New-onset diabetes after transplantation: Risk factors and clinical impact

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Abstract

With improvements in patient and graft survival, increasing attention has been placed on complications that contribute to long-term patient morbidity and mortality. New-onset diabetes after transplantation (NODAT) is a common complication of solid-organ transplantation, and is a strong predictor of graft failure and cardiovascular mortality in the transplant population. Risk factors for NODAT in transplant recipients are similar to those in non-transplant patients, but transplant-specific risk factors such as hepatitis C (HCV) infection, corticosteroids and calcineurin inhibitors play a dominant role in NODAT pathogenesis. Management of NODAT is similar to type 2 diabetes management in the general population. However, adjusting the immunosuppressant regimen to improve glucose tolerance must be weighed against the risk of allograft rejection. Lifestyle modification is currently the strategy with the least risk and the most benefit.

Keywords: Post-transplant diabetes mellitus; Tacrolimus; Cyclosporin; Corticosteroids; Review

Résumé

Diabète de novo post-greffe : facteurs de risque et conséquences cliniques.

Grâce à l’amélioration des survies des patients et des greffons, les complications post-greffe, qui contribuent à la mortalité et à la morbidité des patients à long terme suscitent un intérêt croissant. Le diabète post-greffe est une complication fréquente de la greffe d’organe solide. C’est un important facteur de risque d’insuffisance du greffon et de mortalité cardiovasculaire dans la population des greffés. Les facteurs de risque de diabète post-greffe sont similaires à ceux du diabète de type 2 dans la population générale. Certains facteurs spécifiques à la greffe tels que l’hépatite C, l’utilisation de corticostéroïdes et d’inhibiteurs de calcineurines jouent un rôle important dans la pathogénèse du diabète post-greffe. Le traitement du diabète post-greffe est similaire à celui du diabète de type 2. Cependant, le risque d’un ajustement du traitement immunosuppresseur afin d’améliorer la tolérance au glucose doit être mis en balance avec le risque de rejet. Pour l’instant un traitement fondé sur un changement des habitudes de vie est probablement celui qui a le meilleur rapport bénéfices/risques.

Keywords: Diabète post-greffe ; Immunosuppresseurs ; Tacrolimus ; Cyclosporin ; Corticostéroïdes ; Revue

1. Introduction

Diabetes was first described as a complication of kidney transplantation 40 years ago by Starzl et al. [1]. Since that time, increasing attention has been directed at the burden of post-transplant diabetes in solid-organ transplant (SOT) recipients. It has become clear that new-onset diabetes after transplantation (NODAT) promotes cardiovascular disease and graft failure, as well as death, in kidney and other SOT recipients [2,3]. By definition, NODAT refers to abnormal glucose metabolism detected after transplantation. The term “new-onset diabetes after transplantation” has replaced the older “post-transplant diabetes mellitus” (PTDM) to differentiate new-onset diabetes from diabetes that was present prior to transplantation. The potentially asymptomatic and transient nature of the disease in a context of corticosteroids and immunosuppressant medications explains
why it was only in 2003 that NODAT guidelines were published, with the recommendation to adopt American Diabetes Association (ADA) criteria [3].

Most experts now use the strict definition of diabetes as given by the ADA in an effort to more rigorously define the prevalence and natural history of the disorder. Diabetes mellitus is defined as a fasting plasma glucose (FPG) level $\geq 7.0$ mmol/L or a plasma glucose level $\geq 11.1$ mmol/L, as measured 2 h after a 75-g oral glucose challenge (oral glucose tolerance test [OGTT]), or symptoms of diabetes plus casual plasma glucose concentrations $\geq 11.1$ mmol/L, confirmed by repeat testing on a different day [4]. FPG values between 6.1 and 6.9 mmol/L are considered impaired fasting glucose (IFG), and 2-h plasma glucose values between 7.8 and 11.1 mmol/L are considered impaired glucose tolerance (IGT). IFG and IGT are both important predictors of progression to overt diabetes, and are also risk factors for micro- and macrovascular disease and, therefore, are important categories of patients to identify. However, there is no consensus on the definition of IFG, and some authors and associations, such as the International Diabetes Foundation, recommend using the lower limit of 5.6 mmol/L to identify IFG patients [5].

More recently, Bloom and Crutchlow [6] introduced the term “transplant associated hyperglycaemia” (TAH) to include the entire spectrum of diabetes and prediabetes encountered after organ transplantation. The fact that NODAT contributes considerably to the morbidity and mortality of patients who have undergone SOT has led to greater interest in clarifying the risk factors associated with the disorder. Therefore, the purpose of the present review was to focus on the:

1. pathophysiology, and modifiable and non-modifiable risk factors;
2. clinical implications associated with NODAT after SOT;
3. strategies of prevention and treatment, with special attention paid to kidney and liver transplantation.

As NODAT is a condition that can develop a few years after transplantation, this review also presents the latest recommendations for NODAT screening in transplant patients.

