Case Study: New-Onset Diabetes After Renal Transplantation

Warren Clayton, Jr., MD, and Shubhada Jagasia, MD

PRESENTATION

U.F. is a 61-year-old woman referred for treatment of new-onset diabetes after a renal transplantation. She underwent a cadaveric renal transplant ~ 3 years before her presentation. After transplantation, she was started on immunosuppressant therapy, initially with thymoglobulin induction for 5 days and varying doses of prednisone, sirolimus, and mycophenolate mofetil (MMF) that were tapered during her postoperative course. Approximately 6 months later, she reported significant elevations in her blood glucose readings. She was initially treated with glyburide, which was subsequently discontinued because of significant hypoglycemia after reductions in her prednisone dose. However, she developed postprandial hyperglycemia after cessation of her oral therapy. She was then treated with aspart insulin, at the dose of 2 units at breakfast and lunch and 4 units at dinner. At the time of referral, her immunosuppressant regimen included prednisone, 5 mg daily; sirolimus, 1 mg daily; and MMF, 200 mg twice daily. She denied polyuria, polydipsia, or blurred vision.

Her medical history was significant for end-stage renal disease resulting from adult polycystic kidney disease. She was treated with hemodialysis for 2 years. Thereafter, she required bilateral native nephrectomies because of a diagnosis of renal cell carcinoma. She also reported a history of hepatitis C infection with liver biopsy results that demonstrated stage I fibrosis. Despite this history, she has had normal liver function tests. She denied any history of diabetes or glucose intolerance before her transplantation.

U.F. also denied a family history of type 2 diabetes. She reported no history of tobacco use, alcohol, or illicit drugs. Her weight at initial presentation was 179 lb, and her BMI was 31 kg/m^2.

Her A1C at her first presentation was 6.2%. Because of further reductions in her immunosuppressant therapy and evidence of good glycemic control on small doses of insulin, a trial on oral therapy was attempted. She was restarted on glyburide, initially at 5 mg twice daily, and insulin therapy was discontinued. She also received dietary counseling and began a weight loss routine. Subsequent A1C measurements were consistently < 7% until the following year, when her A1C was found to be 8.4%.

A review of her home blood glucose readings revealed postprandial elevations resulting from reported dietary indiscretions. She again underwent dietary counseling, and her glyburide was increased to 10 mg twice daily. However, she began to have persistently elevated blood glucose readings. Insulin therapy was initiated after failure of lifestyle modifications; basal coverage was prescribed as glargine, 8 units at bedtime, and glyburide, 10 mg twice daily, was continued.

QUESTIONS

1. What is new-onset diabetes after transplantation (NODAT)?
2. How is it diagnosed?
3. What is the impact on the morbidity and mortality of transplant patients?
4. What are the risk factors?
5. What is the treatment strategy?

COMMENTARY

NODAT is a form of type 2 diabetes that is diagnosed in patients after undergoing organ transplantation. Although the patient in this case had a renal transplant, NODAT is also described in patients after cardiac and liver transplantation. It is also referred to in the literature as post-transplant diabetes mellitus.[1] It is most frequently diagnosed in the first 3–6 months post-transplant;[2] however, there is an increasing prevalence of NODAT throughout each successive year.[3]

The reported incidence of NODAT has a wide variation in the literature, ranging from 2 to 53%,[4] because of differences in diagnostic criteria. Previous investigators have defined NODAT based on varying measures of blood glucose, whereas others have based diagnostic criteria on the requirement of insulin for glycemic control. There are now international consensus guidelines recommended for defining NODAT[5] that are based on the established criteria from the World Health Organization and American Diabetes Association (ADA). The standard definition is:

- A random plasma glucose ≥ 200 mg/dl with symptoms including polyuria, polydipsia, and unexplained weight loss
- A fasting plasma glucose ≥ 126 mg/dl, where fasting is defined as no caloric intake for at least 8 hours
- A 2-hour plasma glucose ≥ 200 mg/dl after an oral glucose load of 75 g of anhydrous glucose dissolved in water

