بسم الله الرحمن الرحیم

Recurrence of diabetic nephropathy in allograft

Dr Roya Hemayati

Introduction

- DM is the most common cause of ESKD in most parts of the word, however, transplant in these patients is less common than in patients with GN because of higher prevalence and severity cardiovascular comorbidities.
- Recurrence of diabetic nephropathy has been shown to occur in about 25% of recipients at an average follow up of 6 years, with some patients diagnosed within 3 years of transplant.

Introduction

- Historically, the vast majority of diabetic transplant recipients have developed histologic changes of recurrent diabetic kidney disease, in some cases within one year posttransplantation .
- In the contemporary era of tacrolimus-based immunosuppression, up to 52 percent of diabetic transplant recipients have histologic evidence of diabetic kidney disease/mesangial sclerosis at 10 years after transplantation.
- However, the incidence of diabetic kidney disease as a cause of graft failure is thought to be rare.

Introduction

- Histologic and clinical features are similar to those of native kidney DN.
- PTDM is associated with increased mortality and morbidity; patients also have higher rates of cardiovascular disease and infection, which are the leading causes of death in renal transplant recipients.

Pathophysiology of DN

Hyperglycemia induced metabolic and hemodynamic pathways are proven to be mediators of kidney disease.

Hyperglycemia causes the formation of Amadori products (the altered proteins) and advanced glycation end products, which are the molecular players in the phases of DN.

Pathophysiology of DN

Activation of electron transport chain induced by hyperglycemia can result in an increase in reactive oxygen species (ROS) formation, which may be the initiating event in the development of complications in diabetes.

Hemodynamic changes, hypertrophy, extracellular matrix accumulation, growth factor/cytokine induction, ROS formation, podocyte damage, proteinuria,and interstitial inflammation are steps in the development of DN.

Pathophysiology of DN

High glucose, advanced glycation end products, and ROS act in harmony to induce growth factors and cytokines through signal transduction pathways involving protein kinase C, mitogen-activated protein kinases, and the transcription factor nuclear factor κB.

Transforming growth factor causes hypertrophy of the renal cells and accumulation of extracellular matrix.

Activation of the renin-angiotensin system with the subsequent formation of angiotensin II is involved in almost all steps in development of DN.

Pathophysiology of DN

Renal inflammation also plays a significant role in DN progression. The previously mentioned changes lead to interstitial infiltration by inflammatory cells, mainly macrophages and lymphocytes, chemoattracted by cytokines released by injured renal cells.

The released proinflammatory cells and cytokines (such as tumor necrosis factor-alpha, interferon gamma,and interleukin 1) can stimulate oxidative stress through activation of nicotinamide adenine dinucleotide phosphate hydrogen oxidase subunits.

Pathophysiology of DN

Massive proteinuria is associated with intense protein reabsorption activity of proximal tubular cells, which is followed by the formation of proteinaceous casts at distal points that cause tubular dilatation and obstruction.

Tubular basement membrane integrity becomes jeopardized, with proteins transported from the urinary space to the interstitium triggering an inflammatory reaction

