Transpl Int (2000) 13: 69–72

ORIGINAL ARTICLE

Eric M. Yoshida
Andrzej K. Buczkowski
Sandra M. Sirrs
Tom G. Elliott
Charles H. Scudamore
Adeera Levin
Hugh D. Tildesley
David N. Landsberg

Post-transplant diabetic ketoacidosis – A possible consequence of immunosuppression with calcineurin inhibiting agents: A case series

Received: 1 February 1999
Revised: 30 September 1999
Accepted: 19 October 1999

E.M. Yoshida (✉)
Vancouver Hospital and
Health Sciences Centre,
100–2647 Willow Street, Vancouver, BC,
V5Z 3P1, Canada
Fax: + 1-604-875-5447

E.M. Yoshida · S.M. Sirrs · T.G. Elliott
A. Levin · H.D. Tildesley · D.N. Landsberg
Department of Medicine,
The University of British Columbia,
and the British Columbia Transplant
Society, Vancouver, BC, Canada

A.K. Buczkowski · C.H. Scudamore
Department of Surgery,
The University of British Columbia,
and the British Columbia Transplant
Society, Vancouver, BC, Canada

Abstract Post-transplant diabetes mellitus, a complication due to corticosteroids and the calcineurin inhibitors, cyclosporine and tacrolimus (FK506), is commonly regarded as a form of type-2 (adult-onset) diabetes mellitus. Diabetic ketoacidosis, which requires relative insulin deficiency to impair fatty acid metabolism, is a complication of type-1 diabetes mellitus. We report three patients who presented with diabetic ketoacidosis post-transplant. All three patients presented with severe hyperglycemia, significant ketosis and metabolic acidosis of variable severity. One patient was a renal transplant recipient on a cyclosporine-based regimen. The other two patients were liver transplant recipients receiving either cyclosporine or tacrolimus-based immunosuppression. Both of the liver transplant recipients were found to have moderate to high serum levels of calcineurin inhibitors on presentation. The liver recipient on cyclosporine (Neoral) had a 4 hour post-dose level of 388 ng/ml and the patient on tacrolimus was found to have a trough level of 21.2 ng/ml. Our experience suggests that post-transplant diabetes mellitus, in association with calcineurin inhibition, may result in ketoacidosis either secondary to relative beta cell dysfunction, peripheral insulin resistance, or a combination of the two effects. Post-transplant diabetes mellitus can be an atypical form of adult-onset diabetes with features of both type I and type II diabetes mellitus.

Key words Kidney transplantation · Diabetes mellitus · Ketoacidosis · Cyclosporine · Tacrolimus

Introduction

Diabetes mellitus is a well-recognized complication of organ transplantation with a reported incidence of 7.8% to over 40% in cyclosporine-treated renal transplant recipients [11, 23, 24] and 20–47% in liver transplant recipients treated with cyclosporine/tacrolimus [5, 21]. Although the usual risk factors for type-2 (adult-onset) diabetes mellitus, such as familial predisposition and obesity may increase the likelihood of post-transplant diabetes mellitus (PTDM), the immunosuppressive medications used in transplantation are themselves agents in the development of this condition. The diabetogenic properties of corticosteroids are well-recognized, and it has become increasingly well-known that the calcineurin inhibitors, cyclosporine [2, 12, 14, 16, 25] and tacrolimus [5, 15, 21, 22], are associated with PTDM.

PTDM is considered by many to be a variant of type-2 diabetes mellitus and, in many cases, resolves or improves with time as the maintenance doses of steroids and calcineurin inhibitors are reduced, beyond the immediate post-transplant period. Similar to the typical, non-transplant cases of type-2 diabetes mellitus, poorly controlled hyperglycemia in PTDM may result in non-ketotic hyper-osmolar coma [8]. True diabetic ketoacidosis (DKA), which implies a degree of insulinopenia so that fatty acid oxidation is impaired, has only occa-

sionally been mentioned in renal transplant studies of PTDM without any description or discussion [6, 9, 11, 16]. We report three cases of post-transplant DKA (two liver- and one renal transplant recipient) who presented to our centre between 1992 and 1998. All three patients were well beyond the early post-transplant period and were on maintenance immunosuppression consisting of prednisone and a calcineurin inhibitor (cyclosporine or tacrolimus). Since a diagnosis of ketoacidosis has differing therapeutic implications from a diagnosis of diabetic hyperosmolarity, the purpose of this series is to increase the awareness of transplant physicians/surgeons to this rarely reported but serious post-transplant complication.