NODAT has been reported as a major contributing factor to the morbidity and mortality of patients after transplantation. Previous studies have demonstrated overall survival rates at 1 year posttransplant of 83 and 98%, respectively, for NODAT patients compared to transplanted patients without diabetes.[6] The 5-year survival rate has been reported as 87 and 93%, respectively.[7]

Cardiovascular disease (CVD) has been shown to be the most common cause of death in patients after renal transplantation.[8] Previous studies have shown that the development of diabetes after transplantation increases this risk. A study of approximately 900 kidney transplant recipients showed an increase in cardiovascular complications among patients with diabetes compared to patients without diabetes (37 vs. 9%, respectively).[9]

Although the exact reason for the increased risk of CVD in NODAT patients is not entirely clear,[5] it is known that hyperglycemia and insulin resistance influence atherogenesis.[10] However, the increased risk for CVD in these patients is also associated with other independent risk factors, including dyslipidemia, increased age, and a history of CVD before transplantation.[9,11]

Also significant to NODAT patients is the risk for allograft survival. There are well-established data indicating an association between impaired graft function and NODAT. A 3- and 4-year graft survival of 71 and 54%, respectively, has been reported in NODAT patients, compared to a respective 86 and 82% in control subjects.[12] Furthermore, a study observing patients 12 years posttransplant has demonstrated a survival of 48% in NODAT patients, compared to 70% in control subjects.[13]

The development of diabetic nephropathy in patients with NODAT is a likely factor in graft failure and has been demonstrated on histological analyses of some cases.[14] However, other studies have shown that not all failed transplants in patients with NODAT have evidence for diabetic nephropathy.[13] It is postulated that other factors, including hypertension and reduced immunosuppressant doses, could be contributing causes.[13]

There is also an increased risk for the development of infectious complications. Sumrani et al.[15] have demonstrated an increased risk for infections in a cohort of NODAT patients of 54% compared to 17% in a control population. Furthermore, von Kiparski et al.[16] have shown an increased risk for hospitalization because of severe infections. In 10 years of follow-up for transplant patients, ~ 37% of patients with NODAT were admitted versus 18% of matched control subjects.[16] Common infections included cytomegalovirus, abscesses, pneumonia, and urinary tract infections.[16]

Many of the risk factors that predispose nontransplant patients to diabetes are also common risk factors for NODAT. Age > 40 years, a BMI > 30 kg/m^2, African-American or Hispanic ethnicity, and a family history of diabetes have all been associated with an increased risk for the development of diabetes.[17] An impaired fasting glucose (100–125 mg/dl after an 8-hour fast) or impaired glucose tolerance (140–199 mg/dl 2 hours after a 75-g oral glucose load) as defined by the ADA is also considered to be a positive predictor for the development of NODAT.[1] Furthermore, studies have shown that there is a greater incidence of NODAT in patients infected with the hepatitis C virus and that successful treatment before transplantation can reduce this risk.[17] Another risk for the development of diabetes in transplant recipients is related to the use of immunosuppressant medications. Glucocorticoids, calcineurin inhibitors, and sirolimus are commonly administered medications in the posttransplant setting.

The diabetogenicitiy of glucocorticoids is known to occur via the induction of insulin resistance and increased hepatic gluconeogenesis.[1] The extent of this effect has been shown to be dose related, with lower doses and shorter treatment courses correlated with a reduced risk for NODAT development.[18,19] Steroid tapering and eventual withdrawal can result in reversal of NODAT in some patients, but this can increase the possibility of graft rejection, and the benefits of dose adjustments must be weighed against this risk.[20,21]

The calcineurin inhibitors cyclosporine and tacrolimus are also used in the treatment of posttransplant patients and can allow for a reduction in glucocorticoid doses.[17] However, both agents can contribute to the development of NODAT, and when used in conjunction with corticosteroids, they can worsen diabetogenicity.[5] Both cyclosporine and tacrolimus increase the risk for diabetes by causing swelling and vacuolization of pancreatic islet cells, leading to a decrease in insulin secretion.

