The Kidney in Diabetes: Dynamic Pathways of Injury and Repair

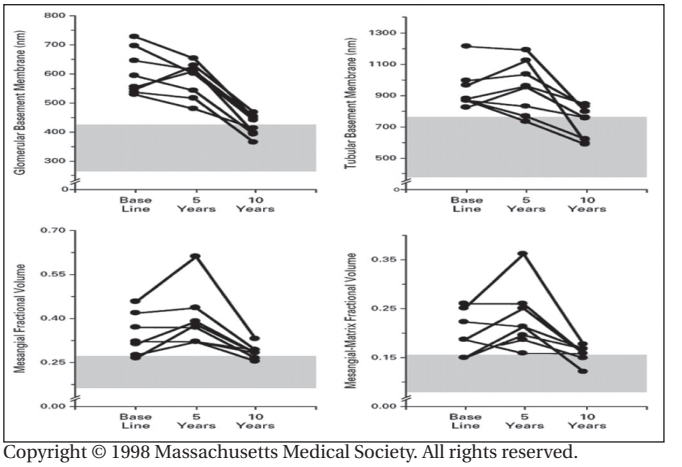
Paola Fioretto, MD, University of Padova, Italy, winner of the Castelli Pedroli Prize, presented the Golgi lecture, "The Kidney in Diabetes: Dynamic Pathways of Injury and Repair." In her lecture, Prof. Fioretto reviewed her own and other's research on the structural lesions leading to renal dysfunction 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.



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 extracellur 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.

Insulin for Life (www.insulinforlife.org) is a non-profit organization that collects and distributes unopened and in-date insulin, test strips, and other diabetes supplies that would otherwise be wasted. Based in Australia, Insulin for Life has affiliates in the United States, Germany, Austria, and the United Kingdom. Donations come from industry, diabetes centers and clinicians, and patients themselves.

Insulin for Life helps a number of developing countries on a continuous basis, and donates to others as needed in emergency situations, such as following the Asian tsunami, the recent earthquake in Peru, and Hurricane Katrina in the US. In addition, Insulin for Life partners with the International Diabetes Federation (IDF) (www.idf.org) on its Child Sponsorship Program in Bolivia, Rwanda, Zimbabwe and Uzbekistan.

"Many of these supplies would have otherwise been wasted. Instead, they are saving many lives," said Ron Raab, President of Insulin for Life Global, who has had type 1 diabetes himself for the last 50 years.

"Until effective health care systems are put in place, organizations like Insulin for Life will need to provide help," said IDF President Martin Silink, MD, Professor of Endocrinology and Diabetes, University of Sydney, Australia.

Over the past 2 years, shipments from Insulin for Life have totaled 250,000 mL insulin (25-30 million units), 400,000 blood glucose test strips, 1,523,500 syringes, and thousands of meters and other items, with an estimated value of € 2.5 million.

During a press conference Wim Wientjens, PhD, Vice President of the IDF, further highlighted the value of these two organizations. He noted that in developing countries, diabetes care can be abysmal. It is often marked by a lack of insulin (which may be unavailable to or unaffordable for families), a lack of expert care and facilities, and a lack of affordable means of self-monitoring. "For children with diabetes in developing countries, the most common complication of diabetes is death," said Dr. Wientjens, who like Mr. Raab has type 1 diabetes.

Alicia Jenkins, MD, a Visiting Professor at the University of Oklahoma Diabetes Center, added that the aim is to "address the great inequality that exists in the world of diabetes care." To illustrate how these programs are successful, Dr. Jenkins described the work being done in support of 42 needy children in Uzbekistan, whose typical life expectancy would be only 4-7 years post-diagnosis.

Since January 2007, when the project was initiated, Uzbekistan has received over 30,000 mL of insulin and 10,000 syringes. Hospital admissions for diabetic ketoacidosis have sharply declined, and mean HbA1c has been reduced from >10% to 8%. There are now new patient advocacy associations and "healthier, happier people," she reported.

Clinicians can help these efforts by donating funds or supplies, by sponsoring a child via the IDF Life for a Child program, or by starting a distribution center in their area. For more information, visit www.idf.org or www.insulinforlife.org.

Glycemic Control Associated with Reductions in Incidence of Macrovascular Events

Results of an analysis of data from a healthcare database including nearly 70,000 patients with diabetes revealed that elevated HbA1c is a significant risk factor for acute myocardial infarction (AMI) and the need for coronary artery bypass graft surgery (CABG).

Introducing the analysis, Joseph E. Thomas, MD, Yale University School of Medicine, Connecticut, United States, said that while tight glycemic control has been associated with improved cardiovascular outcomes in both type 1 and type 2 diabetes, the relationship between glycemic control and cardiovascular outcomes in clinical practice is not well understood. Thomas and colleagues conducted a retrospective chart analysis of data from 69,418 patients with diabetes from the Integrated Health Care Information System (IHCIS).

For purposes of the analysis, patients were stratified into four index HbA1c groups: <6%, 6-7%, 7-9%, ≥9%. Mean patient age was ~57 years (~54% male), with prior AMI in 1.0-1.5% and prior CABG surgery in 0.1-0.5%. Mean follow-up was 27 months. In the HbA1c ≥9% group at baseline, total cholesterol, LDL-cholesterol, and triglycerides were higher, and HDL-cholesterol was lower than in the other groups. About a third of patients were receiving ACE inhibitors or angiotensin receptor blockers. As expected, use of oral antidiabetic agents and insulin was higher in patients with poorer glycemic control.

The unadjusted incidence rate for AMI, CABG, stroke, and their combination increased generally with increasing HbA1c with the exception of stroke (Table 1). "We were unable to explain the lower stroke incidence," Dr. Thomas said, although he commented that TIAs had been excluded.