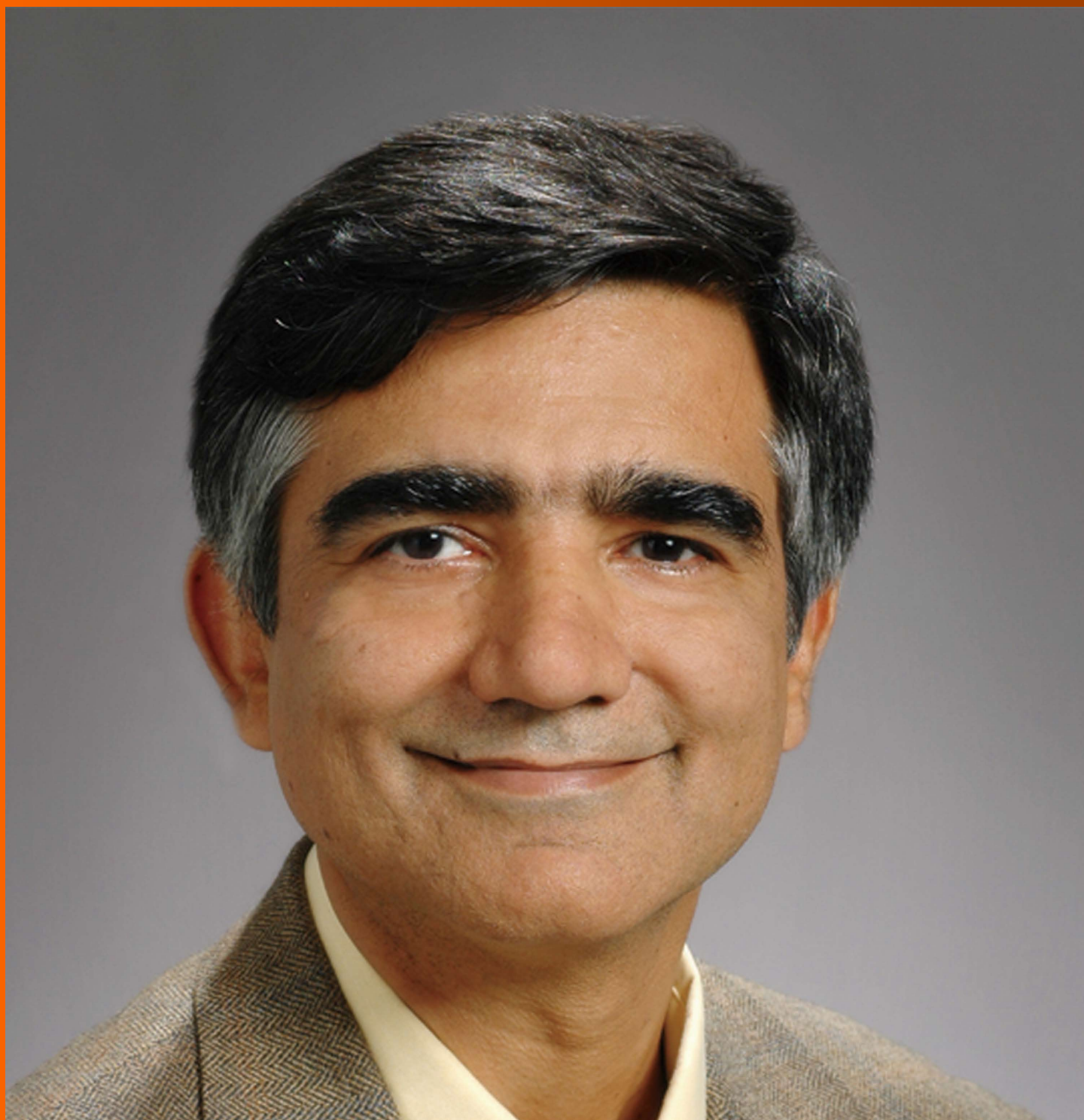


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## Retrospective Study

# New-onset diabetes after kidney transplantation: Incidence and associated factors

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**Author contributions:** Gomes V wrote the manuscript, collected the data and performed the data analysis; Guerra J collected the data; Guerra J, Ferreira F and Bugalho MJ reviewed the manuscript for important intellectual content; all authors participated in designing the study.