Tacrolimus has been shown to be more diabetogenic than cyclosporine. A meta-analysis of 16 randomized controlled studies from

1992 to 2002 comparing tacrolimus to cyclosporine showed that diabetes developed in 7.8% of renal transplant patients on tacrolimus compared to 2.7% of renal allograft recipients treated with cyclosporine.[18]

Animal studies have demonstrated decreased β-cell functionality with exposure to sirolimus.[1] Other studies have shown an increase in the development of NODAT in patients treated with sirolimus, whether treatment was converted to sirolimus from calcineurin inhibitors or given in conjunction with cyclosporine and tacrolimus.[22,23]

Azathioprine and mycophenolate mofetil are also used for antirejection therapy in transplant patients, and treatment with these agents has been associated with a decreased risk of developing NODAT.[19] Whether this benefit is achieved because of an improvement in glucose intolerance or as a result of the ability to decrease doses of glucocorticoids or calcineurin inhibitors is not clearly known.[1]

In screening patients for NODAT, Davidson et al.[5] have recommend that all patients undergo fasting plasma glucose testing after transplantation, irrespective of a history of diabetes or impaired glucose tolerance. It is also recommended that testing should occur weekly for the first month posttransplant, then at 3, 6, and 12 months, and yearly thereafter.[5] If a patient is found to have an impaired fasting glucose, an oral glucose tolerance test should be performed.[5]

On diagnosis of NODAT, treatment should be approached in progressive intervals, with a plan to proceed to the next step if goals for glycemic control are not achieved with the previous step.[5] Management options include nonpharmacological therapy, oral monotherapy, oral combination therapy, and insulin. Before the initiation of medical therapy, weight loss, healthy dietary practices, and regular physical activity should be incorporated into a management strategy. These have been shown to contribute to a reduction in peripheral insulin resistance in patients with type 2 diabetes.[5] If goals for glucose control are not achieved with diet and exercise, medical therapy should be initiated.

To date, only a small number of studies have been performed to evaluate the efficacy of specific oral therapies in patients after kidney transplantation. As with diabetes in the general population, each therapy carries specific advantages and disadvantages, and the choice of medication should be based on the individual characteristics of each patient.

Sulfonylureas are one of the oldest antihyperglycemic agents, are relatively inexpensive, and have demonstrated an average reduction in A1C levels up to 2%.[21] Of the sulfonylureas, glipizide is advantageous in patients with renal insufficiency because this medication is mostly metabolized into inactive compounds by the liver. Other medications in this class are broken into active metabolites that are mostly excreted by the kidneys.[24] As a result, glipizide has less risk for hypoglycemia, which may occur with other sulfonylureas because of the delayed clearance of circulating metabolites in patients with renal disease. Likewise, the meglitinides are also favored oral agents because they mainly undergo hepatic clearance and can be considered with less risk for hypoglycemia in this population of patients.[25]

Metformin carries an increased risk for lactic acidosis in patients with renal insufficiency or cardiac dysfunction and is generally contraindicated in such patients.[21] Rosiglitazone has been studied in a small cohort of patients with NODAT and was found to have no injurious effects on the graft or harmful interactions with immunosuppressants.[26] Although this study demonstrated an improvement in fasting blood glucose levels in patients on rosiglitazone, the full onset of therapeutic action is not seen for several weeks, and some patients required the addition of a second agent.[26] This finding is confirmed elsewhere in the literature.[21]

The α-glucosidase inhibitors have not been studied in transplant recipients and in general are considered for use as adjunctive agents.[21] Other newer agents (glucagon-like peptide 1 agonists and dipeptidyl peptidase-4 inhibitors) have been approved by the Food and Drug Administration and show a comparable therapeutic profile to older antihyperglycemic medications but have not been specifically studied in patients after transplantation.[21] Table 1 reviews common characteristics and potential disadvantages of oral medications and subcutaneously administered noninsulin agents.[21]

