are more pronounced in patients with heavy proteinuria. These abnormalities should, at least theoretically, contribute to the development of the CV disease and possibly to the progression of renal failure.

Some of the lipid disorders are improved by a keto diet through, for example, a reduction of serum triglycerides and an increase of the ApoA1/ApoB ratio.[34,35] In addition, a vegetarian low-protein regimen has been reported to reduce in a parallel way proteinuria and serum total and LDL cholesterol in nephrotic patients.[36]

Moreover, a cross-sectional study including non-nephrotic patients with severe renal failure showed that a vegetarian low-protein diet was associated with a better

lipid profile, reduced oxidative stress, and reduced CRP levels when compared to patients on a conventional low-protein diet.[37] Another option is the use of a soy protein diet that was able to reduce serum cholesterol in nephrotic patients[38] and also ameliorate endothelial function in renal transplanted patients.[39,40]

Proteinuria

More than twenty years ago, results from the Framingham Study had shown that proteinuria was associated with increased CV risk in the general population. Since then, several studies have confirmed that in the general population, the elderly, and high-risk patients with diabetes and/or hypertension, increased urinary albumin excretion indicated an incremental risk for CV mortality. In a cohort of more than 40,000 subjects selected from the general population, with a median follow-up of 961 days, Hillege et al. found a positive dose-response relationship between urinary albumin excretion and death, particularly from CV causes.[41] It has been suggested that proteinuria could be considered as one of the main targets for CV protective treatment.

In the double-blind randomized RENAL Study, which concerned 1513 type 2 diabetic patients with nephropathy, albuminuria was the strongest risk factor for CV events.[42] During the first six months on the Angiotensin II Antagonist Losartan, an 18% reduction in CV risk and a 27% reduction in heart failure risk were observed for every 50% reduction in albuminuria. Similar results have been observed in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial.[43] In these different studies, the reduction in proteinuria seemed to afford cardiac protection independently of the effects of the drugs on blood pressure. Most of these studies have been performed in patients on ACE inhibitors or Angiotensin II receptor blockers; however, it must be recalled that a beneficial effect on urinary protein excretion has also been reported in patients on protein restricted diets.[36,44,45] A significant fall in proteinuria is observed as soon as the first week of dietary changes.[46] The mean percent change of proteinuria ranged between 20% and 37%. Summarizing the results of 14 studies in 202 nephrotic patients on protein-restricted diet, Walser et al. reported a reduction in proteinuria of 27% on average.[45] These percentages are similar to those observed with drugs antagonizing renin activity, and it is likely that the effects on CV outcome are similar. It is noticeable that when protein restriction and ACE-inhibitors or sartans add their anti-proteinuric effects, their combination results in a further reduction in proteinuria compared to single management separately; this additive effect is linked to different mechanisms, respectively, pre-glomerular vasoconstriction and post-glomerular vasodilation.[46,47]

Inflammation

Chronic inflammation, which is present in about 30–50% of predialysis patients, is strongly associated with the "inflammatory driven" malnutrition and atherosclerosis,[7] resulting in increased CV mortality. Dietary patterns are liable to directly modify markers of inflammation and endothelial function.[48,49] In a single-blind trial concerning 180 patients with the metabolic syndrome, Esposito et al. compared the outcome of markers of endothelial dysfunction and of inflammation in two groups of patients following either a Mediterranean-style diet or a control diet. After two years, the level of physical activity increased similarly in both groups, but reduced serum concentration of CRP and interleukin 6, decreased insulin resistance, and endothelial function assessed with the L-arginine test improved only in the intervention group. In another prospective study, TNF-alpha level was significantly reduced in CRF patients after several months on a conventional low-protein, low-phosphorus diet.[50] The long-term effects of protein restriction on markers of inflammation could not be appreciated from the MDRD Study in which only a baseline cross-sectional dosage of CRP was performed[51]; however, a lower CRP level in a cohort of patients with advanced CKD (stages 4–5) on keto diet[37] has been reported.

In addition to protein intake, other components of the alimentary intake should also be taken into account. A mainly or totally vegetarian diet obviously has a high fiber content,[52] which is associated with a lower risk of elevated CRP levels, and natural sources of such anti-oxidants as vitamin C, vitamin E, and carotenoid; this can explain the anti-inflammatory effect of plant-based dietary regimens.[53]

Chronic uremia is a condition of increased oxidative stress, too. Cross-sectional and prospective studies suggest that a vegetarian, low-protein diet supplemented with ketoacids may have anti-oxidant effects.[37,54] In particular, a randomized, controlled study has reported that the supplementation of essential amino acids and keto analogues per se was associated with a reduction of circulating markers of oxidative stress.[55]

SUMMARY AND CONCLUSIONS

In summary, the review of the existing literature suggests that the dietary treatment usually implemented in

chronic renal failure patients may exert favorable effects on some traditional and nontraditional CV risk factors, although quality studies are lacking in this field. Namely, blood pressure control may be favored by the reduction of sodium intake and by the vegetarian nature of the diet, which is very important also for lowering serum cholesterol and improving lipoprotein profile. The low protein and phosphorus intake has a crucial role for the prevention and reversal of hyperphosphatemia and secondary hyperparathyroidism, which are major causes of the vascular calcifications and mortality risk of uremic patients. A reduction of nitrogenous waste products and lowering of serum PTH levels may also contribute to ameliorate insulin sensitivity and metabolic control in diabetic patients, as well as to increase the responsiveness to erythropoietin therapy, thus allowing a better control of anemia. Anti-inflammatory and anti-oxidant properties are also reported. However, all of these cardiovascular risk factors are only intermediate factors toward the hard outcomes of cardiovascular events or mortality that remains to be assessed.[11]

In conclusion, proper dietary manipulation, including protein, phosphorus, and sodium restriction, coupled with a vegetarian nature of the diet and ketoacid supplementation can potentially exert a CV protective effect in CKD patients by acting on both traditional and nontraditional CV risk factors. However, further studies are needed to assess definite conclusion, especially to assess the effect of renal diets on hard outcomes such as cardiovascular events or mortality.

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