

Tacrolimus and diabetic ketoacidosis after kidney transplantation in a 15-year-old girl (Case Report)

Case Report

Hadi Sorkhi (MD) ^{*1}
Morteza Alijanpour (MD) ²
Sahar Sadr Moharrerpour ¹

1. Non-communicable Pediatric Disease
Research Center, Department of Pediatric Nephrology, Amirkola Children's Hospital, Health Research Institute, Babol University of Medical Sciences, IR Iran.
2. Non-communicable Pediatric Disease
Research Center, Department of Pediatric Endocrinology, Amirkola Children's Hospital, Health Research Institute, Babol University of Medical Sciences, IR Iran.

* Correspondence:

Hadi Sorkhi (MD), Non-Communicable Pediatric Diseases Research Center, No 19, Amirkola Children's Hospital, Amirkola, Babol, Mazandaran Province, 47317-41151, IR Iran.

E-mail: hadisorkhi@yahoo.com
Tel: +98 1132346963
Fax: +98 1132346963

Received: 21 June 2016
Revised: 17 July 2016
Accepted: 15 Aug 2016

Abstract:

Tacrolimus is a main drug for induction and maintenance immunosuppression for patients with kidney transplants in many centers. One of important side effect of drug is post-transplant diabetes mellitus. Of course, diabetes ketoacidosis (DKA) is rare. In this report, a 12-year-old girl with DKA was presented after 45 days of kidney transplantation.

Keywords: Tacrolimus, Children, diabetes ketoacidosis, Kidney Transplantation

Citation:

Sorkhi H, Alijanpour M, Sadr Moharrerpour S. Tacrolimus and diabetic ketoacidosis after kidney transplantation in a 15-year-old girl (Case Report). *Caspian J Pediatr* Sep 2016; 2(2): 171-4.

Introduction:

Tacrolimus (FK 506) is a calcineurin inhibitor. It was derived from streptomyces tsukubaensis. The drug has been used for immunosuppression for kidney transplant patients since mid-1990s [1-2]. The immunosuppressive effect of tacrolimus (Tac) is same as of cyclosporine. It inhibits many T-cell lymphokines productions such as interleukin II (IL -2), IL 3, IL4 and gamma interferon. So, the drugs suppress T-helper and cytotoxic T-cell function [3]. Due to similar mechanism effect of Tac and cyclosporine, the side effects of two drugs are the same [4]. One of the major and important side effects of Tac in pediatric renal transplantation is post-transplant diabetes mellitus (PTDM). This effect of drug may be due to the decrease of insulin secretion and may be associated with concurrent use of corticosteroids. [5]. Although, the risk of PTDM was higher with Tac than other kidney transplant drugs, but the risk of PTDM can be decreased with lower dose of Tac [6]. Al-uzri et al reported the incidence of 3% diabetes mellitus after kidney transplantation, but the risk of diabetes ketoacidosis (DKA) is rare [7]. This case report is a 15 years old girl that was presented with PTDM and diabetic ketoacidosis (DKA) after 45 days kidney transplant.

Case Report:

Kidney transplantation (KT) was conducted on a 15-year-old girl on 26 Feb. 2016. She was on tacrolimus, prednisone and mycophenolate mofetil (MMF) for maintenance immunosuppression therapy. About 45 days of after KT, she was referred to hospital with headache, polyuria and polydipsia. Her laboratory exams on admission time were showed: FBS: 482mg/dl, BUN: 34 mg/dl, Creatinin: 1.2 mg/dl, VBG (PH: 7.21, HCO₂: 5.9, PCO₂: 14.7), U/A (WBC: 0-1, RBC: 0-1, SG: 1.025, Sugar: 1+, Ketone: 1+)

She was admitted in hospital with diagnosis of diabetes ketoacidosis. She took daily doses of prednisolone 25 mg, Tac 8 mg and MMF 500 mg. After admission, she was treated by insulin (Crystal and NPH) and tacrolimus was changed to cyclosporine. Her blood sugar was controlled in hospital during 1 week and she was discharged with insulin. After discharge, her laboratory findings were: BUN=23mg/dL, Creatinin=0.9mg/dL, FBS=114mg/dL. Her last BUN, Creatinin and FBS were 33, 0.9 and 113 mg/dl, respectively.

