New-Onset Diabetes Mellitus Associated with Sirolimus Use in Renal Transplant Recipients

Vural Taner Yilmaz1, Huseyin Kocak1, Ayhan Dinckan2, Ramazan Cetinkaya1
1Department of Internal Medicine, Division of Nephrology, Akdeniz University School of Medicine, Antalya, Turkey
2Department of General Surgery, Akdeniz University School of Medicine, Antalya, Turkey

Abstract
New-onset diabetes after transplantation and impaired glucose tolerance are very common in renal transplant patients. New-onset diabetes after transplantation (NODAT) is associated with increased cardiovascular morbidity and mortality, reduced graft and patient survival. Several risk factors for NODAT have been identified: age, obesity, family history of diabetes mellitus and HCV infection. In addition, steroid and calcineurin inhibitors also contribute to the development of NODAT. Sirolimus causes immunosuppressive effects by inhibiting mammalian target of rapamycin (mTOR), and has well known side effects. The effects of sirolimus on glucose metabolism and contribution to NODAT development are not clearly known. In this report, we presented five RTX patients who developed NODAT under the treatment of sirolimus.

Keywords: Renal transplantation, diabetes mellitus, sirolimus

Introduction
New-onset diabetes after transplantation (NODAT) and impaired glucose tolerance are very common among RTX patients. It has been reported in different studies that NODAT rates have ranged between 20% and 50% [1]. NODAT is associated with increased cardiovascular morbidity and mortality, reduced graft and patient survival. With regard to cardiovascular risk factors, NODAT is a more serious risk factor compared to hypertension and hyperlipidaemia [2].

Several risk factors for NODAT have been identified: family history, cytomegalovirus infection, hepatitis C virus infection, age and weight [3]. In addition, steroid and calcineurin inhibitors also contribute to the development of NODAT. In the early period of transplantation, it has been reported that tacrolimus is more diabetogenic than cyclosporine, although it has been shown that both cause similar rate of NODAT development in long term follow up [4]. In the pathogenetic process of NODAT, calcineurin inhibitors inhibit insulin secretion by causing beta cell damage [5].

Sirolimus, new immunosuppressive drugs, causes immunosuppressive effects by acting on mammalian target of rapamycin (mTOR) [6]. Although side effects of sirolimus are well described, its effects on glucose metabolism and association with NODAT are not clear. Herein, we present five renal transplant patients who developed NODAT under the treatment of sirolimus.

Case Reports
Case 1
A 42 years old female end stage renal disease patient referred to our centre for renal transplantation. Past medical history revealed that the etiology of ESRD was hypoplastic kidney and she was maintained on haemodialysis for 4 years. Her height was 150 cm (4.9 feet), her body mass index was 21...
kg/m², her blood type was 0 Rh (-). Preoperative laboratory tests were: blood urea nitrogen (BUN): 38 mg/dL, serum levels of creatinine (Cr): 7.4 mg/dL, creatinine clearance (CrCL): 8mL/minute, hepatitis-C virus antibody (HCV Ab) (-), fasting blood glucose (FBG): 78 mg/dL. In 2009, she received kidney from a 53 years old deceased donor with five HLA mismatches. Antithymocyte globulin was introduced as an induction treatment. Immunosuppressive therapy consisted of sirolimus (initial dose: 3 mg/day, target blood level: 8-10 ng/mL), mycophenolate mofetil (1.5 gr/day) and prednisolone (1. day: 1000 mg, 2. day: 500 mg, 3. day: 250 mg, 4. day: 160 mg, 5. day: 80 mg, 6. day: 40 mg, 7. day-1. month: 20 mg, 1.-2. month: 17.5 mg, 2.-3. month: 15 mg, 3.-6. month: 10 mg, 6.-12. month: 7.5 mg, >1.year: 5 mg/day). At the early post-operative periods, acute rejection attack, delayed graft function and infection were not observed. In routine biochemical examination, FBG was >90 mg/dL and creatinine level was 1.5 mg/dL. At the second month of renal transplantation operation, patient’s FBG raised (140-160 mg/dL), patient was diagnosed as diabetes mellitus according to the criteria of American Diabetes Association (ADA). We initiated nateglinide 120 mg as an anti-diabetic treatment and achieved adequate blood glucose control. Her last glomerular filtration rate was 80 ml/minute, FBG was under 100 mg/dL.

Cases 2-3-4-5

We also observed NODAT development in four renal transplant patients receiving sirolimus (3 mg/day , target blood level: 8-10 mg/mL), mycophenolate mofetil (1.5 gr/day ) and prednisolone (doses were same amount of firs patients) treatment. General characteristic features are presented in Table 1. All renal transplantation types were living-related. There is only family history of DM in second case. However, acute rejection attacks were not observed in any case. In our patients, at the first three months of post-transplant period, FBG started to rise. All our patients were diagnosed as diabetes mellitus according to the criteria of ADA between 5th and 6th months. Adequate blood glucose level was achieved by diet at the 2nd case, by nateglinide treatment for the 3rd and 4th cases and glyburide treatment for the 5th case. When DM was diagnosed, LDL, triglyceride and total cholesterol levels also increased to approximately 2-2.5 folds of preoperative values. The serum levels of fasting blood glucose, postprandial blood glucose and hemoglobin-A1C are presented in Table 2.

Informed consent was obtained from all patients for this study.

Discussion

In this study, we presented five renal transplant patients who developed NODAT under the treatment of sirolimus. NODAT has multifactorial aetiology. Drugs (steroids, calcineurin inhibitors, proliferation signal inhibitors), obesity, family history, male sex, positive test results for hepatitis-c virus, transplantation from deceased-donor are identified risk factors associated with NODAT. Evidence suggests that obesity and immunosuppressive drugs are major risk factors for the development of NODAT. Among the immunosuppressive drugs, cyclosporine and tacrolimus are well known drugs associated with NODAT [1].

