renal replacement therapy being federally funded in the United States, the ideal way to deliver dialysis and the best modality to use for individual patients remains uncertain. However, in the era of bundled payments, it has been proposed that the prevalence rates of PD will rise, as it remains a lower-cost therapeutic option. This study by Perl *et al.* supports the individualized use of PD as an equivalent dialysis modality to HD and as a preferred modality if the alternative is to start hemodialysis with a catheter.

DISCLOSURES

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See related article, "Hemodialysis Vascular Access Modifies the Association between Dialysis Modality and Survival," on pages 1113–1121.

REIN on Obesity, Proteinuria and CKD

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Chronic Kidney Disease (CKD) is a major public health concern worldwide[1] and obesity is increasingly recognized as an independent risk factor for development of CKD.[2] There has been a global epidemic of obesity and a parallel rise in the prevalence of metabolic syndrome that likely have contributed to the increasing incidence of CKD.[3] Culprits implicated in this epidemic include the development of a general tendency toward sedentary lifestyles together with a diet with excessive caloric intake linked to junk food and high fructose consumption, largely in the form of high-fructose corn syrup in sugary sodas.[4–6] Epidemiologic and experimental studies have linked high fructose intake with the development of obesity and metabolic syndrome, insulin-resistant diabetes, and albuminuria.[3,7]

Obesity is associated with proteinuria and a more rapid progression of CKD[8] and the reversal of obesity can improve proteinuria[9,10] and GFR.[11] Moreover, there is evidence that obesity causes glomerular hypertrophy and impaired glomerular function, even in the absence of a primary kidney disease. An obesity-related glomerulopathy akin to focal segmental glomerulosclerosis has been observed in morbidly obese patients, often accompanied by massive proteinuria and rapid loss of kidney function.[10,11] Based on the high prevalence, associated complications, and rising cost, obesity that parallels an increase in the prevalence of CKD has become a global burden.

There is now convincing evidence for proteinuria as a marker of kidney injury and a surrogate outcome in CKD, and that reducing proteinuria can prevent or delay cardiovascular events and the progression of kidney disease.[12] Blockers of the renin-angiotensin system (RAS) have emerged as the mainstay of therapy in large part due to their antiproteinuric effects in preventing the progression of kidney disease. Randomized trials assessing the efficacy of angiotensin-converting-enzyme (ACE) inhibitors with respect to kidney-protection have been studied in diabetic[13,14] as well as nondiabetic nephropathies.[15,16] Notably, the Ramipril Efficacy In Nephropathy (REIN) study-1 was the first to demonstrate that an ACE inhibitor, ramipril, had a kidney-protective effect in slowing the decline of GFR in nondiabetic CKD patients with a proteinuria of 3 g or more per day.[16]

In this issue, Mallamaci and colleagues,[17] through a *post hoc* analysis of the REIN study cohort, asked two critical questions, whether body mass index (BMI) influences the incidence rate of renal events, defined as either doubling of serum creatinine or end-stage renal disease (ESRD), and whether obesity modifies the effect of ramipril on these outcomes. The latter question was not addressed previously. In the placebo-treated group, the incidence rate of renal outcomes was higher in obese patients than those with normal BMI. Importantly, treatment with ramipril not only reduced the incidence rate of renal

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events in all BMI strata but the effect was greater in the obese patients compared with nonobese patients. Similarly, a more pronounced reduction in proteinuria was seen in obese patients than those with normal BMI.

The present study is significant for several reasons. First, it confirms previous reports that in patients with CKD of various etiologies, both diabetic and nondiabetic, the presence of obesity accelerates progression. It further establishes a firm link between obesity, proteinuria, and the development of CKD. Moreover, this study demonstrates for the first time that obese patients appear to be especially responsive to the kidney-protective effects of ramipril. Thus, it takes us one step forward in the battle against obesity-related complications.

A significant body of evidence suggest that drugs that inhibit the actions of RAS yields superior renal outcomes compared with other drugs that act through calcium channel blockade or through beta blockade. BP control in the REIN study was similar in the ramipril and placebo-treated groups, advocating for a unique effect of ACE inhibition, beyond BP lowering, for protection against progression of CKD. Indeed, preclinical evidence in animals and clinical studies have shown that adipose tissue, particularly visceral fat, produces angiotensinogen, and circulating angiotensinogen as well as renin and angiotensin-converting enzyme levels increase with increasing BMI.[18–22] Adipocytes also express adipocyte-specific metabolites such as free fatty acids, adiponectin, and leptin which can affect kidney function and structure. Hence, activation of RAS is considered as a major factor implicated in CKD associated with obesity, and therefore therapies aimed at inhibiting RAS would seem particularly beneficial in attenuating the progression of obesity related kidney disease.

