

The Kidney in Diabetes: Dynamic Pathways of Injury and Repair

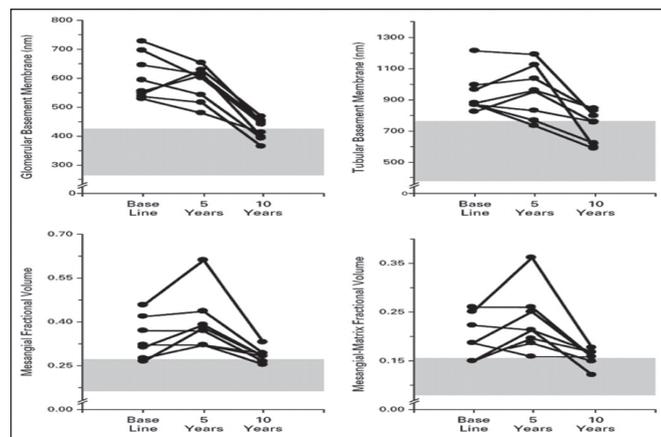
Paola Fioretto, MD, University of Padova, Italy, winner of the Castelli Pedroli Prize, presented the Golgi lecture, "The Kidney in Diabetes: Dynamic Pathways of Injury and Repair." In her lecture, Prof. Fioretto reviewed her own and other's research on the structural lesions leading to renal dysfunction in diabetes. She discussed in detail the relationship of structural changes to dysfunction in both type 1 and type 2 diabetes, emphasizing the complexity of these relationships in type 2 diabetes. The highlight of her talk, however, was her presentation of evidence that established lesions of diabetic renal injury can be reversed.

Introducing this topic, Prof. Fioretto said, "This is an area that I find personally exciting." Noting that the scientific literature consistently contains the statement that the lesions of diabetic nephropathy are irreversible, she said, "We decided to test whether or not this is true." The ideal models for this testing would be recipients of pancreas transplants alone because they are not uremic they have their own kidneys and long duration of diabetes with established lesions of diabetic nephropathy.

Prof. Fioretto and her colleagues at the University of Minnesota, Minneapolis, Minnesota, United States, studied 13 pancreas transplant recipients who were normoglycemic and insulin-independent. She reported that biopsies revealed that after 5 years of prolonged normoglycemia, renal lesions were unchanged [Fioretto P et al. *Lancet* 1993] "We agreed with the idea that the lesions of diabetic nephropathy are irreversible."

Prof. Fioretto continued tracking these patients, however, and 8 of them came back after 10 years for their third biopsy. "The scenario was very different. In all of them there was substantial improvement in glomerular structure, and in many of them the glomeruli were normal again." Glomerular basement membrane width had been abnormally increased in all of the patients before pancreas transplant, had been unchanged at 5 years, but was markedly reduced after 10 years. In 5 patients, this parameter was back to the normal range. "Since then we have done more patients, and I can tell you that the more patients we do, the more reversal we find, with marked improvement at 10 years." (Figure 1)

Figure 1 Reversal of Lesions of Diabetic Nephropathy after Pancreas Transplantation.



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Prof. Fioretto concluded, "These studies provide the first evidence in humans that established lesions of diabetic glomerulopathy are reversible after 10 years of euglycemia. Whether similar architectural remodeling with reabsorption of accumulated extracellular matrix and, ultimately, healing can be obtained with other treatments is currently unknown."

Prof. Fioretto cautioned, however, that her research does not signify that pancreas transplantation can currently be considered a treatment for diabetic nephropathy. The patients studied had received calcineurin inhibitors, well known to be nephrotoxic and to cause interstitial fibrosis and tubular atrophy. These lesions, present at 5 years after pancreas transplantation, were markedly improved at 10 years, consequent to prolonged euglycemia and, especially, reduction in cyclosporine dose. "Thus, also the tubules and interstitium can undergo repair and healing. I believe that if we could understand the mechanisms regulating these processes we could offer better treatment options to our diabetic patients."

In closing Prof. Fioretto stated, "These results were obtained in an experimental setting, in recipients of pancreas transplantation. Our goal today should be to obtain the same results in clinical practice."

Supplying Insulin to Those Who Need It

In many developing countries, insulin can cost more than 50% of the average per capita annual income. As a result, for many who live in these countries, type 1 diabetes can be a death sentence. Diabetes organizations around the world are working together, however, to find ways to provide insulin to patients who need it but cannot easily obtain it.