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## Abstract

### AIM

To determine the incidence and associated factors of new-onset diabetes after transplantation (NODAT) in a Portuguese central hospital.

### METHODS

This single-center retrospective study involved consecutive adult nondiabetic transplant recipients, who had undergone kidney transplantation between January 2012 and March 2016. NODAT was diagnosed according to the criteria of the American Diabetes Association. Data were collected from an institutional database of the Nephrology and Kidney Transplantation Department (Santa Maria Hospital, Lisbon, Portugal) and augmented with data of laboratorial parameters collected from the corresponding patient electronic medical records. Exclusion criteria were preexisting diabetes mellitus, missing information and follow-up period of less than 12 mo. Data on demographic and clinical characteristics as well as anthropometric and laboratorial parameters were also collected. Patients were divided into two groups: With and without NODAT - for statistical comparison.

### RESULTS

A total of 156 patients received kidney transplant



during the study period, 125 of who were included in our analysis. NODAT was identified in 27.2% of the patients ( $n = 34$ ; 53% female; mean age:  $49.5 \pm 10.8$  years; median follow-up:  $36.4 \pm 2.5$  mo). The incidence in the first year was 24.8%. The median time to diagnosis was  $3.68 \pm 5.7$  mo after transplantation, and 76.5% of the patients developed NODAT in the first 3 mo. In the group that did not develop NODAT ( $n = 91$ ), 47% were female, with mean age of  $46.4 \pm 13.5$  years and median follow-up of  $35.5 \pm 1.6$  mo. In the NODAT group, the pretransplant fasting plasma glucose (FPG) levels were significantly higher [ $101 (96.1-105.7)$  mg/dL *vs*  $92 (91.4-95.8)$  mg/dL,  $P = 0.007$ ] and pretransplant impaired fasting glucose (IFG) was significantly more frequent (51.5% *vs* 27.7%,  $P = 0.01$ ). Higher pretransplant FPG levels and pretransplant IFG were found to be predictive risk factors for NODAT development [odds ratio (OR): 1.059,  $P = 0.003$ ; OR: 2.772,  $P = 0.017$ , respectively].

### CONCLUSION

NODAT incidence was high in our renal transplant recipients, particularly in the first 3 mo posttransplant, and higher pretransplant FPG level and IFG were risk factors.

**Key words:** New-onset diabetes after transplant; Incidence; Kidney transplantation; Impaired fasting glucose; Immunosuppression

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**Core tip:** New-onset diabetes mellitus after transplantation (NODAT) is a major complication of kidney transplant. The aim of this study was to evaluate the incidence and associated factors of NODAT among kidney transplant recipients in a single center. A total of 125 patients transplanted at Santa Maria Hospital (Lisbon, Portugal) were assessed, and NODAT was identified in 27.2%. The median time to diagnosis was  $3.68 \pm 5.7$  mo after transplantation and most patients (76.5%) developed NODAT in the first 3 mo posttransplant. Higher pretransplant fasting plasma glucose level and pretransplant impaired fasting glucose were predictive risk factors for NODAT development.

Gomes V, Ferreira F, Guerra J, Bugalho MJ. New-onset diabetes after kidney transplantation: Incidence and associated factors. *World J Diabetes* 2018; 9(7): 132-137 Available from: URL: <http://www.wjgnet.com/1948-9358/full/v9/i7/132.htm> DOI: <http://dx.doi.org/10.4239/wjcd.v9.i7.132>

### INTRODUCTION

New-onset diabetes after transplantation (NODAT) is a frequent metabolic complication of kidney transplantation, and associated with increased morbidity and

mortality<sup>[1,2]</sup>. However, due to the absence of a standard definition of NODAT, it has been difficult to determine a reliable incidence rate. The first International Consensus Guidelines published in 2003 for the diagnosis and management of NODAT were updated in 2014 and advocate the World Health Organization (WHO) and American Diabetes Association (ADA) criteria for the diagnosis of diabetes mellitus (DM) and impaired glucose tolerance (IGT)<sup>[3,4]</sup>. Recent studies using these criteria found incidences of NODAT to be 7%-30% in the first year after transplant<sup>[5-8]</sup>.