Case reports

Case one

A 50-year-old Caucasian woman had undergone liver transplantation for of end-stage liver disease secondary to autoimmune hepatitis. Her induction immunosuppression consisted of cyclosporine (Neoral), tapering corticosteroids and azathioprine. Maintenance immunosuppression initially consisted of cyclosporine, prednisone and azathioprine, but after an episode of moderate rejection on the eighteenth post-transplant day, the cyclosporine was changed to tacrolimus which was titrated to maintain a trough level of 5–10 mg/ml after the third month post-transplant. The post-transplant course was otherwise unremarkable except for the occasional episode of transient hyperglycemia with a serum glucose of 16.2 mmol/l at eight months post-transplant (trough tacrolimus level was 8.7 ng/ml).

Nine months post-transplant, the patient was admitted to a general medical ward after presenting with polyuria, polydipsia, visual blurring and transient tremours. Her medication consisted of tacrolimus 4 mg BID, prednisone 10 mg daily, and azathioprine 50 mg daily. The results of her physical examination was unremarkable except for a thin body habitus. Her initial laboratory tests revealed: serum glucose 68.2 mmol/l, sodium 123 mmol/l, chloride 89 mmol/l, potassium 3.2 mmol/l, carbon dioxide (CO_2) 28 mmol/l (range of normal: 22–31 mmol/l), creatinine 127 umol/l, serum albumin 34 g/l, trough tacrolimus level 21.2 ng/ml (target range 5–10 ng/ml). Initial management consisted of intravenous fluid resuscitation, but within 24 h of admission her level of consciousness deteriorated, and seizure activity was noted. Her repeat serum electrolytes revealed: sodium 145 mmol/l, chloride 123 mmol/l, potassium 3.3 mmol/l, carbon dioxide (CO2) 6 mmol/l, creatinine 72 umol/l, serum albumin 28 g/l, with a calculated anion gap of 16. Her arterial blood gas (ABG) revealed: pH 6.93, pCO_2 13 mm Hg, pO_2 176 mm Hg, HCO_3 3.0 mmol/l. A serum lactate was 1.08 mmol/l (0.5–1.8 mmol/l). Urinary ketones were positive, and serum ketones revealed large amounts in an undiluted sample. Serial dilutions were positive to a dilution of 1:8. The patient's condition deteriorated, and she was admitted to the intensive care unit. Treatment consisted of an insulin infusion, continued fluids and antibiotics for aspiration pneumonia. Her hyperglycemia, acidosis, and ketosis resolved, however, she required prolonged mechanical ventilation for adult respiratory distress (ARDS). She was eventually discharged from hospital on subcutaneous insulin injections.

Case two

A 58-year-old Caucasian man of thin body habitus had received a liver allograft 5 years and 10 months previously for end-stage cirrhosis secondary to hepatitis C (HCV). His induction immunosuppression immediately post-transplant consisted of OKT3, cyclosporine, and tapering steroids. His long-term maintenance immunosuppression consisted of cyclosporine (Neoral, Novartis Pharma Canada, Dorval PQ) 125 mg BID, titrated to achieve a target trough level of 123–150 ng/ml, and prednisone 5 mg on alternate days. His post-transplant course had been complicated by significant cyclosporine neurotoxicity and recurrent allograft infection with HCV. His post-transplant course was otherwise stable, and he did not suffer from obesity, but was, in fact, slightly underweight. There was no history of diabetes mellitus, and his last serum glucose, two months prior to presentation was 7.7 mmol/l.

