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Effects of Pancreas Transplantation on the Prevention and Reversal of Diabetic Nephropathy

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Synopsis

Pancreas transplantation is the only available treatment which has restored long-term (10 or more years) normoglycemia without the risks of severe hypoglycemia, allowing testing of the reversibility of diabetic nephropathy lesions. We studied renal structure before and 5 and 10 years after pancreas transplantation in non-uremic patients with long-term type 1 diabetes, with established diabetic nephropathy lesions at baseline. Diabetic glomerular lesions were not significantly changed at 5 years but were dramatically improved after 10 years, with most patients' glomerular structure returning to normal at 10 year follow-up. These studies also showed that tubulointerstitial remodeling, including decreased interstitial collagen, was possible.

Introduction

Diabetic nephropathy (DN) is the most important cause of end stage renal disease (ESRD) [1, 2], leading to >45% of all new cases in the USA. The specific DN lesions leading to renal dysfunction in DN are secondary to the diabetic state. DN in type 1 diabetes (T1D) begins primarily as a glomerular disease [2, 3]. At onset of T1D the two major early glomerular lesions, mesangial expansion and increased thickness of the glomerular basement membrane (GBM), are not present but may be demonstrable over the next 5-10 years [4]. DN lesions recur in the renal allograft and T1D patients randomized to maximized glycemic control in the first 5 years following kidney transplantation have less mesangial matrix expansion than patients randomized to standard control [5]. There were also lower incidences of microalbuminuria and proteinuria after 7 to 8 years of follow-up [6] in T1D patients randomized to strict control in the Diabetes Control and Complications Trial (DCCT). However, the critical role of glycemia in DN pathogenesis was finally proven by the dramatic demonstration of reversal of DN lesions in the T1D patients following successful pancreas transplantation alone (PTA) [7].

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Pancreas Transplantation and Diabetic Renal Disease

DN largely results from the accumulation of extracellular matrix (ECM) (basement membrane proteins) in the glomerular (GBM), tubular (TBM) basement membranes, and mesangium [2, 3, 8-10]. Fibrillar types I and III collagens are absent from the glomerulus throughout most of the evolution of DN lesions, appearing only in advanced Kimmelstiel-Wilson nodules and in the final stages and of glomerular scarring [11]. Moreover, these “scar” collagens, normally present in modest quantities in the interstitium of the kidney, increase at this site only after the glomerular lesions are well established and interstitial expansion is quite advanced [2].

In normal people the fraction of the volume of the glomerulus occupied by the mesangium (mesangial fractional volume or $V_v(\text{Mes}/\text{glom})$) and GBM width do not change between ages 16 and 60 years [12]. Thus there is a remarkable ability for the cells of the kidney, throughout adult life, to maintain a near perfect balance between glomerular ECM production and removal, while DN lesions result from a disturbance in this balance due to increased production, decreased removal, or both [12].

Pancreas transplantation and reversibility of DN lesions

Animal studies provided proof of concept that DN lesions may, at least in part, be reversible. Thus, after 7 months of diabetes, cure of diabetes in rats by islet transplantation resulted, in the next 2 months, in reversal of mesangial matrix and cell expansion but did not affect the increased GBM width [13], perhaps because follow up time was not long enough. However, reversal of mesangial expansion did not occur in the first 5 years after pancreas transplantation in humans [14]. Moreover, while mesangial expansion in human DN is mainly the result of mesangial matrix accumulation, in rats mesangial matrix and cellular expansion are equivalent. Thus, animal models of development and reversal of DN are imperfect models of the human condition.

As alluded to above, our initial report on the effects of pancreas transplant alone (PTA) on DN lesions in the native kidneys 13 PTA recipients was extremely disappointing. Thus, despite five years of normoglycemia and insulin independence, established DN lesions did not improve [14], increased GBM width was unchanged, and $V_v(\text{Mes}/\text{glom})$ actually increased further, this due decreased glomerular volume (GV), while the total volume of the mesangium per glomerulus (TM) did not change. On the other hand, control patients with persistence of T1D had further increases in both $V_v(\text{Mes}/\text{glom})$ and TM [14].

Eight of these 13 PTA recipients returned for repeat research biopsies 10 years after cure of T1D by PTA [7] while 2 patients required kidney transplant 6 and 8 years after PTA, 2 lost graft pancreatic graft function and became diabetic again, and 1 refused the 10-year biopsy. At PTA these 8 patients were 33 ± 3 years old, had T1D duration of 22 ± 5 years, and their HbA1c was $8.7 \pm 1.5\%$. Renal function was difficult interpret, given that cyclosporine causes substantial reductions in glomerular filtration rate (GFR) [15] and may also reduce albuminuria. We observed dramatic reversal of diabetic glomerulopathy lesions in all 8 patients returning for their 10 year PTA biopsies [7]. GBM and TBM width were all increased at baseline, remained unchanged at 5-years, and were decreased at 10-years compared to baseline and to 5 years, several of the 10 year values falling into the normal range and approached normal in the others (Figure 1A and 1B). As noted above, $V_v(\text{Mes}/\text{glom})$ and mesangial matrix fractional volume, increased significantly from baseline to 5 years (Figure 1C and 1D) due to a decrease in glomerular volume. Glomerular volume was stable from the 5th to the 10th post-PTA years and $V_v(\text{Mes}/\text{glom})$ and mesangial matrix fractional volume were now much lower at 10 years than either the baseline or 5 years values (Figure 1). Total mesangial and total mesangial matrix volumes per glomerulus,