Nonetheless, extrapolation of the present findings by Mallamaci and colleagues[17] to the general population should be done with caution. This post hoc analysis utilized data from a randomized trial in Europe where participants are predominantly white and the findings may not apply to different ethnic groups. Recent studies suggest that obesity and metabolic syndrome may be heterogeneous disease states that differ in regard to proteinuria, GFR, and the pathophysiology of CKD in African Americans and whites.[23] Furthermore, the incidence and prevalence of obesity and CKD are increasing in the United States population as a whole, but much more rapidly among ethnic minorities.[24] Thus, it is imperative that future studies are directed toward understanding racial and ethnic differences in seeking efforts to reduce health disparities. Another shortcoming of the present study is the relatively small number of obese patients in the REIN study, and specific trials are necessary in obese patients randomized *a priori* within predefined BMI strata. It is important to note that, although BMI is generally used in studies including the present, BMI is a measure of generalized obesity and not abdominal obesity, and there is evidence that argue for measurement of the latter may be more appropriate. Patients with central adiposity or high waist-to-hip ratios appear to have a substantially greater risk for progression of CKD.[25]

Current therapies aimed at slowing obesity related progressive kidney damage include weight reduction and drugs that inhibit the RAS such as ramipril. While it may not completely substitute for the benefits of weight reduction and it does not claim to be the highly sought after diet pill, ramipril treatment represents an attempt to place a rein on progression of CKD in obese patients. It remains to be established if this represents a class effect for all ACE inhibitors as well as angiotensin receptor blockers to provide kidney protective effects in obesity. Future investigations are needed, particularly ones seeking to uncover the mechanisms underlying obesity-related kidney disease. Additional mechanistic insight could lead to development of new interventions, for instance, aimed at directly targeting adipocyte-driven cytokines that may be beneficial to ameliorate the progression of obesity-related kidney disease.

DISCLOSURES

None.

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See related article, "ACE Inhibition Is Renoprotective among Obese Patients With Proteinuria," on pages 1122–1128.

Trials and Tribulations of New Agents, Novel Biomarkers, and Retarding Renal Progression

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Inflammation and fibrosis are important processes that mediate progression of kidney disease. Agents that interfere with these processes need to be studied in sufficient detail in humans so we may begin to offer some hope to patients and populations with kidney disease. Diabetic nephropathy remains the most common cause of end-stage renal disease (ESRD) worldwide, and as there are an increasing number of people developing diabetes, in both developed and developing countries, the need for treatments that delay progression or attenuate the course of the disease is ever pressing.

Sharma *et al.*, in the current issues of *JASN*, describe the results of a small, randomized control trial with an oral antifibrotic, anti-inflammatory agent, pirfenidone.[1] This agent has shown promise in animal studies of diabetes or lung fibrosis and small human open-label studies in patients with FSGS and with pulmonary fibrosis.[2–5] This study enrolled 77 patients who were randomly assigned to placebo or two different doses of the pirfenidone. All patients received baseline medication for renin-angiotensin system blockade and the majority were type 2 diabetics. Overall, the study reports only the results of those who actually completed the study ($n = 52$) over a period of one year and notes the relatively high number of dropouts, particularly in the high-dose pirfenidone group. The authors describe statistically different changes in eGFR between low-dose pirfenidone and placebo, and a nonsignificant result when the placebo group was compared with those who received pirfenidone at any dose. The authors acknowledge the shortcomings of the trial but are encouraged by the results and then call for larger studies.

Close review of this paper and accompanying literature, however, reveals that there are a number of unanswered questions that need to be carefully considered before embarking on these larger trials. First, those on the higher dose of pirfenidone had a greater drop in their eGFR in the first 3 mo of the study than either placebo or low dose groups. This is not explained and is counterintuitive. The higher-dose group had substantial side effects, mostly gastrointestinal, so that tolerability of the drug is an important issue for future consideration. There are no changes in the inflammatory or pro-fibrotic serum biomarkers over time, despite their correlation with eGFR at baseline, nor are there any changes in these serum biomarkers as a function of treatment, despite the purported mechanism of action of the agent being the inhibition of TGFβ production and subsequent matrix accumulation. Furthermore, even in patients with response to the drug, there are no changes in urine levels of the albumin-creatine ratio or TGFβ over the study duration. The end point in this study is a surrogate: eGFR using standardized creatinine measurements and the four variable MDRD equation

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