He presented to hospital with polyuria, polydipsia and malaise. His serum glucose at presentation was 67 mmol/l, serum electrolytes: sodium 125 mmol/l, chloride 90 mmol/l, potassium 4.5 mmol/l, carbon dioxide (CO2) 21 mmol/l, creatinine 180 umol/l. The calculated anion gap was 14, the lab determined anion gap was 18.5. Undiluted serum ketones were determined to be large. Serial dilutions revealed serum ketones at 1:2 to be moderate, 1:4 were determined to be small with trace amounts at a dilution of 1:8. A 4-h-post-dose cyclosporine level was 388 ng/ml. A C-peptide level drawn 10 h after the start of treatment, when a capillary glucose was 19.2 mmol/l, was 846 pmol/l (165–1000 pmol/l). The patient was treated with intravenous fluids and an insulin infusion with resolution of the hyperglycemia. A work-up for secondary causes was negative and he was changed to subcutaneous insulin injections.

Case three

A 37-year-old, mildly obese East Indian man with chronic renal failure secondary to hypertensive nephrosclerosis, received a cadaveric renal transplant. Immunosuppression consisted of Minnesota antilymphocyte globulin (ALG), prednisone and azathioprine (AZA), followed by cyclosporine (Sandimmune, Sandoz Canada, Dorval PQ) 220 mg BID, AZA 100 mg daily and prednisone 15 mg daily. His discharged serum creatinine was 230 umol/l. There was no prior history of diabetes mellitus, although two episodes of glycosuria had been documented during methylprednisolone therapy for acute rejection, 2 and 3 months post-transplant. His family history revealed that his father has non-insulin dependent diabetes mellitus (NIDDM).

Four months post-transplant, the patient suffered from polyuria, polydipsia, and increasing lethargy, and was brought to the emergency department obtunded. The leukocyte count was 10.6×10^9/l, blood glucose 42.8 mmol/l, arterial blood gases (ABG) drawn on room air were: pH 7.38, pO_2 52 mm Hg, pCO_2 17 mm Hg and bicarbonate 10 mmol/l. The serum sodium was 141 mmol/l, chloride 111 mmol/l, potassium 4.7 mmol/l, carbon dioxide (CO_2)14 mmol/l, urea 26.5 mmol/l, creatinine 360 umol/l. The anion gap was 16, serum ketones were moderate, and serum lactate 1.3 mmol/l (0.5–1.8 mmol/l). His salicylate screen was negative, and there was no history of organic acid ingestion. His cyclosporine level was 78 ng/ml.

Diabetic ketoacidosis was diagnosed and resuscitation undertaken with large volumes of intravenous saline and an insulin infusion. A work-up for secondary causes was unrevealing. Response to treatment was rapid and he was switched to subcutaneous insulin. Four days after admission his fasting blood glucose was 4.0 mmol/l, serum CO_2 22 mmol/l, creatinine 223 umol/l, anion gap 11; a C-peptide level was 4833 pmol/l (165–1000 pmol/l). Eight

days after admission the C-peptide was 667 pmol/l. The patient was discharged on subcutaneous insulin, and a fasting blood glucose 20 days after admission was 4.1 mmol/l. One month after discharge, insulin was discontinued and diabetic therapy consisted of dietary management.

Discussion

Although the exact definition of diabetic ketoacidosis is arbitrary and differs depending on source, we present three cases of ketoacidosis in the late post-transplant period. Our three patients all suffered from severe hyperglycemia, significant ketosis which was, in fact, underestimated, since the Acetest (Miles Inc.) reagent used detects acetoacetate and acetone but not beta-hydroxybutyrate, and a metabolic acidosis of varying severity. All three patients exhibited some features of type 2 diabetes mellitus: the third patient had a marked C-peptide level after the ketosis was subsiding reflecting insulin resistance, the first and second patients, despite a marked ketosis, had only a mild metabolic acidosis, although unequivocal and life-threatening acidosis would rapidly develop in the first case. Despite initial presenting features of type 2 diabetes mellitus in these cases, the development of ketoacidosis suggests a significant degree of beta cell impairment, compounded by peripheral insulin resistance, which in our second patient was demonstrated by an inappropriately normal C-peptide level in the context of marked hyperglycemia. In this regard, the PTDM of these three patients, none of whom were African-American, closely resembles the unusual subset of African-American adult-onset diabetic patients (non-transplant) who present with ketoacidosis yet behave like type II diabetics both before and after the episode of ketoacidosis [1, 20]. These African-Americans with ketoacidosis and adult-onset diabetes have been found to show both insulin-resistance and impaired insulin secretion [1, 20].