Increased insulin resistance and impaired insulin production are likely to contribute to the development of NODAT<sup>[2]</sup>. Both traditional type 2 DM and transplant-related risk factors affect this condition<sup>[9]</sup>. The NODAT risk factors can be categorized into three groups: Non-modifiable, modifiable and potentially modifiable<sup>[10]</sup>. The non-modifiable factors include age, race/ethnicity, family history of DM, male recipient sex, the presence of certain human leukocyte antigens (HLAs; such as HLA A30, B27 and B42), increased HLA mismatches, donor-recipient mismatch, deceased donor kidney, male donor sex and history of acute rejection<sup>[10]</sup>. Polycystic kidney disease may confer an increased risk of NODAT, although results of the related studies remain conflicting<sup>[11]</sup>. On the other hand, the modifiable risk factors comprise obesity and type of immunosuppressive agents used to prevent or treat rejection. Finally, the potentially modifiable risk factors include pretransplant impaired fasting glucose (IFG) or IGT, and infection with hepatitis C or cytomegalovirus (CMV)<sup>[10]</sup>.

The aim of this study was to evaluate the incidence of NODAT and its associated factors among kidney transplant recipients who were treated in a transplant center of a central Portuguese hospital.

### MATERIALS AND METHODS

This is a single-center retrospective study of consecutive adult nondiabetic patients, who underwent kidney transplant between January 2012 and March 2016 at Santa Maria Hospital, Lisbon, Portugal. Data were collected retrospectively from an institutional database created by the Nephrology and Kidney Transplantation Department and completed with data for laboratorial parameters collected from the respective patients' electronic medical records, in agreement with our institutional ethical recommendations.

#### Inclusion and exclusion criteria

NODAT was diagnosed according to the ADA criteria (2017), which involves the following: Symptoms of diabetes (*i.e.*, polyuria, polydipsia or unexplained weight loss) plus random plasma glucose of  $\geq 200$  mg/dL; fasting plasma glucose (FPG) of  $\geq 126$  mg/dL, with fasting defined as no caloric intake for at least 8 h; and 2-h plasma glucose of  $\geq 200$  mg/dL during an oral glucose tolerance test (OGTT). IFG was defined as FPG

between 100 mg/dL and 125 mg/dL<sup>[3]</sup>.

In the first 3 mo after transplant, glycated hemoglobin was not used as diagnostic criteria, since its validity can be affected by the processes of new hemoglobin synthesis and glycation in the posttransplant setting<sup>[12]</sup>. The OGTT is considered the gold standard for diagnosing NODAT, enabling the identification of more patients than FPG measurement alone; likewise, it allows for diagnosis of IGT<sup>[4]</sup>. However, in our kidney transplantation center, the OGTT is not routinely performed in transplant recipients. The NODAT diagnosis was established when the immunosuppressive therapy and kidney allograft were stable and in the absence of acute infections or other stress factors, in order to exclude patients who developed transient hyperglycemia in the early posttransplant period<sup>[4]</sup>.

Data on demographic/clinical characteristics, anthropometric and laboratorial parameters included age at transplant, sex, race, weight, height, calculated body mass index (BMI), etiology of primary renal disease, pretransplant FPG, history of hepatitis C or CMV infection, acute rejection episodes, type of transplant (deceased or living donor), type of immunosuppressive drugs for induction and maintenance therapy, follow-up time, graft loss and death. Exclusion criteria were preexisting DM, missing information (*i.e.*, pretransplant FPG) and follow-up period of less than 12 mo. A total of 156 patients were transplanted during the study period, and 125 of these were eligible for the study.

### Immunosuppression regimen

All patients received induction therapy, consisting of either basiliximab (an interleukin-2 receptor monoclonal antibody; Protocol A) or rabbit antithymocyte globuline (ATG; Protocol B). Prior to the transplant, all patients received tacrolimus at 0.2 mg/kg. For Protocol A, the patient was administered 20 mg basiliximab pretransplantation and at 4 d posttransplantation; these patients also received tacrolimus at 0.075 mg/kg every 12 h and mycophenolate mofetil (1500 mg pretransplantation, followed by 1000 mg every 12 h for 1 wk posttransplantation and then 500 mg every 12 h). For Protocol B, the patient was administered 1.5-2 mg/kg ATG pretransplantation; methylprednisolone (500 mg) before ATG and tacrolimus at 0.05 mg/kg every 12 h.

