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# Incidence and Risk Factors for the Development of New-Onset Diabetes after Kidney Transplantation

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## Abstract

**Objective** New-onset diabetes mellitus after transplantation (NODAT), also known as posttransplant diabetes mellitus, is a common complication after kidney transplantation. It is associated with an increased risk of graft failure and death. Therefore, minimizing the risk of NODAT is a priority after kidney transplantation. This study aimed to determine the incidence of NODAT, the risk factors for its development, and the therapeutic drugs used for its management.

**Patients and Methods** This is an observational, retrospective study on kidney recipients who were followed up in our center in 2021. After excluding known diabetic patients, second transplant patients, and those with follow-up periods less than 6 months, 308 recipients were included in the study. Demographic, clinical, and laboratory data were collected from the patient records. The patients were categorized as diabetic or nondiabetic.

**Results** All patients' mean age was 35.9 ± 11.6 years (standard deviation). The male-to-female ratio was 2.13:1. The overall incidence of NODAT was 38.3%. The median time to NODAT diagnosis was 6 months. Patients older than 40 were more likely to develop NODAT (61.1%; $p = 0.000$). The prevalence of pretransplant body mass index (BMI) more than 25 was significantly higher (67.6%) in diabetic than among nondiabetic patients ($p = 0.000$). NODAT patients were more likely to have had a rejection episode (65 vs. 35% in nondiabetic patients; $p = 0.011$). A high trough level of calcineurin inhibitors carried a significant risk of NODAT development. Tacrolimus trough level more than or equal to 10 ng/mL had an odds ratio of 57.9 (95% confidence interval [CI] 7.689–1262.2; $p = 0.0007$) for the development of NODAT. Likewise, a cyclosporine-A trough level more than or equal to 150 ng/mL had an odds ratio of 100.7 (95% CI: 7.31–4293.5; $p = 0.0028$).

**Conclusion** NODAT incidence was high in this study. Older age, high BMI, prior rejection episode, steroid dose, and high calcineurin inhibitors trough levels were significant risk factors for developing NODAT.

**Keywords**

- new-onset diabetes after transplantation
- tacrolimus
- cyclosporine-A
- kidney transplant
- calcineurin inhibitors

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## Introduction

Kidney transplantation is the only currently available cure for end-stage renal disease .[1] Renal transplant recipients' survival time has gradually increased because of the improved survival rate during the perioperative period and enhancements in treatment with antirejection drugs.[2] Hence, long-term complications and the quality of life of transplant recipients have received more attention. Among these, new-onset diabetes after transplant (NODAT) is a serious and frequent metabolic complication after renal transplantation and is considered a risk for patients undergoing renal transplantation.[3] NODAT may severely impact both short- and long-term outcomes of renal transplant recipients in terms of graft and patient survival.[4] It has been shown that NODAT significantly increases acute rejection, kidney graft loss, mortality, and healthcare costs.[5,6] However, it too often goes undiagnosed, underestimated, or poorly managed. There is a wide variation in the incidence of NODAT, ranging from 2 to 53%.[7,8] This wide range of reported incidence may be due in part to the lack of a standard definition of the condition, differences in the duration of follow-up, and the presence of both modifiable and nonmodifiable risk factors.[9] Another possible reason is the lack of screening for hyperglycemia in the posttransplant setting since some patients have transient hyperglycemia after the transplant, whereas others develop persistent diabetes.[7] Several risk factors for NODAT have been identified. These include older age,[5] obesity,[10] metabolic syndrome,[11] family history of diabetes,[3] and history of glucose intolerance.[12] Furthermore, cytomegalovirus infection,[13] hepatitis C infection,[14] and the use of certain medications such as calcineurin inhibitors (CNIs)[15] and corticosteroids are other risk factors.[16,17] It has been recognized that autosomal dominant polycystic kidney disease is a risk factor for developing NODAT.[18] NODAT shares features of type 1 diabetes (caused by β-cell destruction leading to insulin deficiency) and type 2 diabetes mellitus (T2DM, characterized by varying degrees of insulin resistance). However, NODAT tends to have more of the criteria of T2DM and is regarded as a form of T2DM.[19] Although hyperglycemia consistent with a diagnosis of diabetes is observed in more than 90% of renal transplant recipients within the first weeks after transplantation, only a fraction of the patients subsequently develop either impaired glucose tolerance or NODAT.[20] This bidirectional nature of glucose metabolism in the setting of solid organ transplantation is unique and clinically well demonstrated.[21] CNIs (i.e., cyclosporine-A [CsA] and tacrolimus) are also associated with an increased risk of NODAT.[6,15] CsA and tacrolimus have direct inhibitory effects on pancreatic β-cells. Tacrolimus exhibits a stronger dose-dependent suppressive effect on insulin secretion; both drugs have also demonstrated adverse effects on insulin sensitivity.[22] An increased risk of NODAT has also been reported with immunosuppressive regimens comprising the mammalian target of rapamycin inhibitors, sirolimus, or everolimus. The latter appears to worsen insulin secretion and insulin resistance, particularly when combined with CNIs (especially with tacrolimus).[23] We aimed to determine the incidence of NODAT in Libyan kidney transplant recipients and study the risk factors associated with its development and the therapeutic options used in its management.