After discharged, her blood sugar was controlled by insulin NPH and its doses were decreased gradually and then discontinued after 3 months.

Discussion:

In our case, a girl (15 y/o) was presented with PTDM and DK after 45 days of KT. She was taken high-dose corticosteroid, MMF and high-dose tacrolimus.

The risk of PTDM after KT on 1580 adult patients from 1976 to 2004 was 18.2% and about half of them were diagnosed 6 months after transplant [8]. The incidences of PTDM in USA were 9.1%, 16% and 12% after 3, 12 and 36 months after KT, respectively. Of course, 25% of them were presented about 1 year after KT [9]. The risk factors for PTDM can be divided into non-modifiable and modifiable factors and are illustrated in table 1 [10]. According to table 1, immunosuppressive drugs such as corticosteroid and tacrolimus are modifiable risk factors of PTDM.

The risk of PTDM after KT and corticosteroids depends on dose and duration of drug therapy [11]. Tacrolimus and cyclosporine are calcineurin inhibitor (CNI) drugs. They are main drugs (with others) for induction and maintenance immunosuppressive therapy. Tacrolimus has higher risk of PTDM and the risk of diabetes may be as high as 50% [11-13]. Although the risk of PTDM by tacrolimus was not dependent on

the drug dose, many centers preferred Tac than cyclosporine [14-16].

The number of glucose transporter type 4 (GLUT-4) receptors of adipocytes was decreased by Tac and then induced hyperglycemia [17]. Also, Tac suppresses release from insulin by pancreases [18]. Other reports showed Tac can manipulate the response of C-peptide and change mitochondrial function of pancreatic B-cells of pancreas islets. [19].

In some studies, the risk of PTDM was reported in 3% of pediatric renal transplant patients [7, 20]. Serial check of blood glucose levels and measurement of Hb A1C were recommended every 3 months [21]. A study was conducted on 5 children (2 patients had PTDM) with history of nephrotic syndrome and they were treated by Tac. Two patients had diabetes for 9 months and 44 months after the start of Tac, respectively [21]. Both patients had relapse of N.S and needed higher doses of prednisolone.

Some risk factors reported for PTMD after KT may be due to the obesity, males and African Americans [20, 22]. In the other study, a 12-year-old child was reported with history of N.S and treated by Tac for 5 months. She took alternate day prednisolone and enalapril. She was referred to hospital with vomiting, abdominal pain, hyperglycemia (600mg/dl) and 4 +urine ketone. Her blood gas indicated metabolic acidosis and she was treated with diagnosis of DKA [23]. She was treated by insulin and her insulin therapy was discontinued after 12 weeks.

According to our case report, it seems that higher dose of corticosteroids for initial treatment of KT and Tac is the most important risk factor of PTMD in our patients. Although the reports of PTMD with DKA, especially, in KT patients were rare, blood glucose level of every patient treated by Tac must be monitored for early detection of DKA.

Table 1. Risk factors for new-onset diabetes after transplantation

Non-modifiable	Modifiable
Advanced age	Obesity
African American, Hispanic, or South Asian descent	Sedentary lifestyle
Genetic, e.g., HLA B27	Metabolic syndrome
Adult polycystic kidney disease	Viral infections, e.g., HCV, cytomegalovirus
Previous glucose intolerance, e.g., during pregnancy, steroid therapy for renal or non-renal disease	Corticosteroids
Male donor	Calcineurin-inhibitors (tacrolimus > cyclosporine)
Deceased donor	Sirolimus
	Acute rejection

Acknowledgment

We are grateful to the Clinical Research Development Committee of Amirkola Children's Hospital, Non communicable Pediatric Diseases Research Center and Health Research Institute of Babol University of Medical Sciences for their support and cooperation with study.

Funding: This study was self-funded.

Conflict of interest: There was no conflict of interest.