All patients received 500 mg methylprednisolone intraoperatively, followed by 1 mg/kg per day for 3 d postoperatively, with progressive tapering until reaching 25 mg/d by the end of the first month after transplant. The maintenance therapy comprised corticosteroids (prednisolone), tacrolimus and mycophenolate mofetil.

### Statistical analysis

Data were analyzed with SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, United States). A biomedical statistician (Nilza Gonçalves, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal) reviewed the study's statistics. For

comparative analysis, the patients were divided into two groups: With and without NODAT. For continuous variables, differences were analyzed using the *Mann-Whitney* test (nonparametric data) and Student's *t*-test (parametric data). For categorical variables, differences were analyzed using the  $\chi^2$  test. Multivariate analysis was performed to identify potential risk factors for NODAT by using a logistic regression test. Data were expressed as mean  $\pm$  SD or median (minimum and maximum) for continuous variables and as percentage for categorical variables.  $P < 0.05$  was considered significant.

## RESULTS

A total of 125 patients were enrolled for the analysis (mean age:  $46.9 \pm 12.9$  years; 51.2% male). The majority of our patients were Caucasian, and the median follow-up was  $35.7 \pm 15.1$  mo. NODAT was identified in 27.2% [ $n = 34$ ; 95% confidence interval (CI): 20.17%-35.59%] of the patients; the NODAT cases were 53% female and had mean age of  $49.6 \pm 10.8$  years. The incidence of NODAT in the first year was 24.8% (95%CI: 18.06%-33.05%).

The median time to diagnosis was  $3.68 \pm 5.7$  mo after transplantation, with the majority of patients (76.5%) developing NODAT in the first 3 mo. NODAT diagnoses at the follow-up intervals of 3-6 mo, 6-12 mo and after 12 mo were 5.9%, 8.8% and 8.8%, respectively. The median follow-up for the NODAT group was  $36.4 \pm 2.5$  mo. In the group that did not develop NODAT ( $n = 91$ ), 47% were female and the mean age was  $46.0 \pm 13.6$  years. The median follow-up was  $35.5 \pm 1.6$  mo, which was not significantly different from that of the NODAT group ( $P = 0.774$ ).

Table 1 compares the clinical and laboratory parameters of patients who developed NODAT with those who did not (NODAT vs non-NODAT). During the follow-up period, 1 patient in the NODAT group and 2 patients in the non-NODAT group died. There was no graft loss in the NODAT group, as opposed to the 5 cases recorded for the non-NODAT group.

In the NODAT group, the pretransplant FPG levels were significantly higher [ $101$  ( $96.1$ - $105.7$ ) mg/dL vs  $92$  ( $91.4$ - $95.8$ ) mg/dL,  $P = 0.007$ ] and the occurrence of pretransplant IFG was significantly more frequent (51.5% vs 27.7%,  $P = 0.01$ ). Furthermore, higher pretransplant FPG levels and pretransplant IFG occurrence were identified as predictive risk factors for NODAT development [odds ratio (OR): 1.059,  $P = 0.003$ ; OR: 2.772,  $P = 0.017$ , respectively].

Patients diagnosed with NODAT were more frequently of African origin (29.4% vs 22%), presented a trend for higher age ( $49.6 \pm 10.8$  years vs  $46.0 \pm 13.6$  years) and BMI ( $25.2 \pm 4.0$  kg/m<sup>2</sup> vs  $24.5 \pm 4.4$  kg/m<sup>2</sup>), as well as a higher frequency of hepatitis C infection (2.9% vs 1.1%), CMV infection (97% vs 93%), acute rejection (14.7% vs 8.8%) and deceased donor (100% vs 91.2%), although none of these parameters