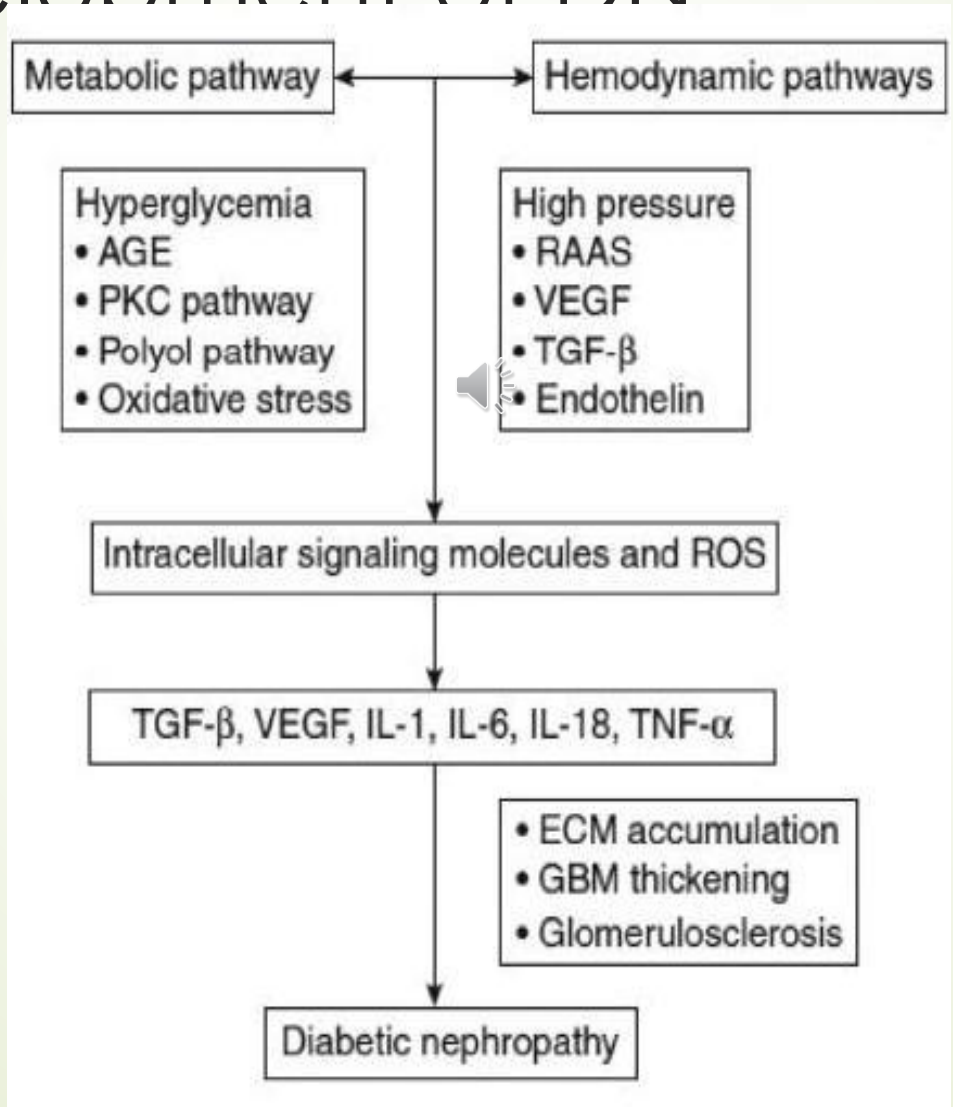
Pathophysiology of DN

Familial or perhaps even genetic factors also play a role. Certain ethnic groups, particularly African Americans, persons of Hispanic origin, and American Indians, may be particularly disposed to renal disease as a complication of diabetes.

Some evidence has accrued for a polymorphism in the gene for angiotensin-converting enzyme (ACE) in either predisposing to nephropathy or accelerating its course.

More recently, the role of epigenetic modification in the pathogenesis of DN has been highlighted.

Pathways involvement in the development of DN



Stages and diagnosis of DN

Stages are similar to those of typical DN in native kidneys, with thickening of the glomerular basement membrane and the tubular basement membrane as the first signs of DN followed by mesangial matrix expansion.

The extracellular matrix forms nodular mesangial changes, which gradually compress glomerular capillaries and lead to end stage

glomerular sclerosis, associated hyalinosis of afferent and efferent arterioles, and tubulointerstitial related chronic changes.

Stage and diagnosis of DN

Diabetic nephropathy in the transplanted kidney is frequently associated with vascular and tubulointerstitial changes due to allograft rejection, viral infection, or calcineurin inhibitor (CNI) nephrotoxicity, which may help to distinguish it from DN in the native kidney.

Although widespread data on DN in the native kidney are available, data on DN after renal transplant are scarce. There have been no studies confirming that similar mechanisms in DN are involved as those in the native kidney.

Stage of diabetes and the clinical correlations

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May be increased	Type 1 normal; type 2 normal or hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickened BM and expanded mesangium	Normal	Type 1 normal; type 2 may be < 30-300 mg/dL	Type 1 normal; type 2 normal or hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/dL	Type 1 increased; type 2 normal or hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below normal	> 300 mg/dL	Hypertension	15-25 years
Stage 5	Uremic	ESKD	0-10	Decreasing	Hypertension	25-30 years

Stage and diagnosis of DN

However, Fiorina and associates described the role of podocyte B7-1 in podocyte injury resulting from hyperglycemia, which in turn leads to upregulated B7-1. This upregulation was shown to be mediated by activation of the 110-kDa catalytic PI3Kα subunit. Addition of CTLA4 immunoglobulin, such as abatacept, also prevented cytoskeleton disruption and adhesion in podocytes that were exposed to hyperglycemia in vitro.