Sirolimus causes immunosuppressive effects by acting on mammalian target of rapamycin (mTOR). mTOR inhibits interleukin-2 mediated signal transduction, resulting in cell cycle arrest in the G1-S phase. By this mechanism, sirolimus blocks the response of T- and B-cell activation by cytokines, which prevents cell-cycle progression and proliferation [6]. It is well known that sirolimus may show adverse effects on gastrointestinal, hematologic and pulmonary system. One

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Blood type</th>
<th>BMI</th>
<th>Miss-match</th>
<th>Preop. FBG</th>
<th>Family history of DM</th>
<th>HCV Ab</th>
<th>Etiology of ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>B (+)</td>
<td>25</td>
<td>2</td>
<td>80</td>
<td>(+)</td>
<td>(-)</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>M</td>
<td>A (+)</td>
<td>29</td>
<td>3</td>
<td>83</td>
<td>(-)</td>
<td>(-)</td>
<td>HT</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>M</td>
<td>B (+)</td>
<td>21</td>
<td>3</td>
<td>88</td>
<td>(-)</td>
<td>(-)</td>
<td>HT</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>M</td>
<td>B (+)</td>
<td>24</td>
<td>2</td>
<td>78</td>
<td>(-)</td>
<td>(-)</td>
<td>HT</td>
</tr>
</tbody>
</table>

BMI: body mass index (kg/m2); HT: hypertension; HCV: Hepatitis-C virus; ESRD: end stage renal disease; DM: diabetes mellitus; FBG: fasting blood glucose; NODAT: new-onset diabetes after transplantation.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>2nd patient</th>
<th>3rd patient</th>
<th>4th patient</th>
<th>5th patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dL)</td>
<td>126</td>
<td>130</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>PBG (mg/dL)</td>
<td>142</td>
<td>154</td>
<td>160</td>
<td>168</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>6</td>
<td>6.1</td>
<td>6.3</td>
<td>6.5</td>
</tr>
</tbody>
</table>

PBG: postprandial blood glucose; HbA1C: hemoglobin-A1C

Table 2. Serum levels of fasting blood glucose, postprandial blood glucose and hemoglobin-A1C when the patient was diagnosed as NODAT

Table 1. General characteristics of patients with diagnosis of NODAT

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Blood type</th>
<th>BMI</th>
<th>Miss-match</th>
<th>Preop. FBG</th>
<th>Family history of DM</th>
<th>HCV Ab</th>
<th>Etiology of ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>B (+)</td>
<td>25</td>
<td>2</td>
<td>80</td>
<td>(+)</td>
<td>(-)</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>M</td>
<td>A (+)</td>
<td>29</td>
<td>3</td>
<td>83</td>
<td>(-)</td>
<td>(-)</td>
<td>HT</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>M</td>
<td>B (+)</td>
<td>21</td>
<td>3</td>
<td>88</td>
<td>(-)</td>
<td>(-)</td>
<td>HT</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>M</td>
<td>B (+)</td>
<td>24</td>
<td>2</td>
<td>78</td>
<td>(-)</td>
<td>(-)</td>
<td>HT</td>
</tr>
</tbody>
</table>

BMI: body mass index (kg/m2); HT: hypertension; HCV: Hepatitis-C virus; ESRD: end stage renal disease; DM: diabetes mellitus; FBG: fasting blood glucose; NODAT: new-onset diabetes after transplantation.
of the discussed subjects for sirolimus is that whether it has beneficial or adverse effect on glucose metabolism.

In our cases, although we cannot exclude genetic susceptibility, family history (in one case) and prednisolone use for the NODAT risk factors, we can say that common risk factors in all cases for NODAT was the use of sirolimus. Therefore, our cases led us to think that sirolimus use in our patients might cause NODAT by clearly unknown mechanism.

New-onset diabetes after transplantation is especially associated with the uses of tacrolimum, cyclosporine and high dose prednisolone due to acute rejection attack in early post-transplant period and the risk of development of NODAT much more raised in the presence of other diabetogenic factors. We almost excluded all other secondary diabetogenic factors for example obesity, the history of family and hepatitis C virus infection except for the using of the immunosuppressive drugs. Acute rejection attacks were not observed in any patients. As well as, NODAT developed in other four patients except for first case at the late post-transplant period. Due to all these causes, we think that using of sirolimus is the most important factor for the developed of NODAT in our cases.

Indeed, the effects of sirolimus on glucose metabolism are not very clear. Insulin receptor substrate-1 (IRS-1) and mTOR play a role in insulin signalling. Early in-vitro studies suggest that it increases insulin responses in chronic insulin stimulation by inhibiting IRS-1 degradation [7]. Contrary to this finding, more recent in-vitro studies showed that long-term mTOR inhibition impairs activation of IRS-1 and AKT and augments insulin resistance and β-cell dysfunction [8, 9]. Other possible mechanisms, by which sirolimus may cause NODAT, include impaired insulin-mediated suppression of hepatic glucose production, insulin resistance from ectopic triglyceride deposition or direct β-cell toxicity. Recently, Johnston et al. [10] analysed the data of USRDS and reported that sirolimus may be independently associated with NODAT. Nevertheless, our cases may support this in-vitro and clinic study reporting that sirolimus may play a role in the development of NODAT and the need for further studies, which contain more patients.

In conclusion, our study has suggested that sirolimus is associated with NODAT, but this is not well established and our findings should be confirmed in prospective studies or in meta-analyses of existing trials that involved sirolimus.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.


**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**References**