## Patients and Methods

### Patient Characteristics

This retrospective study was carried out in 2022 on all adult kidney allograft recipients at the Libyan National General Authority for Organ, Tissue, and Cell Transplantation in Tripoli, Libya, who were followed up in the outpatient clinic during 2021. Exclusion criteria were known history of diabetes, age under 18 years at the time of transplantation, multiorgan transplantation, follow-up period less than 6 months, and patients who had undergone two or more renal transplants. The demographic characteristics such as age, gender, body mass index (BMI), etiology of primary renal disease, history of dialysis, pharmacologic therapy (maintenance therapy), family history of diabetes, and follow-up period were recorded.

### Definitions

The diagnosis of NODAT was based on the diagnostic criteria for diabetes proposed at the International Consensus Meeting on Post-Transplantation Diabetes Mellitus in 2013, which recommends delaying the screening and diagnosis of NODAT until at least 45 days after transplantation to allow stabilization of the immunosuppression levels.[24] These include polyuria, polydipsia, or unexplained weight loss plus random blood glucose more than or equal to 200 mg/dL, or the presence of fasting plasma glucose (FPG) of more than or equal to 126 mg/dL, or second-hour plasma glucose more than or equal to 200 mg/dL during an oral glucose tolerance test.[24] In addition, NODAT is considered to have developed when the patient is using glucose-lowering medications (insulin and oral hypoglycemic agents for $>1$ month) prescribed by a nephrologist or endocrinologist at the time of the study. The diagnosis should be confirmed by measuring FBG and hemoglobin A1c (HbA1c), but our study was a retrospective analysis. Therefore, patients with transient hyperglycemia were not considered as having NODAT and were included in the non-NODAT group. In other words, only the patients who still had diabetes and were treated with antidiabetic agents on the day of the study were included in the NODAT group. HbA1c was not a diagnostic criterion in the first 3 months after transplantation. After that, it was used as a diagnostic criterion in combination with elevated FBG levels.

The NODAT group was divided into four subgroups according to the time interval between renal transplantation and diagnosis of NODAT: less than 3 months, 3 to 6 months, 6 to 12 months, and more than 12 months. The clinical and laboratory findings of the NODAT and non-NODAT groups were compared to identify the risk factors associated with NODAT.

### Immunosuppressive Medications

Induction therapy was given to all the patients. According to induction therapy, immunosuppression comprises rabbit

 

antithymocyte globulin or interleukin-2 receptor monoclonal antibody (basiliximab). Methylprednisolone (1,000 mg) is given intraoperatively, followed by tapering oral prednisolone 30 mg for 1 week, 10 mg for 1 month, and 5 mg on the 12th week posttransplantation. Mycophenolate-mofetil (MMF) or mycophenolate sodium (MMY) at 1,000 mg or 720 mg twice daily, given postoperatively, with dose adjustment to avoid side effects. CsA was started at 8 mg/kg/day,