**Table 1** Clinical and laboratory parameters

	NODAT group	Non-NODAT group	P
No. of patients	34 (27.2%)	91 (72.8%)	
Age at transplant (yr)	49.6 ± 10.8	46.0 ± 13.6	0.165
Female sex	53% (18/34)	47% (43/91)	0.571
Race			
Caucasian	70.6% (24/34)	78% (71/91)	0.387
African	29.4% (10/34)	22% (20/91)	
Body mass index (kg/m <sup>2</sup> )	25.2 ± 4.0	24.5 ± 4.4	0.418
Pre-transplant FPG (mg/dL)	101 (96.1-105.7)	92 (91.4-95.8)	0.007
Pretransplant IFG	51.5% (17/33)	27.7% (23/83)	0.01
Hepatitis C infection	2.9% (1/34)	1.1% (1/91)	0.472
CMV infection	97% (33/34)	93% (82/88)	0.672
Acute rejection	14.7% (5/34)	8.8% (8/91)	0.338
Type of transplant			
Deceased donor	100% (34/34)	91.2% (83/91)	0.106
Living donor	0% (0/34)	8.8% (8/91)	
Follow-up (mo)	36.4 ± 2.5	35.5 ± 1.6	0.774

CMV: Cytomegalovirus; FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; NODAT: New-onset diabetes after transplantation.

reached statistical significance. The most frequent etiology of end-stage renal disease was hypertensive nephropathy ( $n = 7$ ) in the NODAT group and polycystic kidney disease ( $n = 17$ ) in the non-NODAT group.

In the NODAT group, induction therapy comprised ATG in 6 patients and basiliximab in 28; in the non-NODAT group, 24 patients received ATG and 67 received basiliximab. No statistically significant difference was found between the two groups for the induction therapies used ( $P = 0.309$ ). In both groups, maintenance therapy consisted of immunosuppression with corticosteroids, tacrolimus and mycophenolate mofetil. Of the 34 patients diagnosed with NODAT, 44.1% ( $n = 15$ ) needed oral hypoglycemic agents, 26.5% ( $n = 9$ ) needed insulin and 5.9% ( $n = 2$ ) were administered combined therapy (insulin and oral hypoglycemic agents). In the remaining 23.5% of the patients ( $n = 8$ ), diabetes was controlled with diet and exercise alone.

## DISCUSSION

Kidney transplant, besides being more cost-effective than dialysis, improves patient survival<sup>[13]</sup>. Nevertheless, NODAT is a frequent complication of kidney transplantation and is associated with poorer outcomes, increased risk of infectious and cardiovascular complications and reduced rates of patient and graft survival<sup>[5,14]</sup>.

The reported incidence of NODAT has varied broadly between studies, probably due to the use of diverse diagnostic criteria, intensity of routine screening and follow-up length<sup>[15]</sup>. Furthermore, variability in the immunosuppressive protocols used in different transplant centers could influence the calculated incidence rates of NODAT. For instance, it is known that tacrolimus is more diabetogenic than cyclosporine<sup>[16]</sup>. Recent studies using the WHO/ADA criteria reported that 7%-30% of nondiabetic kidney transplant recipients develop NODAT in the first year after transplant<sup>[5-8]</sup>. In our study,

NODAT was diagnosed in 34 patients (27.2%), with an incidence of 24.8% in the first year after transplant. Therefore, our findings are in agreement with previous studies. NODAT occurrence reportedly peaks in the first 3-6 mo posttransplant<sup>[17,18]</sup>. Studies have also shown that the incidence is higher when higher dosages of immunosuppressive medications are used<sup>[17]</sup>. After the 3-6 mo period, the annual incidence of diabetes is comparable to that observed in pretransplant patients<sup>[17,18]</sup>. In the present study, the median time to diagnosis was  $3.68 \pm 5.7$  mo, with the majority of patients (76.5%) developing NODAT in the first 3 mo, which is also consistent with the literature.

