# Traditional and Novel Dietary Interventions for Preventing Progression of Chronic Kidney Disease

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Treatment of chronic kidney disease (CKD) and its complications remain largely unresolved. Currently used treatments include blood pressure control and the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which can slow down the progression of CKD but are unable to halt or reverse it. Dietary protein restriction represents an additional therapeutic measure used to slow the progression of CKD. The putative mechanisms of action responsible for its therapeutic effects include beneficial hemodynamic effects and the limitation of absorbable protein breakdown products that could lead to the accumulation of uremic waste and consequent various deleterious effects. The practical implementation of protein restriction through dietary intervention has been hindered on multiple levels, including patient nonadherence, lack of health care resources, and concerns related to adverse effects associated with the development of protein-energy wasting (PEW). As a result, alternative interventions have been designed to address some or all of these shortcomings and concerns. One such intervention is the administration of medications that prevent the absorption of protein catabolic products from the gut. This article reviews the various interventions using such a strategy to prevent or slow the progression of CKD, with special focus on recent advances in this field.
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## Introduction

THE WIDESPREAD USE of estimation formulas to diagnose chronic kidney disease (CKD) has shed light on the common nature of this disorder, which is also associated with very high morbidity and mortality. The most widely applied therapeutic measures aimed at retarding the progression of CKD include blood pressure control and the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). These interventions have been proved to slow the progression of CKD[1] but are unable to halt or reverse it, thus creating an unmet therapeutic need. Dietary protein restriction has also been advocated to slow the progression of CKD,[2] based on favorable glomerular hemodynamic effects[3] and the limitation of protein catabolic products with adverse effects on kidney function. Despite the sound pathophysiologic science, protein restriction has not gained significant ground as a widely implemented therapeutic strategy, in part because of the negative primary results of the Modification of Diet in Renal Disease study.[4] Other reasons include the practical difficulty of correct implementation and patient adherence to a proper low-protein diet and the concerns about protein-energy wasting (PEW) resulting from an improperly implemented low-protein diet. Consequently, there have been multiple attempts to address some or all of these shortcomings. Such attempts include the supplementation of very low-protein diets with essential amino acids or keto acids to ensure proper amounts of protein and energy intake and to make dietary choices easier and food more palatable (reviewed in more detail elsewhere in this issue) and the administration of various medications to address specific biochemical aspects of protein catabolism that have an effect on kidney function. The latter include binding medications that limit the gut absorption of putatively nephrotoxic food components and medical interventions that correct deficiency states with nephrotoxic potential, such as hypokalemia and metabolic acidemia. Here we review dietary interventions based on limiting uremic toxin absorption and the role of hypokalemia in progressive CKD. Other therapeutic strategies aimed at retarding the progression of CKD, such as protein restriction, supplemented very-low protein diets, and correction of metabolic acidemia are discussed elsewhere in this issue.

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## Role of Dietary Protein Restriction in Retarding Progression of CKD

Reduction in dietary protein intake can have a variety of positive effects in the uremic patient, including the alleviation of uremic symptoms; control of hyperparathyroidism, hyperphosphatemia, and hyperkalemia; favorable glomerular hemodynamic effects; and a reduction of proteinuria.[5] After the initial negative results of the Modification of Diet in Renal Disease study, follow-up analyses indicated that perhaps these negative results could have been caused

by design flaws (such as an acute negative effect of protein restriction on the glomerular filtration rate [GFR] caused by hemodynamic effects, and the use of high-tryptophan–containing keto acid supplements in the supplemented very low-protein intake arm of study B), and that there may actually have been a beneficial effect on progression of CKD. Subsequently, numerous smaller studies also examined the effects of protein restriction on clinical outcomes in patients with CKD. A recent meta-analysis that incorporated data from 10 randomized controlled studies in 2,000 nondiabetic patients with moderate and advanced CKD suggested that protein restriction resulted in a 32% lower incidence of renal death (defined as dialysis, death, or renal transplantation), and to avoid 1 renal death, 2 to 52 patients needed to be treated with low-protein intake over 1 year.[6] These meta-analyses suggest benefits from protein restriction in terms of slowing progression of CKD.