**Table 1** Epidemiologic characters of the study group

| Variable | All patients | DM group | Non-DM group | *p*-Value |
|---|---|---|---|---|
| **Follow-up period (mean ± SD, years)** | 6.46 (± 3.32) | 6.47 (±3.25) | 6.45 (±3.38) | |
| **Recipients** | | | | |
| **Age (mean ± SD) years** | 35.9 ± 11.6 | 40.5 ± 11.4 | 32.9 ± 10.7 | |
| **Age category (years)** | | | | |
| ≤ 40 | 213 (69.2%) | 60 (28.2%) | 153 (71.8%) | 0.000 |
| > 40 | 95 (30.8%) | 58 (61.1%) | 37 (38.9%) | |
| **Sex** | | | | |
| Male | 209 (68%) | 83 (39.7%) | 126 (60.3%) | 0.531 |
| Female | 99 (32%) | 35 (35.4%) | 64 (64.6%) | |
| **Body mass index** | | | | |
| Mean (± SD) | 23.4 ± 3.8 | 24.1 ± 4.0 | 22.9 ± 3.6 | |
| ≤ 25 | 82 (26.6%) | 23 (28.0%) | 59 (72.0%) | 0.000 |
| > 25 | 34 (11.0%) | 23 (67.6%) | 11 (32.4%) | |
| **Donors** | | | | |
| **Age (**mean ± SD) | 22.2 ± 18.4 | 20.1 ± 17.6 | 23.6 ± 18.7 | |
| ≤ 40 | 146 (75%) | 61 (41.8%) | 85 (58.2%) | 0.028 |
| > 40 | 50 (25%) | 12 (24.0%) | 38 (76.0%) | |
| **Sex** | | | | |
| Male | 164 (68%) | 62 (37.8%) | 102 (62.2%) | 0.272 |
| Female | 77 (32%) | 28 (36.4%) | 49 (63.6%) | |
| **Consanguinity** | | | | |
| Live related | 237 (76.9%) | 89 (37.6%) | 148 (62.4%) | 0.866 |
| Live unrelated | 58 (18.8%) | 24 (41.4%) | 34 (58.6%) | |
| Cadaveric | 13 (4.2%) | 5 (38.5%) | 8 (61.5%) | |
| **HLA-DR** | | | | |
| Zero mismatch | 30 (20.0%) | 12 (40%) | 18 (60%) | 0.814 |
| ≤ 3 mismatch | 96 (64.4%) | 35 (36.5%) | 61 (63.5%) | |
| > 3 mismatch | 23 (14.4%) | 9 (39.1%) | 14 (60.9%) | |
| **Family history of DM** | | | | |
| Negative | 92 (29.9%) | 35 (38%) | 57 (62.0%) | 0.474 |
| Positive | 49 (15.9%) | 22 (44.9%) | 27 (55.1%) | |
| **Hemodialysis duration** | | | | |
| Mean ± SD (months) | 17.6 ± 22.8 | 16.9 ± 23.0 | 18.1 ± 22.8 | 0.683 |
| **Place of transplant** | | | | |
| Tripoli | 139 (45.1%) | 53 (38.1%) | 86 (61.9%) | 0.52 |
| Abroad | 169 (54.9%) | 65 (38.5%) | 104 (61.5%) | |
| **Prior rejection** | | | | |
| Yes | 20 (6.5%) | 13 (65%) | 7 (35%) | 0.011 |
| No | 288 (93.5%) | 105 (36.5%) | 183 (63.5%) | |

Abbreviations: DM, diabetes mellitus; HLA-DR, —; SD, standard deviation.

 

tacrolimus at 0.2 mg/kg/day, and then adjusted according to trough blood levels. Target CsA levels at 3 months were 150 to 250 ng/mL and then tapered to 100 to 150 ng/mL by 1 year. Target tacrolimus levels were 7 to 10 ng/mL in the first 3 months and then tapered to 4 to 7 ng/mL. The standard immunosuppressive protocol (maintenance therapy) consisted mainly of triple therapy composed of steroids, a CNI (CsA or tacrolimus), and MMF/MMY in most recipients.

