genetic architecture of common kidney disease, especially diabetic nephropathy. Understandably, both nephrologists and kidney disease patients are hopeful these findings will lead to new therapies and tests that identify individuals at risk for kidney disease progression.

Although novel pathways that potentially regulate the pathogenesis of diabetic nephropathy and other chronic kidney diseases are being identified, much work needs to be done. The common variants associated with most common diseases including kidney disease only explain a small percentage of overall risk. We need to understand the mechanisms responsible for the missing heritability. Although genetic tests are marketed directly to consumers, studies of their clinical validity and utility, which are required of all other laboratory tests, must to be established. Of equal importance, we must understand how our patients will respond to genetic risk information for kidney diseases. Despite these issues, I am confident that studies of genetic causes of kidney and other common chronic diseases will positively impact personal and public health and help stem the worldwide epidemic of chronic diseases (7).

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The Risk of Posttransplant Diabetes Mellitus in Renal Transplant Recipients

By James T. Lane

New-onset diabetes after transplantation (NODAT) affects up to 50 percent of nondiabetic patients post-kidney transplant depending on the type of study (retrospective versus prospective), the patient population, frequency of sampling, posttransplantation complications, the immunosuppression regimen, duration of follow-up, and diagnostic criteria. The 2003 International Consensus Guidelines (1) unified the diagnosis and brought NODAT in line with the more commonly used American Diabetes Association (ADA) criteria for diabetes diagnosis, namely more than one fasting glucose ≥ 126 mg/dL. Although this brief review focuses on NODAT after kidney transplantation, this condition follows all forms of solid organ transplantation.

Pretransplant risk factors for NODAT, similar to those for type 2 diabetes, include older age, increased body mass index, positive family history of type 2 diabetes, hepatitis C infection, cytomegalovirus (CMV) infection, and genetic factors. No conclusive gender differences have been demonstrated. NODAT was also associated with TCF7L2 polymorphism, another factor shared with type 2 diabetes. Autosomal dominant polycystic kidney disease associates with insulin resistance and hyperinsulinemia, and may increase risk. Children also experience NODAT, although not at the same rate as adults.

Several posttransplant factors increase risk for NODAT including the use of certain types of drugs for immunosuppression, marked weight gain after transplant, and the inflammatory response surrounding transplant. It was hoped that movement away from glucocorticoids as a cornerstone of immunosuppression would reduce glucose intolerance; however, alternative drugs produce additional risk. Calcineurin inhibitors, including both cyclosporine and tacrolimus, are strongly associated with NODAT (2). These agents impair insulin secretion and damage pancreatic islets, increasing apoptosis of B-cells. Tacrolimus increases insulin resistance in animal studies. Sirolimus is also diabetogenic with insulin resistance as the likely cause.

NODAT produces more than long-term microvascular risks; it also increases cardiovascular death and decreases graft survival (3). Cardiovascular risk is not related to degree of hyperglycemia; even mild levels of hyperglycemia increase risk above and beyond what is seen with chronic kidney disease alone.

Given the need for renal replacement therapy, but sobered by the risk of NODAT to patient and graft survival, how should we proceed? Patients first need to know about NODAT. Very often patients anticipate the benefits of renal transplantation without considering the risks and are not necessarily willing to think about negative outcomes. Patients appropriately informed about NODAT may be able to minimize weight gain following the transplant through appropriate counseling. A thorough history can identify the mentioned risk factors for NODAT. An oral glucose tolerance test prior to transplant will identify patients with preexisting impaired glucose tolerance. There should be an ongoing strategy to monitor glucose, especially the fasting glucose, posttransplant. Monitoring one to two times per week is not unreasonable. Elevated glucose levels early in the posttransplant period predict NODAT later on. In our patient population, NODAT peaked at three months after kidney transplant; monitoring has to be in place to address this time course. When NODAT is diagnosed, early referral to a diabetes educator for counseling and glucose monitoring is essential.

Patients with the highest risk of NODAT may warrant immunosuppressive regimens with less diabetogenic potential while weighing the risk of acute rejection. Antibody induction therapy, an area of interest at our center, may allow for lower levels of diabetogenic immunosuppressive drugs and less inflammation at the time of transplantation (4).

A recent retrospective study investigated NODAT, type of immunosuppression, and observed hypomagnesemia in renal transplant recipients (5). Hypomagnesemia occurs in the immediate posttransplant period in association with calcineurin-inhibitor therapy and was an independent predictor of NODAT. It is not known whether more aggressive magnesium replacement may prevent NODAT.

The use of HbA1c has recently been adopted by the ADA to diagnose diabetes, but its utility in the transplant population remains unclear. Pretransplant HbA1c levels may be falsely decreased related to uremia. Because it reflects hyperglycemia over several months, it is not sensitive posttransplant, especially for onset of disease within the first few months. HbA1c remains a helpful test to follow patients after three to six months.

Medical therapy for NODAT is similar to that for type 2 diabetes, with some exceptions. Unlike usual type 2 diabetes, metformin as a first-line single agent is controversial because of the risk of lactic acidosis in patients with reduced renal function or in patients at risk for rapid decline in renal function. Sulfonylureas have been used with success, but they have the potential to increase weight and cause hypoglycemia. Thiazolidinediones (TZDs) have been used with success, have less hypoglycemia potential as monotherapy than other agents, but should be used with caution in patients with congestive heart failure or in patients with increasing edema. TZDs can also cause marked weight gain. Exenatide is not an ideal drug in the post-kidney transplant patient since it may cause nausea. However, we have used DPP-IV inhibitors in patients with mild hyperglycemia with good results. Finally, many of these patients require insulin therapy. HbA1c goals recommended by the ADA should be followed. Additional cardiovascular risk factors, such as hypertension, hyperlipidemia, and obesity need to be concomitantly addressed.

Challenges remain for the prevention of NODAT and the threat it poses to patients and their transplanted organs, but we can reduce risk and ensure early diagnosis. Potential interventions undergoing prospective study may prevent NODAT. Until that time, NODAT is a formidable opponent in the quest to improve the lives of patients requiring transplantation.

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