Dr. Schatz and his colleagues explored the use of autologous cord blood for stem cell therapy. He explained that cord blood has a high capacity for T cell regulation, has a greater regenerative capacity than bone marrow, and has been used effectively for other autoimmune diseases. In addition, cord blood may be naïve to the environmental insult that initiated the autoimmunity and, therefore, induce tolerance. The researchers' Phase 1 study enrolled 24 young children who received a transfusion when they were aged a mean of 5.25 years (range: 3.1 to 7.3 years). The treatment substantially reduced HbA1C levels and insulin requirements, which were maintained through 2 to 2.5 years of follow-up [Haller MJ et al. *Diabetes Care* 2009]. The level of regulatory T cells increased between 0 and 6 months, which suggested that the treatment favored a regulatory/protective immune response, said Dr. Schatz. He pointed out that the results should be interpreted with caution, as a limitation of the study is the use of historical controls as the comparator group.

The results of these studies are encouraging, but none of the treatments has improved insulin production, which is necessary to reverse the disease process. The one exception is a study in which nonmyeloablative stem cell transplantation increased insulin production in a study of 15 subjects (aged 14 to 31 years) with new-onset diabetes, with significant increases in C-peptide levels that were maintained at a mean of nearly 30 months of follow-up. Most subjects were insulin-independent and had good glycemic control [Voltarelli JC et al. *JAMA* 2007; Couri CE et al. *JAMA* 2009]. Despite the positive results, Dr. Schatz noted that the potential morbidity and mortality of the approach may be unacceptable.

New Biomarkers Needed for Early Diabetic Nephropathy

Written by Rita Buckley

Nephropathy is a major complication of diabetes, and its incidence has been increasing despite improvements in renal protection and glycemic control. Thus, it is crucial to identify patients who are at risk for early diabetic nephropathy and to develop preventive interventions. Since the 1980s, microalbuminuria has been an early marker of progressive kidney disease in diabetes, and although this marker is a "great example of predictive validity, [it] is no longer predictive on its own," said Bruce Perkins, MD, MPH, University Health Network, Toronto, Ontario, Canada. Instead, he said, early progressive glomerular filtration rate (GFR) loss should be the focus, and new biomarkers must be identified.

Dr. Perkins noted that several studies have indicated that microalbuminuria is a functional abnormality in diabetes and remits to normoalbuminuria over time in most patients. Although it was once thought that renal function decline was a late-occurring event that was associated with proteinuria, later studies have indicated that the initiation of renal function decline occurs soon after the onset of microalbuminuria and is not conditional on progression to proteinuria.

Early GFR loss begins at the onset of microalbuminuria in about 30% of patients with type 1 diabetes, said Dr. Perkins, and "represents a committed step—a point of no return," with the constant loss of renal function leading to advanced stages of chronic kidney disease. However, early GFR loss does not have very good agreement with the degree of microalbuminuria or its subsequent course.

In contrast, serial measurements of serum cystatin C can accurately assess GFR changes over time. Cystatin C is a nonglycosylated basic protease inhibitor that is produced by all nucleated cells, and it has estimated GFR well, even in patients with normal or elevated renal function [Cherney DZ et al. *Diabet* Med 2010]. Dr. Perkins said that taking serial measurements of cystatin C over time is one improved strategy for predicting the risk of diabetic nephropathy.

Another strategy for predicting the risk of renal disease is to find an accurate and reliable single measure, and Dr. Perkins noted that several urinary and systemic factors have been associated with subsequent early GFR loss. For example, early GFR loss has been associated with urinary excretion of some advanced glycation end products and chemokines, urinary proteomics, and tubular markers.

With regard to systemic factors, in patients with type I diabetes, high levels of soluble tumor necrosis factor receptors are strongly associated with decreased renal function, and serum uric acid concentrations at the high end of the normal range have been associated with impaired renal function in patients, with effects that are independent of those of microalbuminuria [Niewczas MA et al. *Clin J Am Soc Nephrol* 2008; Rosolowski ET et al. *Clin J Am Soc Nephrol* 2008]. Dr. Perkins said that these findings suggest that it may be possible to slow renal function loss in patients with early diabetic renal failure through the use of anti-TNF drugs and therapies that reduce serum uric acid.

Dr. Perkins emphasized the need for research to identify biomarkers for early GFR loss. Research must move beyond the reporting of associations between factors and renal failure to determine biomarker thresholds through diagnostic study methodology. Studies should also be conducted to determine the mechanisms of early GFR loss and to discover therapies that slow this loss.