### Statistical Analysis

Data were analyzed with SPSS software version 25. All continuous data are expressed as mean ± standard deviation (SD) and were analyzed by unpaired t-test. Categorical data are expressed as numbers and percentages and analyzed by the X2 test. Binary logistic regression analysis was done to evaluate the odds ratios of various parameters associated with the increased risk of NODAT. *p*-Value less than 0.05 was considered statistically significant.

## Results

### Characteristics of the Study Population

The study was done on 308 kidney transplant patients who fulfilled the inclusion and exclusion criteria. The mean age (SD) of the recipients was 35.9 ± 11.6 years. Male recipients were predominant (68% males and 32% females), with a sex ratio of 2.13:1. The mean duration (SD) of hemodialysis before transplantation was 17.6 ± 22.8 months (SD). The graft was from living-related donors in 76.9% of the cases, and 4.2% were from cadaveric donors (done abroad). A family history of diabetes was documented as either positive or negative in 141 patients in the study, of which 49 (15.9%) cases have a positive family history of diabetes. Almost half of the transplants (45%) were performed in Tripoli (►**Table 1**). The original kidney disease was not established in 61.0% of the cases. It was glomerulonephritis in 15.3%, hypertension in 10.7%, and autosomal dominant polycystic kidney disease in 4.2% of the patients. There was a significant association between the original kidney disease and the development of diabetes ($p = 0.005$; ►**Table 2**).

### NODAT Frequency and Timing

The NODAT occurred in 38.3% of the cohort. The mean time between the transplant and the onset of NODAT was 12 ± 14.7 months, and the median time was 6 months. NODAT was diagnosed in 41.3, 32.1, and 26.6% of the patients within 3 months, 3 to 12 months, and beyond 12 months, respectively (►**Fig. 1**). The mean fasting blood sugar at the diagnosis was 181.37 mg/dL ± 55.57 (SD). Of the patients who developed NODAT, 58.5% required oral agents for treatment, 9.3% required insulin therapy, and 16.9% required more than one drug (►**Table 3**).

### NODAT Risk Factors

When comparing those who developed NODAT with those who did not, we found that the recipient's age more than 40 years was significantly associated with NODAT (61.1% in NODAT vs. 38.9% in nondiabetic, $p = 0.000$). The recipient's BMI more than 25 before the transplant was also significantly associated with NODAT (67.6% in NODAT vs. 32.4% in nondiabetic, $p = 0.000$).

Prior transplant rejection also had a significant impact on the development of NODAT: 65% of those who had experienced rejection developed NODAT versus 35% for those who did not develop diabetes ($p = 0.011$). Moreover, donor age and the original kidney disease were also significantly associated with developing NODAT ($p = 0.028$ and 0.005, respectively). Other factors, such as the recipient's sex, family history of diabetes mellitus, duration of hemodialysis before transplant, and the number of HLA mismatches, were not associated with the development of NODAT ($p > 0.05$; ►**Tables 1** and **2**). The associations of immunosuppressive drugs with NODAT are presented in ►**Table 4**. There was no significant association between the drug regime and the development of NODAT ($p = 0.688$). However, the drug trough levels were significantly associated with the development of NODAT. Tacrolimus trough

**Table 2** Original kidney disease

| Disease | All patients | DM group | Non-DM group | *p*-Value |
|---|---|---|---|---|
| GN | 47 (15.3%) | 12 (25.5%) | 35 (74.5%) | 0.005 |
| Autosomal dominant polycystic kidney disease | 13 (4.2%) | 7 (53.8%) | 6 (46.2%) | |
| Hypertension | 33 (10.7%) | 21 (63.6%) | 12 (36.4%) | |
| Congenital (VUR, PUV, horseshoe kidney) | 10 (3.2%) | 3 (30.0%) | 7 (70.0%) | |
| Renal stone | 7 (2.3%) | 4 (57.1%) | 3 (42.9%) | |
| Hyperoxalosis | 2 (0.6%) | 0 | 2 (100%) | |
| Systemic lupus erythematosus, rheumatoid arthritis, Wegener's granulomatosis | 3 (1.0%) | 3 (100%) | 0 | |
| Pre-eclampsia | 4 (1.3%) | 1 (25%) | 3 (75%) | |
| Drugs (contrast) | 1 (0.3%) | 1 (100%) | 0 | |
| Undetermined | 188 (61.0%) | 66 (35.1%) | 122 (64.9%) | |

Abbreviations: GN, glomerulonephritis; PUV, posterior urethral valve; VUR, vesicoureteric reflux.

