Does Losartan Prevent Progression of Early Diabetic Nephropathy in American Indians With Type 2 Diabetes?

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Approximately 346 million individuals worldwide and 25.8 million individuals in the U.S. have diabetes (1,2). The high prevalence of diabetes results in a persistently increased prevalence of diabetic nephropathy, which is the leading cause of kidney failure and premature cardiovascular mortality (3). In the U.S., diabetic nephropathy is represented disproportionately in several minority populations including American Indians (4). Of the American Indian tribes in which type 2 diabetes develops at an alarming rate in children as a result of childhood obesity, the Pima Indians tend to have even higher rates of diabetic nephropathy (up to 65%; age-group 45–74 years) and concomitant end stage renal disease (ESRD; as high as 3.5 times) compared with white Americans (5–7). Fasting hyperglycemia and hemoglobin A1C are strong predictors of albuminuria in Pima Indians. Research has established that strict control of plasma glucose in the prediabetic stage can preempt a diagnosis of diabetes in some indigenous peoples (8). Further, in Pima Indians, the combination of macroalbuminuria and worsening estimated glomerular filtration rate (eGFR) strongly predict ESRD and death (9). Several large, well-designed clinical trials in diabetic cohorts have shown that blockade of the renin angiotensin system (RAS) prevents the progression of microalbuminuria to macroalbuminuria as well as the progression of macroalbuminuria to overt proteinuria and subsequent ESRD (10–12). Despite the fact that RAS blockade has shown no effect on primary prevention of diabetic nephropathy in mainly white, normotensive, normoalbuminuric, type 1 diabetic individuals, the importance of defining the renal outcome of RAS blockade in high-risk Pima Indians in particular cannot be overstated.

Indeed, primary prevention of diabetic nephropathy in Pima Indians could potentially have significant ramifications regarding preemptive therapy with an enormous impact on the economic, societal and personal burden related to renal replacement therapies, transplantation, and cardiovascular morbidity and mortality in this population. For example, there is compelling support for a genetic predisposition to diabetic nephropathy and the association of microvascular complications as major contributors to the high levels of morbidity and morbidity (13). Genome-wide association studies have uncovered evidence for chromosomal linkage for albuminuria, eGFR, and renal failure in diabetic families from several ethnic groups, including American Indians (14–16). Notably, Pima Indians develop diabetic nephropathy at an early age and have more advanced kidney disease and lower rates of spontaneous regression from microalbuminuria compared with whites (17). The observed differences in chromosomal linkage among ethnic groups in general, and Pima Indians in particular, may eventually uncover mechanisms of accelerated disease in American Indians and other high-risk groups. Although much is known about the natural clinical history of diabetic nephropathy in Pima Indians, a clinical trial could establish the therapies that are meaningful for primary prevention in this population. This type of investigation could also provide new insights into pathological mechanisms.

Routine biopsies are neither part of the diagnosis nor the management of diabetic nephropathy. Though there has been some discussion regarding the structural classification of diabetic nephropathy, glomerular basement membrane thickening and volume fraction of mesangium and mesangial matrix are consistently increased in both type 1 and type 2 diabetes (18). Of these, mesangial expansion is the earliest change and has been shown to correlate well with clinical progression of diabetic nephropathy, and podocyte loss has been shown to correlate with proteinuria (19). Although the effect of RAS blockade with either losartan or enalapril in patients with normotensive, type 1 diabetes and normoalbuminuria showed no effect on mesangial fractional volume or eGFR (podocyte number was not determined) after 5 years (20), the effect of RAS blockade in normotensive, normoalbuminuric Pima Indians had not been established until now.

In the current issue, Weil et al. (21) describe the results of a longitudinal study in type 2 diabetic Pima Indians treated with losartan. The study is a 6-year, single-center, randomized, double-blind, placebo-controlled trial of losartan in a cohort of 169 Pima Indians, aged 18–65 years with type 2 diabetes duration of at least 5 years, and either normoalbuminuria (albumin/creatinine [ACR] $<$30 mg/g) or microalbuminuria (ACR = 30–299 mg/g). The primary outcome was a reduction in GFR $\leq$60 mL/min or 1/2 baseline with GFR $<$120 mL/min (measured annually). Another outcome was the difference in structural changes resulting from extensive morphometric analyses in 111 participants at the study end to examine glomerular volume; filtration surface area density; fractional interstitial area; mesangial fractional volume; percent globally sclerotic glomeruli; glomerular basement membrane width; number of endothelial cells, mesangial cells, and podocytes per

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glomerulus; filtration slit frequency; and foot process width.

Unfortunately, the results of the study in these type 2 diabetic participants only served to further support previous observations in type 1 diabetes that RAS blockage with losartan neither prevented primary development of microalbuminuria nor attenuated increased mesangial fractional volume (20). However, RAS blockade did prevent progression of microalbuminuria to macroalbuminuria, and reduced the risk of GFR decline. Thus, the structure-function association of increased mesangial fractional volume and reduced GFR was confirmed. Further, there was no difference in glomerular volume or filtration surface area density between the placebo and losartan treated normoalbuminuric subjects, and a small but significant ($P = 0.05$) reduction in total surface area. No difference in podocyte number was observed. Of interest, treatment with losartan in normoalbuminuric subjects who developed microalbuminuria tended to have worse progression to macroalbuminuria ($P = 0.02$)—a finding that was previously recognized in a type 1 diabetic cohort (20).

The study has many strengths. For example, previous trials did not include significant proportions of high-risk individuals such as Pima Indians; renal function was measured by high-performance liquid chromatography–iothalamate concentration; renal biopsies were performed and extensive morphometric analyses were conducted. The primary weakness of the study was that an unexpectedly small number of participants reached the primary end point during follow-up, a fundamental methodological issue that resulted in the study being underpowered. This may have been related to a federal mandate to include the use of other RAS-blocking agents (66.3%) midway through the study. Also, biopsies were performed only at the end of the follow-up period, and the incidence of nondiabetic glomerular diseases in the treatment versus the placebo group was not defined. Since American Indians tend to have high incidence of concomitant nondiabetic glomerular lesions, it is unknown whether these lesions may impact diabetic nephropathy progression or treatment response in this setting.

Despite its limitations, this study provides another installment by these investigators to further define the natural history of diabetic nephropathy in Pima Indians. The study may have also uncovered the potential adjunctive pathologic role of podocyte loss to increased mesangial fractional volume in the early development of diabetic nephropathy as well as to effective RAS blockade. Weil et al. have previously quantified podocyte detachment in a subset of this cohort and showed no evidence of podocyte detachment in normoalbuminuric subjects; but they observed strong correlations of podocyte detachment and reduced podocyte number with worsening albuminuria (22). It is still unknown whether increased mesangial fractional volume actually promotes podocyte loss early in the course of diabetic nephropathy. Novel therapies that directly target early mesangial expansion or biomarkers more specific for mesangial expansion rather than functional decline may be more revealing.

An important question that may still be considered is whether primary RAS blockade in normoalbuminuric Pima Indians, who are also hypertensive, might alter disease progression. It has been suggested that hypertension in both parents and prediabetic hypertension in an affected offspring may play a causal role in the development of diabetic nephropathy in Pima Indians (23). Notably, the 2012 KDIGO Clinical Practice Guidelines recommends the use of RAS blockade for blood pressure management in diabetic patients with albuminuria >30mg/24h or equivalent (24). Thus, there is still no indication to use RAS-blocking agents prior to clinical development of diabetic nephropathy in either type 1 or type 2 diabetes.

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