References:

- Shapiro R, Jordan ML, Scantlebury VP, et al. The superiority of tacrolimus in renal transplant recipients-the Pittsburgh experience. *Clin Transpl* 1995; 199-205.
- Ellis D. Clinical use of tacrolimus (FK-506) in infants and children with renal transplants. *Pediatr Nephrol* 1995; 9(4): 487-94.
- Shaw LM, Holt DW, Keown P, et al. Current opinions on therapeutic drug monitoring of immunosuppressive drugs. *Clin Ther* 1999; 21(10): 1632-52.
- McKee M, Segev D, Wise B, et al. Initial experience with FK506 (tacrolimus) in pediatric renal transplant recipients. *J Pediatr Surg* 1997; 32(5): 688-90.
- Filler G, Neuschulz I, Vollmer I, et al. Tacrolimus reversibly reduces insulin secretion in pediatric renal transplant recipients. *Nephrol Dial Transplant* 2000; 15(6): 867-71.
- Dharnidharka VR, Ho PL, Stablein DM, et al. Mycophenolate, tacrolimus and post-transplant lymphoproliferative disorder: a report of the North American Pediatric Renal Transplant Cooperative Study. *Pediatr Transplant* 2002; 6(5): 396-9.
- Al-Uzri A, Stablein DM, A Cohn R. Posttransplant diabetes mellitus in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation* 2001; 72(6): 1020-4.
- Kamar N, Mariat C, Delahousse M, et al. Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 2007; 22(7): 1986-93.
- Greenspan LC, Gitelman SE, Leung MA, et al. Increased incidence in post-transplant diabetes mellitus in children: a case-control analysis. *Pediatr Nephrol* 2002; 17(1): 1-5.
- Palepu S, Prasad GV. New-onset diabetes mellitus after kidney transplantation: Current status and future directions. *World J Diabetes* 2015; 6(3): 445-55.
- Midtvedt K, Hjelmsaeth J, Hartmann A, et al. Insulin resistance after renal transplantation: the effect of steroid dose reduction and withdrawal. *J Am Soc Nephrol* 2004; 15(12): 3233-9.
- Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003; 3(2): 178-85.
- Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among U.S. wait-listed and transplanted renal allograft recipients. *Am J Transplant* 2003; 3(5): 590-8.
- Gourishankar S, Jhangri GS, Tonelli M, et al. Development of diabetes mellitus following kidney transplantation: a Canadian experience. *Am J Transplant* 2004; 4(11): 1876-82.
- Romagnoli J, Citterio F, Violi P, et al. Post-transplant diabetes mellitus: a case-control analysis of the risk factors. *Transpl Int* 2005; 18(3): 309-12.
- Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; 357(25): 2562-75.
- Pereira MJ, Palming J, Rizell M, et al. Cyclosporine A and tacrolimus reduce the amount of GLUT4 at the cell surface in human adipocytes: increased endocytosis as a potential mechanism for the diabetogenic effects of immunosuppressive agents. *J Clin Endocrinol Metab* 2014; 99(10): E1885-94. doi: 10.1210/jc.2014-1266.
- Radu RG, Fujimoto S, Mukai E, et al. Tacrolimus suppresses glucose-induced insulin release from

- pancreatic islets by reducing glucokinase activity. *Am J Physiol Endocrinol Metab* 2005; 288(2): E365-71.
19. Filler G, Neuschulz I, Vollmer I, et al. Tacrolimus reversibly reduces insulin secretion in paediatric renal transplant recipients. *Nephrol Dial Transplant* 2000; 15(6): 867-71.
 20. Trompeter R, Filler G, Webb NJ, et al. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. *Pediatr Nephrol* 2002; 17(3): 141-9.
 21. Dittrich K, Knerr I, Rascher W, Dotsch J. Transient insulin-dependent diabetes mellitus in children with steroid-dependent idiopathic nephrotic syndrome during tacrolimus treatment. *Pediatr Nephrol* 2006; 21(7): 958-61.
 22. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003; 3(2): 178-85.
 23. Sarkar S, Mondal R, Nandi M, Das AK. Tacrolimus induced diabetic ketoacidosis in nephrotic syndrome. *Indian J Pediatr* 2013; 80(7): 596-7.