Despite the sound underlying pathophysiologic science and the indication from clinical trials of a potential benefit, dietary protein restriction–based strategies have not been widely implemented in routine clinical practice. One reason for this may be related to concerns of inducing PEW and potentially causing adverse outcomes such as increased mortality.[7] Although a properly implemented low-protein diet is not believed to engender PEW, proper implementation of such a diet is not easy and requires resources that health care providers often do not have, as well as motivation and material resources on the patients' end, which they often do not possess. Insufficient energy intake is a common reason why low-protein diets may lead to the development of PEW, especially with a dietary prescription of 0.58 g/kg/day, of which 50% of the protein has to be of high biologic value, making the provision of adequate energy sources difficult. Consumption of primarily proteins of low biologic value with the low-protein diet (because of greater convenience or better palatability of foods containing low-quality protein) can also increase the risk of negative protein balance followed by PEW. Consequently, other therapeutic strategies addressing the pathomechanism of dietary protein-related nephrotoxicity have been explored.

## Intestinal Binding Medications

The mechanisms whereby dietary protein affects kidney function are complex. The previously mentioned difficulties surrounding protein restriction have provided an impetus to better delineate these mechanisms and to examine renoprotective strategies that address the specific pathways responsible for the nephrotoxic effects of dietary protein. One such approach is to selectively prevent absorption by the gut of only certain dietary components that may be responsible for dietary protein-related deleterious effects in patients with CKD. Several such dietary components have been postulated, with various mechanisms of action responsible for their deleterious effects.

*Phosphorus* has numerous adverse effects, including direct vascular toxicity and an association with increased mortality and progression of CKD,[8,9] and the application of phosphorus binders in patients with non–dialysis-dependent CKD has been associated with lower mortality in observational studies.[10] The potential role of serum phosphorus in engendering progression of CKD was also supported by small clinical trials in patients with CKD[11] that showed an attenuation of progression after dietary restriction of phosphorus. These studies were, however, unable to differentiate the impact of dietary protein restriction and that of uneven blood pressure control from that of serum phosphorus restriction and thus did not provide conclusive evidence about the role of the latter. To date, the use of phosphorus-binding medications as a renoprotective strategy cannot yet be recommended until proper randomized controlled trials confirm the effects that can be implied from observational studies.

Other potential uremic toxins linked directly or indirectly to intestinal absorption are uremic toxins such as *indoles, cresols, phenols* and *advanced glycation end products,* which are products of protein catabolism in the gut that have been linked to deleterious processes such as increased oxidative stress, inflammation, vascular and renal toxicity, and increased mortality.[12] Of the various uremic products resulting from intestinal protein absorption or abnormal metabolism and excretion, or both, indoxyl sulfate is one of the most frequently studied; the consequences of its elevated levels have been examined in a variety of in vitro, in-vivo animal, and human observational and interventional studies. Besides numerous deleterious effects—such as oxidative stress, enhanced leukocyte adhesion and inflammation, endothelial toxicity and abnormal wound healing, parathyroid hormone resistance, inhibition of nitric oxide production, stimulation of vascular smooth muscle proliferation, reduction in *klotho* expression, and induction of cell senescence—indoxyl sulfate (IS) also promotes kidney damage and progression of CKD.[13] Based on these considerations, it has been postulated that medications that are capable of lowering IS levels could be renoprotective. The oral administration of the medication AST-120 (Kremezin, Daiichi Sankyo, Inc, Parsippany, NJ) has been shown to effectively lower IS levels in animal models and in humans,[14] and in animal models it has resulted in amelioration of renal interstitial fibrosis, glomerular sclerosis, and proteinuria.[13] This drug has also been approved in Japan with an indication to relieve symptoms of uremia and progression of CKD in patients with non–dialysis-dependent CKD.[15] Smaller randomized controlled trials (Table 1) showed benefits in this regard[16-21] but because of their limited size cannot be used as unequivocal proof of the drug's efficacy and safety. A larger clinical trial that examined 460 patients with advanced non–dialysis-dependent CKD (mean creatinine clearance, 22 ml/minute) failed to find a significant benefit in lowering the composite outcome