When patients fail oral therapy, they will require treatment with insulin. To improve fasting hyperglycemia, the choice of insulin may be an intermediate- or long-acting insulin. These preparations are referred to as basal insulin and are used for glycemic control to offset hepatic glucose production and improve fasting and premeal blood glucose levels. Glargine and detemir are long-acting preparations and NPH is considered to be intermediate-acting. To treat postprandial hyperglycemia, bolus therapy with a rapid-acting preparation (aspart, lispro, or glulisine) or short-acting regular insulin can be considered. In some cases, it may be possible to achieve adequate glycemic control with basal insulin therapy and concomitant oral therapy. However, in cases in which glycemic goals are not met, patients may require physiologi-

Table 1. Common Noninsulin Medications for the Treatment of Type 2 Diabetes

Agent	Mechanism of Action	Disadvantages
Sufonylureas Glipizide Glyburide Glimepiride	Stimulation of insulin secretion by β-cells	Risk for hypoglycemia; risk for weight gain
Meglitinides Repaglinide Nateglinide	Stimulation of insulin secretion by β-cells	Risk for hypoglycemia; risk for weight gain
Biguanides Metformin	Increase in tissue sensitivity to insulin; decrease in hepatic glucose production	Nausea; diarrhea; increased risk for lactic acidosis in patients with renal or cardiovascular compromise
Thiazolidinediones Rosiglitazone Pioglitazone	Increase in tissue sensitivity to insulin	Risk for weight gain; risk for edema (contraindicated in N.Y. Heart Association class III and IV heart failure); prolonged onset of action potential for hepatotoxicity
α-Glucosidase inhibitors Acarbose Miglitol	Slows carbohydrate absorption in gastrointestinal tract; decreased postprandial blood glucose levels	Flatulence; diarrhea
Glucagon-like peptide 1 agonists Exenatide	Increase in glucose-stimulated insulin release; decrease in glucagon production; slows gastric emptying; stimulates early satiety	Risk for hypoglycemia; nausea
Dipeptidyl peptidase-4 inhibitors Sitagliptin	Decrease in inactivation of endogenous incretins with resultant increase in glucose-stimulated insulin release and decrease in glucagon production	Dose adjustment required with renal dysfunction

cal insulin therapy. Such patients are treated with daily basal insulin and bolus insulin at mealtimes. Patients who require a physiological insulin regimen should be referred to an endocrinologist.[5]

Additional management strategies for patients with NODAT include regular monitoring of all patients after transplantation. Davidson et al.[5] have recommended A1C testing every 3 months. However, the results of this test can be complicated in patients with severe anemia or in transplant recipients who have undergone blood transfusions during the 3 months before the test is performed.[1,5] The Diabetes Control and Complications Trial and the U.K. Prospective Diabetes Study showed that an A1C below or near 7% is associated with fewer long-term microvascular complications in patients with diabetes.[27,28] Correspondingly, the ADA has recommended treatment to an A1C goal < 7% to aid in preventing such complications in nonpregnant adults.[29]

As with patients diagnosed with diabetes in the general population, patients with NODAT should be screened for signs of diabetic retinopathy and neuropathy. Patients should undergo annual ophthalmological and podiatric examinations and should be educated on proper foot inspection and care. Although routine screening for microalbuminuria is also recommended for patients with diabetes in the general population, this may be complicated in renal transplant recipients because useful results may be affected by allograft nephropathy or diseased native kidneys that continue to release protein in the urine.[1]

The ADA also recommends that patients with diabetes undergo blood pressure management with a goal of < 130/80 mmHg and routine cholesterol screening (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) with goals for treatment based on established guidelines.[29] However, statins can interact with calcineurin inhibitors, and their use in this population should be considered carefully.[30]

Finally, the adjustment of immunosuppressants may improve glycemic control in patients with NODAT. However, the benefit of this improvement should be carefully weighed against the potential risk for rejection. Some researchers

report a lower graft survival rate in patients who develop acute rejection than in patients who develop NODAT.[31] Other researchers suggest that, even with alterations in the immunosuppressant regimen, diabetes will recur or continue in some patients.[21] Moreover, the reduction or substitution of immunosuppressant medications has not been studied as a standard of care for improving blood glucose control. If considered, it should be approached with extreme caution to avoid the potential deleterious effects on the allograft.[21]