Stage and diagnosis of DN

Belatacept, a CTLA4 immunoglobulin with higher affinity to B7-1, has been approved as a maintenance immunosuppressive therapy in renal transplant. Therefore, it will be of great interest to evaluate the effects of belatacept in preventing the development of DN after kidney transplant.

Stage and diagnosis of DN

The circulating soluble urokinase plasminogen activator receptor (suPAR) has been shown to play a dynamic role in patients with DN. Increased suPAR serum levels cause podocyte apoptosis through its link with acid sphingomyelinase-like phosphodiesterase 3b on podocytes.

In addition, suPAR was shown to be a predictor of proteinuria in patients with DM. Therefore, suPAR can be a novel approach to treat DN in native and perhaps in transplanted kidneys.

Occurrence of diabetic nephropathy after renal transplantation despite intensive glycemic control: an observational cohort study.Diabetes care, february14, 2019.

OBJECTIVE

The kinetics and risk factors of diabetic nephropathy after kidney transplantation remain unclear. This study investigated the posttransplant occurrence of diabetic nephropathy and the contribution of posttransplant glycemic control.

RESEARCH DESIGN AND METHODS

We performed a single-center prospective cohort study of 953 renal allograft recipients and 3,458 protocol-specified renal allograft biopsy specimens up to 5 years after transplantation. The effects of pretransplant diabetes and glycemic control (glycated hemoglobin levels) on the posttransplant histology were studied.

RESULTS

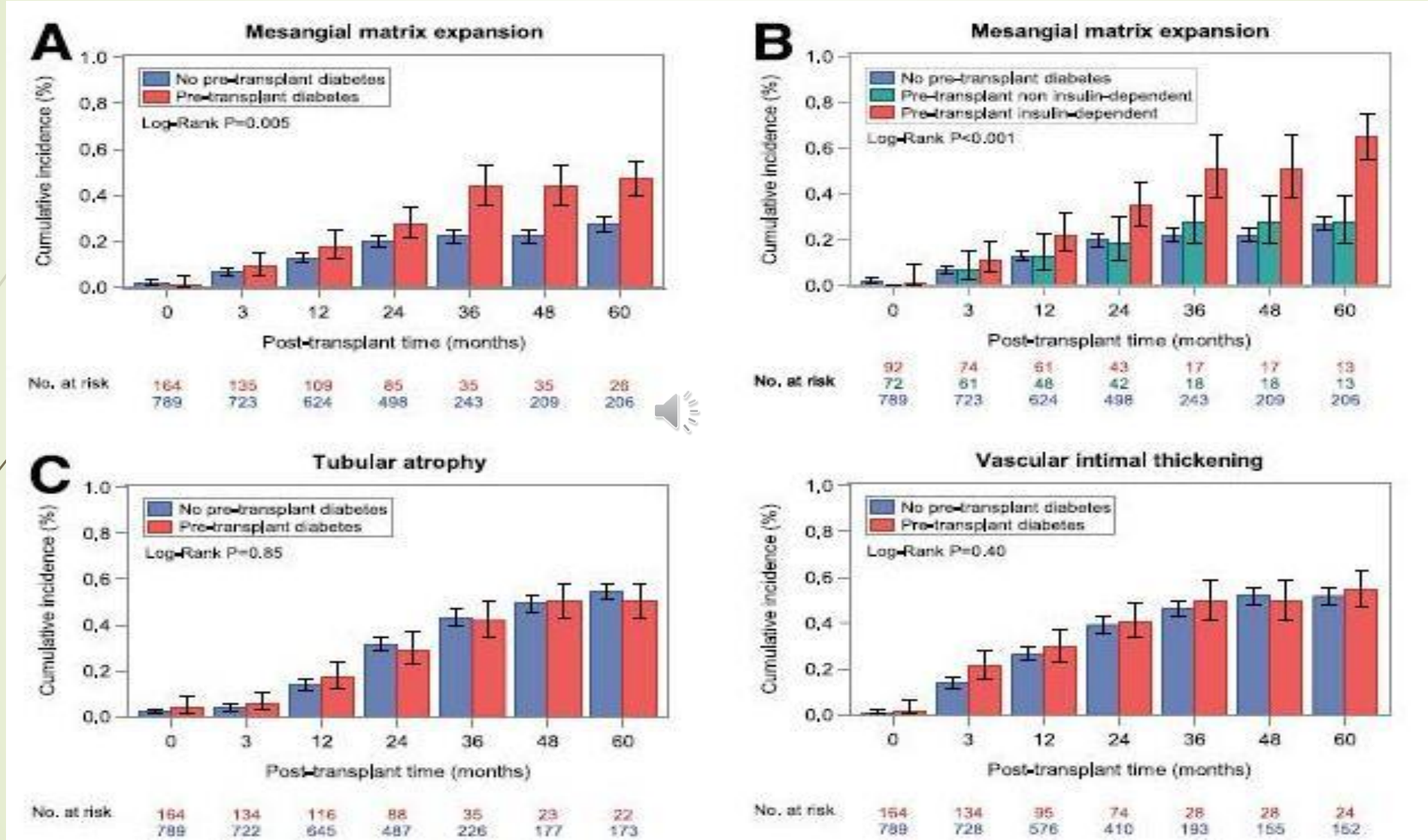
Before transplantation, diabetes was present in 164 (17.2%) renal allograft recipients, primarily type 2 (*n* = 146 [89.0%]). Despite intensive glycemic control (glycated hemoglobin 7.00 ± 1.34% [53 ± 14.6 mmol/mol], 6.90 ± 1.22% [52 ± 13.3 mmol/mol], and 7.10 ± 1.13% [54 ± 12.4 mmol/mol], at 1, 2, and 5 years after transplantation), mesangial matrix expansion reached a cumulative incidence of