Another interesting aspect of our series is, that in the first and second patients, the marked hyperglycemia and ketoacidosis occurred when the measured levels of calcineurin inhibitors (cyclosporine/tacrolimus) were within the moderate-to-high-range after periods of stability at lower levels. This may suggest a contributing role for calcineurin inhibitors in the etiology of the patients' diabetic ketoacidosis, either through impaired beta cell secretion of insulin, enhanced peripheral insulin resistance so that fatty acid metabolism was impaired, or a combination of the two. The exact etiological role of calcineurin inhibitors in PTDM and their effects on beta cell secretion of insulin has been a controversial topic for many years. Earlier, a few investigators failed to demonstrate any role for cyclosporine in impaired glucose tolerance [3, 4]. In-vitro studies, however, demonstrated an inhibitory effect of cyclosporine on human beta cells [10], and clinical studies reported C-peptide suppression [2], altered insulinogenic indices pre and post-cyclosporine [25], impaired glucose tolerance [12] and increased incidence of PTDM in cyclosporine-base regimens compared to azathioprine-based protocols [14, 23, 24]. With tacrolimus, however, some investigators report a lack of correlation between tacrolimus-doses and blood glucose as well as findings suggesting that requirements for insulin are better correlated with prednisone dosing [17]. Other studies, however, report an increased incidence of hyperglycemia in tacrolimus versus cyclosporine-based regimens 5, 15, 24]. The mechanism of possible tacrolimus-induced diabetes mellitus is unclear, with in-vitro studies reporting beta-cell impairment at high doses [8, 13, 18, 19], and clinical reports of hyperglycemia with elevated C-peptide levels indicating insulin resistance [7]. Our experience suggests a possible contributing role for calcineurin inhibitors in the pathogenesis of post-transplant diabetes mellitus, with the potential for the development of ketosis in susceptible individuals.

In conclusion, these observations suggest that post-transplant diabetes mellitus may be more complicated than typical type-2 diabetes mellitus, and some patients may demonstrate ketoacidosis which is more commonly associated with type-1 diabetes mellitus. Awareness of the subacute presentation of post-transplant diabetic ketoacidosis should confer a heightened level of suspicion upon clinicians, so that diagnostic monitoring and therapeutic strategies can be optimized.

References

1. Banerji MA, Chaiken RL, Huey H, Tuomi T, Norin AJ, Mackay IR, Rowley MJ, Zimmet PZ, Lebovitz HE (1994) GAD antibody negative NIDDM in adult black subjects with diabetic ketoacidosis and increased frequency of human leukocyte antigen DR3 and DR4. Diabetes 43: 741–745
2. Bending JJ, Ogg CS, Viberti GC (1987) Diabetogenic effect of cyclosporin. Br Med J 294: 401–402
3. Boudreaux JP, McHugh L, Canafax DM, Asher N, Sutherland DE, Payne W, Simmons RL, Najarian JS, Fryd DS (1987) Cyclosporine, combination immunosuppression, and posttransplant diabetes mellitus. Transplant Proc 19: 1811–1813
4. Esmatjes E, Ricart MJ, Ferrer JP, Oppenhaimer F, Vilardell J, Casamitjana R (1991) Cyclosporine's effect on insulin secretion in patients with kidney transplants. Transplantation 52: 500–503
5. European FK506 Multicentre Liver Study Group (1994) Randomized trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. Lancet 344: 423–428