 

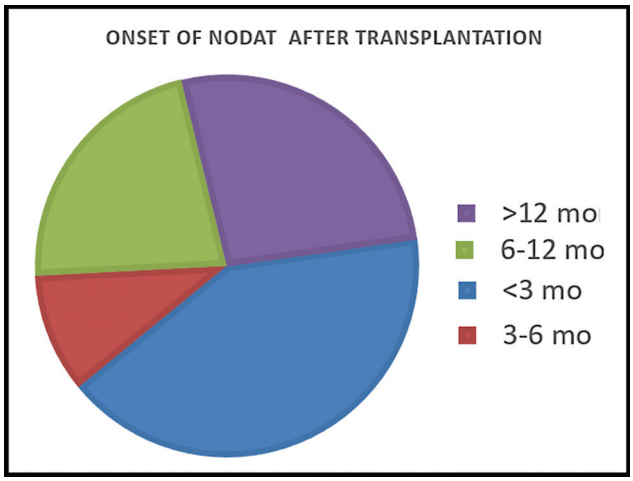


**Fig. 1** Time interval between transplantation and onset of NODAT.

level more than or equal to 10 ng/mL was a significant risk factor for NODAT compared to a level less than 10 ng/mL ($p = 0.000$). Those with a CsA trough level more than or equal to 150 ng/mL were more likely to develop NODAT than those with lower levels ($p = 0.000$). Furthermore, prednisolone more than 5 mg per day was significantly associated with the development of NODAT compared to lower levels ($p = 0.001$; ►**Table 4**). We identified five factors associated with an increased risk of NODAT in kidney recipients. These factors and the fold increase in the risk were as follows: age more than 40 years (x 2.3), BMI more than 25 (x1.35), prior graft rejection (x 5.5), tacrolimus level more than or equal to 10 - ng/mL (x57.9), and CsA level more than or equal to 150 ng/mL (x100; ►**Tables 5** and **6**).

**Table 3** Blood glucose control parameters and used antidiabetic medications

| Parameter | At diagnosis | On last visit |
|---|---|---|
| **Fasting blood sugar** (mg/dL) | | |
| • Mean ± SD | 181 ± 56 | 120 ± 33 |
| • Median | 163 | 116 |
| **HgbA1c (%)** | | |
| • Mean ± SD | 6.2 ± 3.1 | 6.3 ± 0.8 |
| • Median | 6.9 | 6.2 |
| **Antidiabetic medications** | **Number (%)** | |
| • Diet only | 18 (15.3%) | |
| • Metformin | 11 (9.3%) | |
| • Insulin | 11 (9.3%) | |
| • Sulfonylurea (Gliclazide) | 58 (49.2%) | |
| • Dual combination | 20 (16.9%) | |
| • All | 118(100%) | |

Abbreviation: SD, standard deviation.

**Table 4** Association of immunosuppressive drugs with development of NODAT

| Drugs (% within the level) | All patients | NODAT group | Non-DM | *p*-Value |
|---|---|---|---|---|
| **Prednisolone dose** | | | | 0.001 |
| Mean ± SD total dose | 7.2 ± 5.3 | 8.8 ± 6.7 | 6.2 ± 4.0 | |
| **Prednisolone dose** | | | | |
| ≤ 5 mg | 91 (35%) | 22 (24.2%) | 69 (75.8%) | |
| > 5 mg | 171 (65%) | 79 (46.2%) | 92 (53.8%) | |
| **Steroid use** | | | | 0.838 |
| Yes | 262 (85.1%) | 101 (85.8%) | 161 (84.7%) | |
| No | 46 (14.9%) | 17 (14.4%) | 29 (15.3%) | |
| **Tacrolimus tough level** (ng/ml) | | | | 0.000 |
| Mean ± SD | 5.0 ± 4.9 | 6.7 ± 6.1 | 4.0 ± 3.7 | |

(*Continued*)

 