CLINICAL PEARLS

- NODAT is a form of type 2 diabetes that develops in patients after solid organ transplantation.
- Many of the risk factors for NODAT are the same as risk factors for developing type 2 diabetes in the general population.
- The use of glucocorticoids, calcineurin inhibitors, and sirolimus increases the risk for developing NODAT.
- Poorly controlled NODAT can result in the same complications that develop in patients with diabetes in the general population and can also lead to decreased allograft function and ultimately graft failure.
- All transplant recipients should undergo weekly screening for NODAT during the first month after transplantation, then at 3, 6, and 12 months, and yearly thereafter.
- Treatment should include lifestyle modifications and preventive screening for micro- and macrovascular complications.
- When medication is required to maintain glycemic control, the choice of therapy should be tailored to the individual patient, giving specific consideration to the potential effects of the medication in patients with impaired renal function.
- Tapering of immunosuppressant medications can reduce glucose intolerance, but consideration must be given to the potential for graft rejection with aggressive decreases in immunosuppressant doses.

REFERENCES

[1]Bodziak K, Hricik D: New-onset diabetes mellitus after solid organ transplantation. *Transpl Int* 22:519–530, 2008

[2]Gaston RS, Basadonna G, Cosio FG, Davis CL, Kasiske BL, Larsen J, Leichtman AB, Delmonico FL :Transplantation in the diabetic patient with advanced chronic kidney disease: a task force report. *Am J Kidney Dis* 44:529–542, 2004

[3]Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM: Patient survival after renal transplantation: impact of post-transplant diabetes. *Kidney Int* 62:1440–1446, 2002

[4]Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC: Posttransplantation diabetes: a systematic review of the literature. *Diabetes Care* 25:583–592, 2002

[5]Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernández D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC: New-onset diabetes after transplantation: 2003 International Consensus Guidelines. *Transplantation* 75:SS3–S24, 2003

[6]Boudreaux JP, McHugh L, Canafax DM, Ascher N, Sutherland DE, Payne W, Simmons RL, Najarian JS, Fryd DS: The impact of cyclosporine and combination immunosuppression on the incidence of posttransplant diabetes in renal allograft recipients. *Transplantation* 44:376–381, 1987

[7]Sumrani N, Delaney V, Ding Z, Davis R, Daskalakis P, Friedman EA, Butt KM, Hong JH: Posttransplant diabetes mellitus in cyclosporine-treated renal transplant recipients. *Transplant Proc* 23:1249–1250, 1991

[8]Vesco L, Busson M, Bedrossian J, Bitker MO, Hiesse C, Lang P: Diabetes mellitus after renal transplantation: characteristics, outcome, and risk factors. *Transplantation* 61:1475–1478, 1996

[9]Cosio FG, Hickson LJ, Griffin MD, Stegall MD, Kudva Y: Patient survival and cardiovascular risk after kidney translantation: the challenge of diabetes. *Am J Transp* 8:593–599, 2008

[10]Manske CL: Hyperglycemia and intensive glycemic control in diabetic patients with chronic renal disease. *Am J Kidney Dis* 32 (5 Suppl. 3):S157–S171, 1998

[11]Ducloux D, Kazory A, Chalopin J: Posttransplant diabetes mellitus and atherosclerotic events in renal transplant recipients: a prospective study. *Transplantation* 79:438–443, 2005

[12]Roth D, Milgrom M, Esquenazi V, Fuller L, Burke G, Miller J: Posttransplant hyperglycemia: increased incidence in cyclosporine-treated renal allograft recipients. *Transplantation* 47:278–281, 1989

[13]Miles AM, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, Distant DA, Hong JH, Sommer BG, Friedman EA: Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes? *Transplantation* 65:380–384, 1998

