# Posttransplantation Normoglycemic Diabetic Nephropathy: The Role of the Allograft Insulin Resistance–A Case Report

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ABSTRACT

Background. The pathogenesis of diabetic nephropathy is incompletely understood. Although the role of hyperglycemia is well-established, the participation of insulin resistance is increasingly appreciated. Podocytes are insulin responsive cells and require normal insulin signaling for sustained viability.

Case Report. We have presented a renal transplant recipient with lupus nephritis who received a deceased donor kidney from a patient with diabetes mellitus (DM). The kidney functioned well initially. Within 2 years, however, nephrotic range proteinuria developed, and a biopsy revealed diabetic nephropathy that had clearly evolved in comparison with the implantation biopsy. The recipient was repeatedly normoglycemic with normal glycated hemoglobin and glucose tolerance, and she was found to be quite insulin sensitive on the basis of a low homeostasis model assessment of insulin resistance.

Conclusions. We argue that the nephropathy developed in the allograft owing to impaired insulin signaling from intrinsic donor-derived insulin resistance that was exacerbated by low insulin levels in the insulin-sensitive recipient. This case has implications for the most appropriate utilization of kidneys from donors with DM.

THE SHORTAGE OF DONOR ORGANS for kidney transplantation is well-established. In an effort to increase the pool, less than ideal kidneys are being increasingly utilized, including expanded criteria donors (ECD), donors with primary cardiac death, diabetic donors, and combinations of these categories. In the case of a diabetic donor, registry data indicate a steady increase in their use from 1.5% of deceased donor (DD) kidneys transplanted in the United States in 1994 to 6.4% in 2008 [1]. The vast majority of these kidneys were from otherwise standard criteria donors (SCD), not ECDs.

Both single-center studies [2] and analyses of registry data [1,3,4] indicate a reasonably successful outcome for diabetic donors, somewhere in between SCDs and ECDs. Although registry data document an equivalent death-censored graft survival (DCGS) between diabetic and nondiabetic recipients, SCD diabetic donors kidneys are suggested to be offered predominantly to euglycemic recipients with lower risk for development of diabetes mellitus (DM), that is, body mass index of 20–30 kg/m$^2$ [1]. When placed in nondiabetic recipients, kidneys with documented diabetic nephropathy (DN) have shown histologic regression over time [5]. When type 1 diabetic patients with biopsy-proven DN underwent successful pancreas transplantation, the histologic lesions in their native kidneys markedly regressed over 5–10 years [6].

In distinction to these data, the case is presented of a thin woman with end-stage renal disease secondary to lupus nephritis who received a DD kidney from a patient with a 30-year history of type 1 DM with evidence of insulin resistance (IR). The graft functioned well over 2 years, but because of proteinuria in the nephrotic range, a biopsy was obtained that revealed DN, which was more pronounced than on the implantation biopsy. This progression occurred despite normoglycemia based on fasting glucose, oral glucose tolerance testing, and glycosylated hemoglobin levels. The patient was, however, quite insulin sensitive, and

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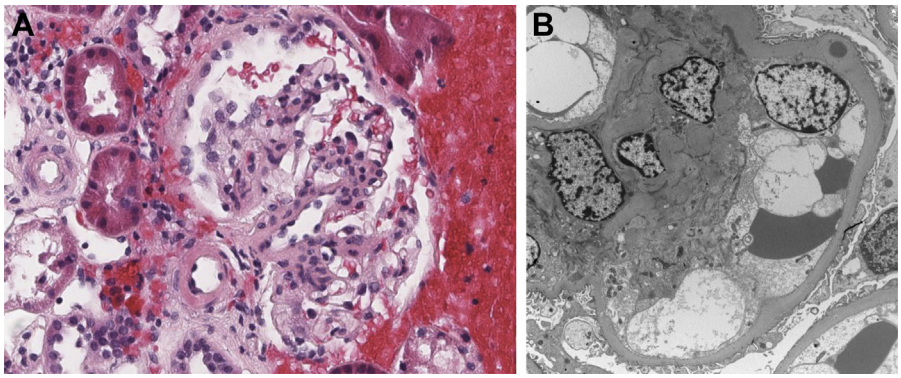


**Fig 1.** Kidney biopsy 2 years posttransplantation. **(A)** Photomicrograph showing mesangial expansion and hypercellularity with hyaline arteriolosclerosis (stain: hematoxylin and eosin; original magnification, ×40). **(B)** Electron micrograph showing thickening of the lamina densa of the glomerular basement membrane with accumulation of basement membrane-like material in the mesangium (original magnification, ×2700).

we argue that placing an insulin-resistant diabetic kidney in an insulin-sensitive patient with relatively low insulin levels resulted in progression of the nephropathy through further impairment of insulin signaling at the level of the podocyte.