**Table 4** (*Continued*)

| Drugs (% within the level) | All patients | NODAT group | Non-DM | *p*-Value |
|---|---|---|---|---|
| < 10 | 157 (80%) | 48 (30.6%) | 109 (69.4%) | |
| ≥ 10 | 38 (20%) | 30 (78.9%) | 8 (21.1%) | |
| **CsA level** (ng/ml) | | | | 0.000 |
| Mean ± SD | 42.2 ± 79.1 | 57.2 ± 99.8 | 32.7 ± 61.2 | |
| < 150 | 52 (62%) | 12 (23.1%) | 40 (76.9%) | |
| ≥ 150 | 32 (38%) | 23 (71.9%) | 9 (28.1%) | |
| **Drug regime** | | | | 0.688 |
| Tacrolimus+ MMF + prednisolone | 206 (66.9%) | 79 (38.3%) | 127 (61.7%) | |
| CsA + MMF + prednisolone | 96 (31.2%) | 37 (38.5%) | 59 (61.5%) | |
| Rapamine + MMF + prednisolone | 4 (1.3%) | 2 (50%) | 2 (50%) | |
| Cellcept + prednisolone | 2 (0.6%) | 0 | 2 (100%) | |

Abbreviations: CsA, cyclosporine A; DM, diabetes mellitus; MMF, mycophenolate-mofetil; NODAT, New-onset diabetes mellitus after transplantation; SD, standard deviation.

**Table 5** Odds ratio for NODAT risk factors

| | Odds ratio exp(B) | 95% CI | *p*-Value (>\|z\|) |
|---|---|---|---|
| Intercept | 0.065 | 0.0033–0.40 | 0.015 |
| Recipient's age > 40 years | 2.362 | 1.013–5.54 | 0.046 |
| Occurrence of prior rejection | 5.534 | 1.115–32.53 | 0.041 |
| CsA level ≥ 150 ng/mL | 100.7 | 7.309–4293.42 | 0.003 |
| Tacrolimus level ≥ 10 ng/ml | 57.93 | 7.69–1262.18 | 0.0007 |
| BMI > 25 | 1.347 | 0.423–4.262 | 0.008 |

Abbreviations: BMI, body mass index; CI, confidence interval; CsA, cyclosporine A; NODAT, new-onset diabetes mellitus after transplantation.

**Table 6** Binary logistic regression of NODAT risk factors

| | Estimate | SE | z value | Pr(>\|z\|) |
|---|---|---|---|---|
| Intercept | –2.7304 | 1.1186 | –2.441 | 0.014653 |
| Recipient's age (>40 vs. ≤ 40) years | 0.8594 | 0.4308 | 1.995 | 0.046029 |
| Prior rejection (yes vs. no) | 1.7109 | 0.8363 | 2.046 | 0.040766 |
| CsA level (≥ 150 vs. < 150) ng/mL | 4.6125 | 1.5471 | 2.981 | 0.002870 |
| Tacrolimus level (≥ 10 vs. < 10) ng/mL | 4.0593 | 1.2015 | 3.379 | 0.000729 |
| BMI (> 25 vs. ≤ 25) | –0.7763 | 0.4396 | –1.766 | 0.0077395 |

Abbreviations: BMI, body mass index; CsA, cyclosporine-A; NODAT, new-onset diabetes mellitus after transplantation; SE, standard error.

## Discussion

The prevalence of diabetes mellitus is rapidly rising worldwide due to a sedentary lifestyle and consumption of high-calorie diets. The global diabetes prevalence was estimated to be 463 million people in 2019 and was expected to rise to 578 million by 2030.[25] Kidney transplantation may increase the risk of diabetes in those receiving transplants. This study found that the incidence of NODAT among kidney recipients was 38.3%, which is similar to that reported from Bahrain (33.5%),[26] and India (33.85%).[27] Nevertheless, it is more often higher than in other Arab countries,[28–30] Japan,[31] France,[32] the United States,[5] Russia,[33] Singapore,[34] and Canada.[35] The rates in these countries ranged between 7 and 24.2%. The differences in the prevalence rates may be attributed to variable numbers of patients, racial differences, differences in the protocols of immunosuppressive agents, and different follow-up periods.