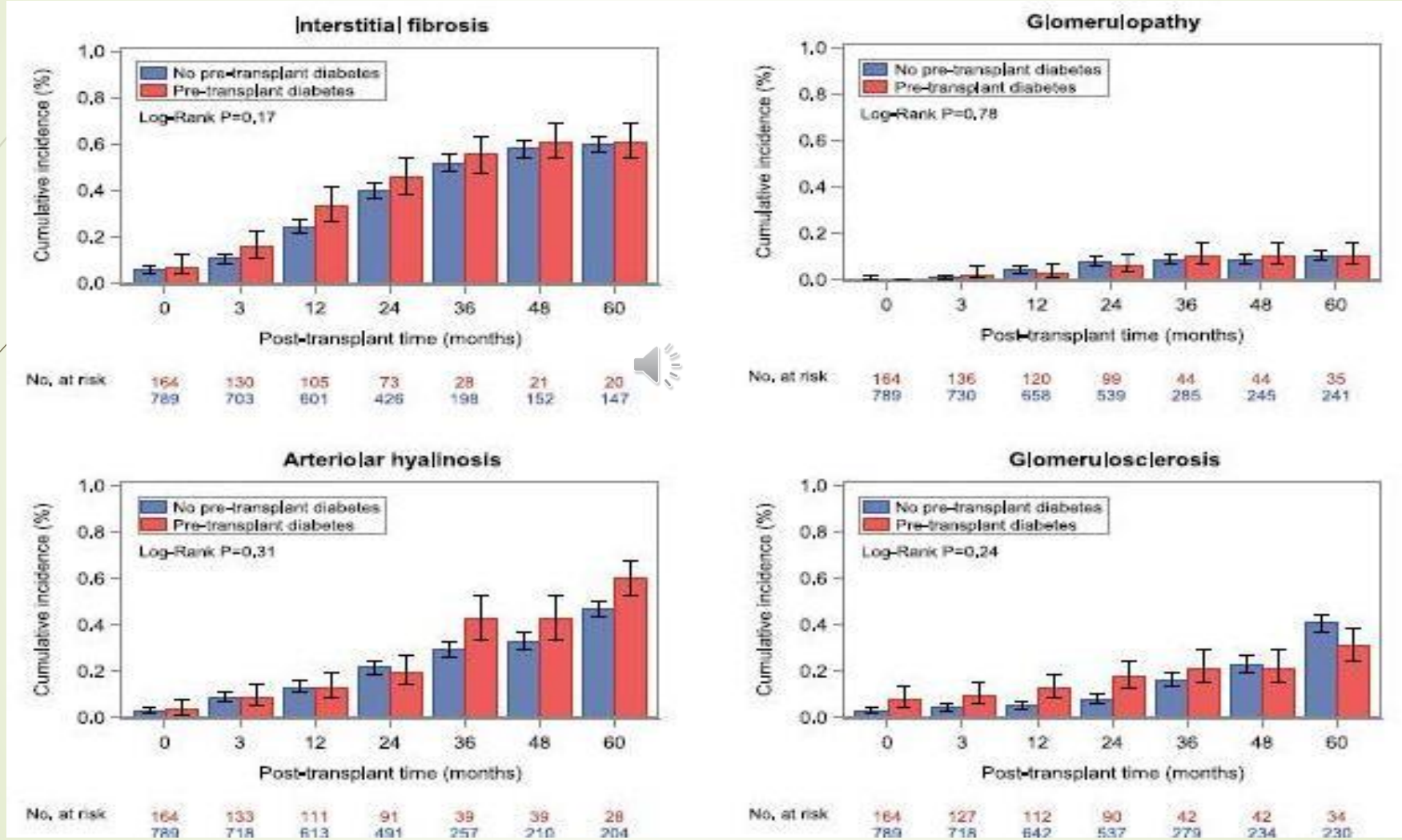
Occurrence of diabetic nephropathy after renal transplantation despite intensive glycemic control: an observational cohort study. Diabetes care, february14, 2019.