6. Fang J, Huang C, Chuang C, Chu S (1998) Diabetes melllitus after renal transplantation. Transplant Proc 30: 3027–3028
7. Kanzler S, Lohse AW, Schirmacher P, Hermann E, Otto G, Meyer zum Bushcenfelde KH (1996) Complete reversal of FK506 induced diabetes in a liver transplant recipient by change of immunosuppression to cyclosporin A. Z Gastroenterol 34: 128–131
8. Loertscher R, Parfrey PS, Guttman RD (1989) Post-operative management of renal transplant recepients and long-term complications. In: Milford EL, Brenner BM, Stein JH (eds) Renal Transplantation. Churchhill Livingstone, New York, pp 219–220
9. Miles AM, Sumrani N, Horowitz R, Homel P, Maursky V, Markell MS, Distant DA, Hong JH, Sommer BG, Friedman EA (1998) Diabetes mellitus after renal transplantation. Transplantation 65: 380–384
10. Nielsen JH, Mandrup-Poulsen T, Nerup J (1986) Direct effects of cyclosporin A on human pancreatic beta cells. Diabetes 35: 1049–1052
11. Onwubalili JK, Obineche EN (1992) High incidence of post-transplant diabetes mellitus in a single-centre study. Nephrol Dial Transplant 7: 346–349
12. Ost L, Tyden G, Fehrman I (1988) Impaired glucose tolerance in cyclosporin-prednisilone-treated renal graft recipients. Transplantation 46: 370–372
13. Rilo HLR, Zeng Y, Alejandro R, Carroll PB, Bereiter D, Venkataramanan R, et al (1991) Effect of FK506 on function of human islets of Langerhans. Transplant Proc 23: 3164–3165
14. Roth D, Milgrom M, Esquenazi V, Fuller L, Burke G, Miller J (1989) Post-transplant hyperglycemia. Transplantation 47: 278–281
15. Scantlebury V, Shapiro R, Fung J, Tsakis A, McCauley J, Jordan M, Jensen C, Hakala T, Simmons R, Starzl TE (1991) New onset diabetes in FK506 vs cyclosporine-treated kidney transplant recipients. Transplant Proc 23: 3169–3170
16. Sumrani N, Delaney V, Ding Z, Davis R, Daskalakis P, Friedman EA, Butt KM, Hong JH (1991) Posttransplant diabetes mellitus in cyclosporin-treated renal transplant recipients. Transplant Proc 23: 1249–1250
17. Tabasco-Minguillan J, Carroll P, Gavaler J, Van Thiel DH, Starzl TE (1993) Insulin requirements after liver transplantation and FK506 immunosuppression. Transplantation 56: 862–867
18. Tze WJ, Tai J, Cheung S (1990) In vitro effects of FK506 on human and rat islets. Transplantation 49: 1172–1174
19. Tze WJ, Tai J, Murase N, Tzakis A, Starzl TE (1991) Effect of FK506 on glucose metabolism and insulin secretion in noraml rats. Transplant Proc 23: 3158–3160
20. Umpierrez GE, Casals MM, Gebhart SS, Mixon PS, Clark WS, Phillips LS (1995) Diabetic ketoacidosis in obese African-Americans. Diabetes 44: 790–795
21. US Multicenter FK506 Liver Study Group (1994) A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 331: 1110–1115
22. Wagner K, Webber SA, Kurland B, Boyle GJ, Miller SA, Cipriani L, Griffith BP, Fricker FJ (1997) New-onset diabetes mellitus in pediatric thoracic organ recipients receiving tacrolimus-based immunosuppression. J Heart Lung Transplant 16: 275–282
23. Yagisawa T, Takahashi K, Teraoka S, Toma H, Agishi T, Ota K (1987) Effects of cyclosporin on glucose metabolism in kidney transplant recipients and rats. Transplant Proc 19: 1801–1803
24. Yamamoto H, Akazawa S, Yamaguchi Y, et al (1991) Effects of cyclosporin A and low dosages of steroid on post-transplantation diabetes in kidney transplant recipients. Diabetes Care 14: 867–870
25. Yoshimura N, Nakai I, Ohmori Y, Aikawa I, Fukuda M, Yasumura T, Matsui S, Hamshima T, Oka T (1988) Effect of cyclosporine on the endocrine and exocrine pancreas in kidney transplant recipients. Am J Kidney Dis 12: 11–17