In this study, the median time to development of NODAT was 6 months. Nearly half of the patients developed NODAT

 

in the first 6 months posttransplantation (47.5%), which resembles previous reports.[6,19,29,30] This result is also concurring with other studies reporting a higher incidence of NODAT in the initial posttransplant period, which could be attributed to the use of immunosuppressive medication in the early posttransplant period, especially high-dose steroids.

This study revealed that the recipient's age has an impact on the development of NODAT. The mean age of the NODAT group was significantly higher than the nondiabetic group ($40.5 \pm 11.4$ vs. $32.9 \pm 10.7$ years, $p = 0.001$). Furthermore, 61% of the kidney recipients with NODAT were older than 40 versus 38.9% in the nondiabetic group ($p = 0.000$). Recipients aged more than or equal to 40 years were 2.3 times more likely to develop diabetes than those below less than 40 years. This results confirm other studies.[7,29,30] On the other hand, the mean age of the patients in other studies was higher than in this study, for example, in Bahrain (51 vs. 41 years) and Japan (46.8 vs. 41 years).[26,31] High BMI at the time of transplantation was associated with the development of NODAT in this study: 67.6% of NODAT recipients had BMI more than 25 vs. 32.4% in the nondiabetic group ($p = 0.000$). This is consistent with most studies confirming this association.[3,5,10,16,28–31] However, Montori et al found no association between the development of NODAT and obesity in transplant recipients.[36]

This study did not demonstrate a significant association between a family history of diabetes and the development of NODAT ($p = 0.474$), which is at odds with many studies reporting a significant association.[26,29,30] This might be due to underdiagnoses of DM in our society in the absence of a sound primary healthcare system, and it is conceivable that our patients did not accurately report their family history of DM.[37]

Although the drug regime had no significant impact on the risk of diabetes in our study, there was a significant association between NODAT development and the prednisolone dose. Of those taking more than 5 mg/day prednisolone, 46.2% developed NODAT, whereas only 24.2% of those receiving lower doses developed the condition ($p = 0.001$). Moreover, the risk of developing diabetes increased 2.7 times in those with prednisolone doses more than 5 mg/day ($p$-value $= 0.000$). These results are compatible with other studies that establish the effect of cumulative dosages and duration of therapy on the development of NODAT.[3,26] Our physicians may include steroids in the drug regime of the patients, especially those who had been transplanted abroad, for whom full information about their transplantation is unavailable. Also, steroids are used to treat rejection episodes, which were significantly associated with the development of diabetes in this study. Patients who had previous graft rejection were 5.5 times more likely to develop diabetes than those who had no such episodes in this study.

Many studies recognized CNIs as a risk factor for developing NODAT because they decrease insulin secretion, increase insulin resistance, and have a direct toxic effect on the pancreatic β-cells.[17,38] This study is in line with these reports, as we found that the development of diabetes was significantly linked to a high trough level of the drug. With tacrolimus trough levels more than 10 ng/mL, the likelihood of diabetes increased, as reported elsewhere.[28,30] High CsA trough level was also associated with an increased risk of diabetes, as reported elsewhere.[39]

As for the management of NODAT, this study showed that most (58.5%) of the patients responded to oral hypoglycemic agents (metformin, gliclazide) and diet and lifestyle modifications. Only 9.3% were managed with insulin, and 16.9% needed a combination of drugs, but 15.3% were treated solely with diet control and lifestyle modification. Almost all the patients were within the target of an HbA1c of less than 7%, as reported in other studies.[8,40]

## Conclusion

There was a high incidence of NODAT in the transplant recipients in the studied setting. Older age, obesity, previous rejection episode, high CNIs trough level, and high steroid dose were risk factors for developing NODAT. Predicting the patients at the highest risk of NODAT based on the tests done before transplantation is of paramount importance, especially in addressing immunosuppressive drug levels according to a patient's immunological status, to decrease the diabetogenic risk of these drugs.

### Author Contributions

Single authorship.

### Compliance with Ethical Principles

Verbal consent was taken from the scientific committee of the transplant center and all data were collected and analyzed nameless. No formal ethical approval was sought.

### Funding and Sponsorship

None

### Conflict of Interest

None declared.

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