transplantation), mesangial matrix expansion reached a cumulative incidence of 47.7% by 5 years in the pretransplant diabetes group versus 27.1% in patients without diabetes, corresponding to a hazard ratio of 1.55 (95% CI 1.07–2.26; *P* = 0.005). Mesangial matrix expansion was not specific for diabetic nephropathy and associated independently with increasing age. Pretransplant diabetes was associated with posttransplant proteinuria but not with estimated glomerular filtration rate, graft failure, or any other structural changes of the glomerular, vascular, or tubulointerstitial renal compartments. The occurrence of diabetic nephropathy was independent of posttransplant glycated hemoglobin levels.

CONCLUSIONS

Mesangial matrix expansion, an early indicator of diabetic nephropathy, can occur rapidly in patients with diabetes before transplantation, despite intensive glycemic control. Prevention of diabetic nephropathy requires more than pursuing low levels of glycated hemoglobin.


A
Mesangial matrix expansion
Cumulative incidence (%)
No pre-transplant diabetes
Pre-transplant diabetes
Log-Rank P=0.005
Post-transplant time (months)
No. at risk
164 135 109 85 35 35 28
789 723 624 498 243 209 206
B
Mesangial matrix expansion
No pre-transplant diabetes
Pre-transplant non insulin-dependent
Pre-transplant insulin-dependent
Log-Rank P<0.001
Post-transplant time (months)
No. at risk
92 74 61 43 17 17 13
72 61 48 42 18 18 13
789 723 624 498 243 209 206
C
Tubular atrophy
No pre-transplant diabetes
Pre-transplant diabetes
Log-Rank P=0.85
Post-transplant time (months)
No. at risk
164 134 116 88 35 23 22
789 722 645 487 226 177 173
Vascular intimal thickening
No pre-transplant diabetes
Pre-transplant diabetes
Log-Rank P=0.40
Post-transplant time (months)
No. at risk
154 134 95 74 28 28 24
789 728 576 410 193 155 152


Interstitial fibrosis
No pre-transplant diabetes
Pre-transplant diabetes
Log-Rank P=0,17
Cumulative incidence (%)
1.0
0.8
0.6
0.4
0.2
0.0
0
3
12
24
36
48
60
Post-transplant time (months)
No. at risk
164 130 105 73 28 21 20
789 703 601 426 198 152 147
Glomerulopathy
No pre-transplant diabetes
Pre-transplant diabetes
Log-Rank P=0,78
Cumulative incidence (%)
Post-transplant time (months)
No. at risk
164 136 120 99 44 44 35
789 730 658 539 285 245 241
Arteriolar hyalinosis
No pre-transplant diabetes
Pre-transplant diabetes
Log-Rank P=0,31
Cumulative incidence (%)
Post-transplant time (months)
No. at risk
164 133 111 91 39 39 28
789 718 613 491 257 210 204
Glomerulosclerosis
No pre-transplant diabetes
Pre-transplant diabetes
Log-Rank P=0,24
Cumulative incidence (%)
Post-transplant time (months)
No. at risk
164 127 112 90 42 42 34
789 718 642 537 279 234 230