[14]Owda AK, Abdallah AH, Haleem A, Hawas FA, Mousa D, Fedail H, Al-Sulaiman MH, Al-Khader AA: De novo diabetes mellitus in kidney allografts: nodular sclerosis and diffuse glomerulosclerosis leading to graft failure. *Nephrol Dial Transplant* 14:2004–2007, 1999

[15]Sumrani NB, Delaney V, Ding ZK, Davis R, Daskalakis P, Friedman EA, Butt KM, Hong JH: Diabetes mellitus after renal transplantation in the cyclosporine era—an analysis of risk factors. *Transplantation* 51:343–347, 1991

[16]von Kiparski A, Frei D, Uhlschmid G, Largiader F, Binswanger U: Post-transplantation diabetes mellitus in renal allograft recipients: a matched-pair control study. *Nephrol Dial Transpl* 5:220–225, 1990

[17]Rodrigo E, Fernández-Fresnedo G, Valero R, Ruiz JC, Piñera C, Palomar R, González-Cotorruelo J, Gómez-Alamillo C, Arias M: New-onset diabetes after kidney transplantation: risk factors. *J Am Soc Nephrol* 17 (12 Suppl. 3):S291–S295, 2006

[18]Heisel O, Heisel R, Balshaw R, Keown P: New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 4:583–595, 2004

[19]Hjelmesaeth J, Hartmann A, Kofstad J, Stenstrøm J, Leivestad T, Egeland T, Fauchald P: Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. *Transplantation* 64:979–983, 1997

[20]Hricik DE, Bartucci MR, Moir EJ, Mayes JT, Schulak JA: Effects of steroid withdrawal on posttransplant diabetes mellitus in cyclosporine-treated renal transplant recipients. *Transplantation* 51:374–377, 1991

[21]Mannon R: Therapeutic management of posttransplant diabetes mellitus. *Transplant Rev (Orlando)* 22:116–124, 2008

[22]Teutonico A, Schena PF, DiPaolo S: Glucose metabolism in renal transplant recipients: effects of calcineurin inhibitor withdrawal and conversion to sirolimus. *J Am Soc Nephrol* 16:3128–3135, 2005

[23]Johnston O, Rose CL, Webster AC, Gill JS: Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J Am Soc Nephrol* 19:1411–1418, 2008

[24]Harrower AD: Pharmacokinetics of oral antihyperglycaemic agents in patients

with renal insufficiency. *Clin Pharmacokinet* 31:111–119, 1996

[25]Türk T, Pietruck F, Dolff S, Kribben A, Janssen OE, Mann K, Philipp T, Heemann U, Witzke O: Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. *Am J Transplant* 6:842–846, 2006

[26]Pietruck F, Kribben A, Van TN, Patschan D, Herget-Rosenthal S, Janssen O, Mann K, Philipp T, Witzke O: Rosiglitazone is a safe and effective treatment option of new-onset diabetes mellitus after renal transplantation. *Transplant Int* 18:483–486, 2005

[27]DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977– 986, 1993

[28]U.K. Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998

[29]American Diabetes Association: Standards of medical care in diabetes—2009. *Diabetes Care* 32:S13–S61, 2009

[30]Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, Kiberd B, Jardine A, Levitt N, Marchetti P, Markell M, Naicker S, O'Connell P, Schnitzler M, Standl E, Torregosa JV, Uchida K, Valantine H, Villamil F, Vincenti F, Wissing M: Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 19:291–298, 2006

[31]Matas AJ, Gillingham KJ, Humar A, Ibrahim HN, Payne WD, Gruessner RW, Dunn TB, Sutherland DE, Najarian JS, Kandaswamy R: Transplant diabetes mellitus and acute rejection: impact on kidney transplant outcome. *Transplantation* 85: 338–343, 2008

Warren Clayton, Jr., MD, is a clinical fellow, and Shubhada Jagasia, MD, is an assistant professor of medicine in the Division of Endocrinology, Diabetes, and Metabolism at Vanderbilt University Medical Center in Nashville, Tenn.