Multiple risk factors have been identified. In our study, higher pretransplant FPG levels and occurrence of pretransplant IFG were predictive risk factors for NODAT development. Other researchers have reported abnormal glucose metabolism as a NODAT risk factor. For example, Cosio *et al.*<sup>[19]</sup> reported that high pretransplant glucose levels represent a risk factor for NODAT at 1-year posttransplant. The risk was shown to increase as pretransplant FPG levels rose. Among patients with pretransplant IFG in that study, 70% had hyperglycemia at 1 year (IFG 43% and NODAT 27%). The strongest risk factor for NODAT seems to be age<sup>[20]</sup>. NODAT development is 2.2 times more likely to occur in patients with age above 45 years<sup>[21]</sup>. Another independent risk factor for NODAT is obesity or overweight status. Previous studies have reported a relative risk of 1.4 and 1.8 for patients with BMI between 25-30 kg/m<sup>2</sup> and > 30 kg/m<sup>2</sup>, respectively<sup>[22]</sup>. We also found a trend for higher age and higher BMI in the NODAT group.

African-Americans have a 2-fold risk of developing NODAT compared to Caucasians. This finding can be, at least partly, related to immunosuppressive agents' pharmacokinetics variation<sup>[15]</sup>. Hepatitis C and CMV infection are also associated with NODAT. Hepatitis C virus causes insulin resistance in the context of liver dysfunction, abnormalities in glucose metabolism and

pancreatic  $\beta$  cell dysfunction<sup>[23]</sup>. Similarly, lower median insulin release has been reported for patients with CMV infection, suggesting impaired pancreatic  $\beta$  cell function as a possible pathogenic mechanism<sup>[24]</sup>.

History of acute rejection episodes requiring elevated doses of glucocorticoids, as well as the type of transplant (deceased donor), have also been implicated in risk of NODAT<sup>[22]</sup>. We found higher frequencies of African-origin individuals, hepatitis C infection, CMV infection, acute rejection and deceased donors in our NODAT group, as suggested in the literature; however, the differences did not reach statistical significance. The majority of NODAT patients in our study required treatment for diabetes, with most responding to oral hypoglycemic agents, followed by insulin, and few requiring combined therapy. Nearly a quarter of the patients were able to achieve diabetes control without medication, based on lifestyle modifications.

Some limitations exist in our study design that may impact the interpretation and/or generalization of our findings. This was a retrospective study with a relatively small sample, only reflecting a single center experience. Moreover, OGTT is not currently used in our center as a NODAT screening test, which is likely to lead to underestimation of its incidence in this cohort.

The incidence of NODAT in renal transplant recipients is high, particularly in the first 3 mo. Recognition of the associated factors may help to prevent this condition. Higher pretransplant FPG levels and occurrence of pretransplant IFG were predictive risk factors for NODAT development, indicating a need for periodical blood glucose screening in patients waiting for a transplant in order to identify those at risk. Using the same rationale as for type 2 DM, early identification of impaired carbohydrate metabolism in the posttransplant setting will allow implementation of lifestyle modifications in order to minimize progression to NODAT and its potentially severe complications.

## ARTICLE HIGHLIGHTS

### Research background

New-onset diabetes after transplantation (NODAT) is a common complication of kidney transplantation, correlated with poorer outcomes. Its incidence varies greatly between studies, and multiple risk factors have been associated with its onset.

### Research motivation

Albeit a frequent complication of kidney transplant, very few studies of NODAT in the Portuguese population have been published.

### Research objectives

To evaluate the incidence and associated factors of NODAT among kidney transplant recipients in a Portuguese hospital.

### Research methods

Retrospective study of consecutive adult nondiabetic patients, who underwent kidney transplant between January 2012 and March 2016 in a central Portuguese hospital.

## Research results

NODAT was identified in 27.2% of the kidney transplant recipients. The median time to diagnosis was  $3.68 \pm 5.7$  mo after transplantation. Higher pretransplant fasting plasma glucose levels and occurrence of pretransplant impaired fasting glucose (IFG) were predictive risk factors for NODAT development.

## Research conclusions

Periodical blood glucose screening in patients waiting for a kidney transplant is important to identify those at risk for and to minimize progression to NODAT and its potentially severe complications.

## Research perspectives

Clinicians should be aware of NODAT risk factors, namely pretransplant IFG, to perform a tighter surveillance of patients in these conditions. Multicentric studies are required to investigate other risk factors possibly implicated in NODAT development.

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