unchanged at 5 years, were now also markedly decreased at 10 years. We also found remarkable remodeling of glomerular architecture in the 10 year vs. the baseline and the 5 year biopsies. In several biopsies there was total disappearance of Kimmelstiel-Wilson nodules and we commonly appreciated open glomerular capillaries where in previous biopsies in the same patients glomerular capillaries were greatly compressed by expansion of the mesangium (Figure 2). Thus, these studies proved that diabetic glomerular and tubular ECM lesions are reversible in humans, but not before a delay of at least 5 years.

The basis for this long delay before is unknown. One possibility is that, secondary to long exposure to hyperglycemia. ECM molecules are heavily glycosylated and, since glycosylated ECM is more resistant to proteolysis [16] there is delay in healing until long lived ECM is replaced by less glycosylated molecules. A more attractive hypothesis is that renal cells have “metabolic memory” for the diabetic state [17] and, thus cells behave as if in a diabetic environment for a long time after the establishment of normoglycemia. Both of these hypotheses may be true. Regardless of the mechanism(s), at some point after cure of diabetes, rates of ECM removal begin to exceed rates of ECM production. This is active healing, clearly different from normal situation in adult life where renal ECM production and removal remain in near perfect balance [12].

All PTA recipients in these studies received cyclosporine, a known nephrotoxic drug [18, 19]. In fact we reported that the increase in interstitial expansion and tubular atrophy at 5 years was related to cyclosporine dose and blood levels in the first year post PTA. [15]. In the 10 year post PTA biopsies we observed remodeling of interstitial and tubular lesions [42]. Thus, interstitial fibrosis and tubular atrophy observed at 5 years post-PTA had significantly improved by 10 years after PTA [20], this demonstrating that the tubulointerstitium can undergo substantial remodeling. There was a decrease in the quantity of renal cortical interstitial fibrillar collagen consistent, once again, with healing characterized by removal of ECM exceeding its rate of production [20]. The findings in these studies were more consistent with the idea that atrophic tubules underwent reabsorption rather than healing. The nature of these studies did not allow determination as to whether the tubulointerstitial improvements resulted from prolonged normoglycemia, decreased cyclosporine dose or both. Nevertheless, these PTA studies revealed that these components of the kidney could also undergo changes in the direction of restoration of renal architecture towards normal from the point of substantial injury,

In summary, these studies have proven that the kidney has intrinsic cellular healing mechanisms for restoring more normal renal structure upon removal of the injury stimuli. These processes, in some ways, recapitulate aspects of renal development in that the renal cells appear to “know” what normal renal structure is and, given the opportunity, will orchestrate the means of getting there. Although there are likely “points of no return,” i.e., severity of structural damage beyond which reestablishment of normal renal architecture is no longer possible, even advanced lesions of diabetic glomerulopathy, including nodular changes, are reversible. Better understanding the regulation of the cellular mechanisms involved in these healing processes could lead to new approaches to the prevention and treatment of DN as well as other slowly progressive renal diseases.

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Key Points

- Pancreas transplantation is the only available treatment which has restored long-term (10 or more years) normoglycemia without the risks of severe hypoglycemia,
- Diabetic glomerular lesions were not significantly changed at 5 years but were dramatically improved after 10 years, with most patients' glomerular structure returning to normal at 10 year follow-up.
- Tubulointerstitial remodeling, including decreased interstitial collagen, was possible.

Figure 1.

Thickness of the GBM (A) and TBM (B), mesangial fractional volume (C) and mesangial matrix fractional volume (D) at baseline and 5 and 10 yrs after PTA. The shaded area represents the normal ranges obtained in 66 age and sex matched normal controls (mean $\pm 2SD$). Data for individual patients are connected by lines. From Ref. 17.

Figure 2.

Glomeruli before and after pancreas transplantation (PTA). A. Typical glomerulus from the baseline biopsy, with diffuse diabetic glomerulopathy and Kimmelstiel-Wilson nodules. B. Typical glomerulus 5 yrs after PTA shows persistence of diabetic glomerulopathy. C. Typical glomerulus 10 yrs after PTA, with marked resolution of diabetic glomerulopathy lesions and substantially normal glomerular structure. From Roys S, Sala R, Cagliero E. et al. Overexpression of fibronectin induced by diabetes or high glucose: Phenomenon with a memory. *Proc Nat Acad Sci USA* 1990; 87:404-08. Permission granted for educational use.