Received: 29 June 2018 | Revised: 31 August 2018 | Accepted: 18 September 2018

DOI: 10.1111/ctr.13425

ORIGINAL ARTICLE

WILEY Clinical TRANSPLANTATION

Diabetic nephropathy after kidney transplantation in patients with pretransplantation type II diabetes: A retrospective case series study from a high-volume center in the United States

Arielle Cimeno[1] | Jennifer Munley[1] | Cinthia Drachenberg[2] | Matthew Weir[3] | Abdolreza Haririan[3] | Jonathan Bromberg[1] | Rolf N. Barth[1] | Joseph R. Scalea[1]

[1]Department of Surgery, University of Maryland School of Medicine, Baltimore, Maryland

[2]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland

[3]Department of Nephrology, University of Maryland School of Medicine, Baltimore,

Abstract

Background: Patients with type II diabetes mellitus (DM) undergoing renal transplantation are at risk of diabetic nephropathy (DN) in the transplanted kidney. The true risk of developing post-transplantation DN is unknown, and post-transplantation DN is poorly characterized in the literature.

Abstract

Background: Patients with type II diabetes mellitus (DM) undergoing renal transplantation are at risk of diabetic nephropathy (DN) in the transplanted kidney. The true risk of developing post-transplantation DN is unknown, and post-transplantation DN is poorly characterized in the literature.

Methods: The biopsy database at the University of Maryland Medical Center was queried for kidney transplant biopsies which demonstrated evidence of DN. The time from transplantation to biopsy-proven DN (time to diagnosis, TTD) was calculated and analyzed in the context of demographics, serum creatinine, and onset of diabetes. By extrapolating the total number of patients who developed DN in the last 2 years, we estimated the recurrence rate of DN.

Results: Sixty patients whose renal biopsies met criteria were identified. The mean age was 56.6 (±1.58) years, and the mean creatinine level at time of biopsy was 1.65 (±0.12) mg/dL. Simultaneous pathological diagnoses were frequent on kidney biopsy; rejection was present at variable rates: classes I, IIA, IIB, and III were 5.0%, 66.7%, 18.4%, and 10%, respectively. The mean TTD was 1456 (±206) days. TTD was significantly shorter for patients receiving a cadaveric vs living donor renal transplant (1118 ± 184 vs 2470 ± 547 days, $P = 0.004$). Older patients ($r = 0.378$, $P = 0.003$) and patients with higher serum creatinine ($r = 0.282$, $P = 0.029$) had shorter TTDs. Extrapolations showed that 74.7% of patients would be free of DN 10 years after renal transplantation.

Conclusions: Diabetic nephropathy occurs after transplantation, and this appears to be due to both donor and recipient-derived factors. Encouragingly, our estimates suggest that as many as 75% of patients may be free of DN at 10 years following kidney transplantation.

NEPHROLOGY

APSN

Nephrology **20, Suppl. 2** (2015) 90–92

Brief Communication

Recurrence of diabetic kidney disease in a type 1 diabetic patient after kidney transplantation

IZUMI NYUMURA,[1,2] KAZUHO HONDA,[2] TETSUYA BABAZONO,[1] SHIGERU HORITA,[2] TORU MURAKAMI,[3] SHOHEI FUCHINOUE[3] and YASUKO UCHIGATA[1]

[1]Department of Medicine, Diabetes Center, [2]Department of Pathology, [3]Department of Surgery, Kidney Center, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

ABSTRACT:

Post-transplant hyperglycaemia of diabetic patients may cause recurrent diabetic kidney disease (DKD) in kidney allografts. We report a patient with slowly progressive DKD with calcineurin inhibitor toxicity (CNI) toxicity after the kidney transplantation. A 28-year-old female with type 1 diabetes mellitus underwent successful kidney transplantation from her mother in April 2003, and the kidney graft survived for more than 10 years. She was treated with combined immunosuppressive therapy consisting of cyclosporine and mycophenolate mofetil. After transplantation, she continued to take insulin injection four times per day, but her glycosylated haemoglobin (HbA1c) was above 10%. Protocol allograft kidney biopsies performed 5 and 10 years after transplantation revealed the recurrence of slowly progressive diabetic kidney disease. In addition, arteriolar hyalinosis partly associated with calcineurin inhibitor toxicity (CNI) was detected with progression. Post-transplant hyperglycaemia causes recurrent diabetic kidney disease (DKD) in kidney allografts, but its progression is usually slow. For long-term management, it is important to prevent the progression of the calcineurin inhibitor arteriolopathy, as well as maintain favourable glycaemic control.