## CASE REPORT

A 43-year-old Asian woman with systemic lupus presented in 2003 with nephrotic syndrome. Renal biopsy showed class 3 lupus nephritis, and she was treated with oral prednisone and mycophenolate mofetil (MMF). When serum creatinine levels increased, another biopsy was obtained in 2005 that showed class 4 lupus nephritis. She was treated with monthly IV cyclophosphamide and oral prednisone. Renal function deteriorated, and in 2006 dialysis was initiated. She underwent DD renal transplant on April 28, 2011, from a 35-year-old, obese (body mass index of 31.6 kg/m$^2$), Caucasian male with type 1 DM since age 4, hypertension, hyperlipidemia, and coronary artery disease. Serum creatinine ranged from 1.7 to 2.1 mg/dL with terminal serum creatinine of 1.8 mg/dL. A urinalysis had 2+ protein and 2+ blood. A postimplantation biopsy revealed moderate acute tubular damage, but no evidence of interstitial fibrosis or glomerulopathy. There was excellent initial graft function. Immunosuppression included thymoglobulin induction, steroids, tacrolimus, and MMF. She was discharged on 20 mg daily of prednisone. This was tapered to 5 mg/d by 90 days and maintained with tacrolimus and MMF. Baseline serum creatinine was 1.2 mg/dL. Spot urine protein/creatinine ratio reached a nadir of 0.3 mg/mg on September 12, 2011. Subsequently, it increased to 2.3 on September 23, 2013, with a serum creatinine of 1.2 mg/dL. Trace hematuria was present on urine dipstick. A transplant biopsy was obtained on May 13, 2013.

The biopsy showed evidence of diabetic glomerulosclerosis, class II [7]. By light microscopy, mesangial expansion and hypercellularity in 15 glomeruli total were accompanied by hyaline arteriolosclerosis (Fig 1A). Immunofluorescence microscopy was negative except for trace mesangial immunoglobulin M staining. By electron microscopy, prominent thickening of the lamina densa of the glomerular basement membranes was evident with accumulation in the mesangium of basement membrane-like material (Fig 1B). There were no electron-dense deposits present. Importantly, these alterations were acquired posttransplantation, as shown by an implantation biopsy obtained at the time of transplantation 2 years previously. As shown in Fig 2A, by light

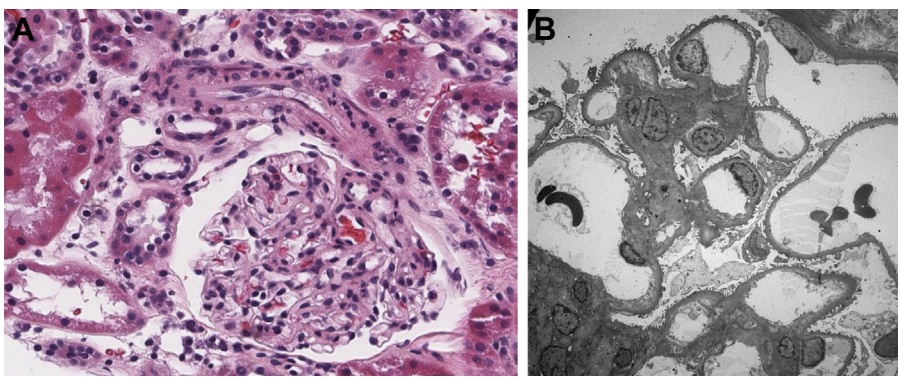


**Fig 2.** Kidney biopsy obtained at the time of transplantation (implantation). **(A)** Photomicrograph showing an essentially unremarkable glomerulus. **(B)** Electron micrograph showing normal thickness of the glomerular basement membrane (original magnification, ×2000). Mesangial region is similarly normal.