The NEW ENGLAND JOURNAL of MEDICINE

IGINAL ARTICLE

Reversal of Lesions of Diabetic Nephropathy after Pancreas Transplantation

Authors: Paola Fioretto, M.D., Ph.D., Michael W. Steffes, M.D., Ph.D., David E.R. Sutherland, M.D., Ph.D., Frederick C. Goetz, M.D., and Michael Mauer, M.D. Author Info & Affiliations

Published July 9, 1998 | N Engl J Med 1998;339:69-75 | DOI: 10.1056/NEJM199807093390202 | VOL. 339 NO. 2

Abstract

Background

In patients with type 1 diabetes mellitus who do not have uremia and have not received a kidney transplant, pancreas transplantation does not ameliorate established lesions of diabetic nephropathy within five years after transplantation, but the effects of longer periods of normoglycemia are unknown.

Methods

We studied kidney function and performed renal biopsies before pancreas transplantation and 5 and 10 years thereafter in eight patients with type 1 diabetes but without uremia who had mild to advanced lesions of diabetic nephropathy at the time of transplantation. The biopsy samples were analyzed morphometrically.

Results

All patients had persistently normal glycosylated hemoglobin values after transplantation. The median urinary albumin excretion rate was 103 mg per day before transplantation, 30 mg per day 5 years after transplantation, and 20 mg per day 10 years after transplantation (P=0.07 for the comparison of values at base line and at 5 years; P=0.11 for the comparison between base line and 10 years). The mean (±SD) creatinine clearance rate declined from 108±20 ml per minute per 1.73 m^2 of body-surface area at base line to 74±16 ml per minute per 1.73 m^2 at 5 years (P<0.001) and 74±14 ml per minute per 1.73 m^2 at 10 years (P<0.001). The thickness of the glomerular and tubular basement membranes was similar at 5 years (570±64 and 928±173 nm, respectively) and at base line (594±81 and 911±133 nm, respectively) but had decreased by 10 years (to 404±38 and 690±111 nm, respectively; P<0.001 and P=0.004 for the comparisons with the base-line values). The mesangial fractional volume (the proportion of the glomerulus occupied by the mesangium) increased from base line (0.33±0.07) to 5 years (0.39±0.10, P=0.02) but had decreased at 10 years (0.27±0.02, P=0.05 for the comparison with the base-line value and P=0.006 for the comparison with the value at 5 years), mostly because of a reduction in mesangial matrix.

Conclusions

Pancreas transplantation can reverse the lesions of diabetic nephropathy, but reversal requires more than five years of normoglycemia.

Posttransplant diabetes melitus

- Posttransplant diabetes mellitus is the occurrence of diabetes in previously nondiabetic individuals after organ transplant. Incidence rates of PTDM vary by organ transplanted and posttransplant interval. The estimated incidence rates at 12 months posttransplant are 10% to 74% for kidney transplants.

Posttransplant diabetes melitus

Posttransplant diabetes mellitus may be diagnosed at any time after transplant by any of the following:

- symptoms of diabetes (including polyuria, polydipsia, and unexplained weight loss), random plasma glucose ≥ 200 mg/dL (11.1 mmol/L),
- fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L, with fasting defined as no caloric intake for at least 8 hours),
- and 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. This test should be performed as described by the World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

Posttransplant diabetes melitus

- Pretransplant assessment should include screening for risk factors for PTDM and for history of gestational diabetes. All patients should be screened with fasting plasma glucose test for evidence of metabolic syndrome and for other cardiovascular risk factors. All patients, whether or not preidentified as having increased risk, should have fasting blood glucose measured weekly during the first 4 weeks posttransplant, then at 3 and 6 months posttransplant, and then yearly.

Thank for attention