2. Incidence

Historically speaking, the reported incidence of NODAT in SOT recipients has been difficult to determine because of the lack of a standard definition of the condition [6]. However, in a meta-analysis of 19 studies, Montori et al. [7] reported that the incidence of NODAT in patients after any SOT, except pancreas or islet-cell transplants, ranged from 2 to 50% at 1-year post-transplantation. It should be noted that the vast majority of published studies of NODAT involved kidney-transplant patients. In one of the largest epidemiological studies, by Woodward et al. [8], an annual incidence of 6% of new-onset diabetes was observed among wait-listed dialysis patients in the US Renal Data System (USRDS), a rate greater than in the general population. Also, a number of patients who developed NODAT had shown evidence of glucose intolerance or insulin resistance before transplantation. In fact, the same study also showed that the post-kidney-transplant incidence rose considerably, from 6 to 13.2%, in those undergoing peritoneal dialysis (PD), and from 6 to 14.9% in those needing haemodialysis (HD). However, in the second year after transplantation, NODAT incidence decreased in those two groups to 4% and 6%, respectively, which was similar to pretransplant rates. Indeed, the true incremental incidence (subtracting the pretransplant incidence from the observed post-transplant rate) was 8.1% for PD and 9.1% for HD patients [8]. These data suggest that NODAT incidence increases sharply within the first few months post-transplant, reflecting the diabetogenic effects of drugs, sedentarity and weight gain. The study by Woodward et al. [8] was based on a Medicare claims database that, in fact, underestimated the incidence of diabetes and prediabetes. In other studies, Cosio et al. [9] showed a 13% incidence at 1-year post-kidney transplant, while Nam et al. [10] reported a 24% incidence of OGTT-defined diabetes at 1-year post-kidney transplant. The type of diagnostic test used to identify diabetes (FPG in the Cosio et al. study and OGTT in the Nam et al. study) may partly explain the difference in NODAT incidences. In a recent study by Luna et al. [11], a total of 203 de novo kidney-transplant recipients underwent an OGTT 10 weeks after transplantation. Approximately 48% met the criteria for a diagnosis of abnormal glucose metabolism (IFG or IGT in 36% and NODAT in 11.8% of cases). Of all kidney transplants performed since 1995, the incidence of NODAT has increased. Among the reasons proposed is that heavier and older patients are now being transplanted [12].

Following liver transplantation, the reported 1-year NODAT incidence has ranged from 2.5 to 38% [7,13–15]. A study by Valderhaug et al. [16] confirmed that the odds of developing NODAT decreased by more than half between 1994 and 2004. Possible explanations are changes in immunosuppressant therapy, fewer organ rejections and lower doses of steroids.

Montori et al. [7] reported a 12-month cumulative NODAT incidence of 13% among heart recipients, and Heisel et al. [13] found that the incidence ranged from 7 to 26% among heart-transplant recipients after a follow-up of 5 to 11 years. In a study by Ye et al. [17], NODAT was reported in 28.6% of 3763 heart-transplant recipients without pretransplant diabetes. In addition, in a population without preexisting diabetes and cystic fibrosis, the 1- and 5-year NODAT incidence in lung-transplant patients was reported to be 6% and 7%, respectively [18]. However, to our knowledge, as none of the liver, lung or heart transplantation studies used OGTT-based diabetes diagnoses, this could have led to underestimation of the true incidence rates.

3. Risk factors associated with NODAT

As with type 2 diabetes, NODAT may result from a combination of increased insulin resistance and decreased insulin production. The risk factors for NODAT vary across studies and according to the organ being transplanted, although it is accepted that they include the conventional risk factors for type 2 diabetes and those specific to transplant patients. Potential risk may include African-American and Hispanic ethnicity, obesity, age $>$40 years, a family history of diabetes, IGT before transplantation, autosomal-dominant polycystic kidney disease
(ADPKD), genetic factors, and cytomegalovirus (CMV) and HCV infections, which could contribute to a baseline risk of glucose dysregulation. Superimposition of transplant-related factors such as immunosuppressant drugs and weight gain may also lead, in predisposed individuals, to the development of NODAT.

3.1. Age

Considering the influence of advancing age in the general population, it is not surprising that older age is also a risk factor for NODAT. In kidney transplantation, using a multivariate Cox model, age correlated with a more rapid increase in the number of NODAT cases (risk ratio [RR]: 2.2 versus patients either under or over 45 years of age; \( P < 0.0001 \)) [12].

3.2. Ethnicity

NODAT is more common in African-Americans and Hispanics than in white and Asian patients. Sumrani et al. [19] reported an overall 3.6% incidence of NODAT with kidney transplants, but rates were 4.8% in Asians, 19.8% in African-Americans, and 21.3% in Hispanics. However, as the data on African-American and Hispanic ethnicities were self-reported in the majority of these studies, and largely from the United States, it is unclear if other ethnicities and those in different countries would also be associated with the same increased risk of NODAT.

3.3. Body weight

As obesity is a well-known risk factor for type 2 diabetes, it is not surprising that the risk of NODAT increases with increased body mass index (BMI). Substantial weight gain is typical after transplantation within the first 2 years, and this could be contributing to the development of insulin resistance [20–23]. Cosio et al. [12] demonstrated that the risk of developing NODAT increased by a factor of 1.4 for every 10 kg of increased body weight in kidney-transplant patients who weighed >60 kg. Weight gain may be explained by glucocorticoid drugs, but it could also be due to appetite recovery once the chronic disease state of organ failure has been corrected. On the other hand, a study by Marrero et al. [24] showed that the pretransplant weight, but not weight gain, was associated with the development of NODAT at 1-year post-transplant.

3.4. Autosomal-dominant polycystic kidney disease (ADPKD)

Two matched historical cohort studies have suggested that ADPKD may be a risk factor for NODAT [25,26]. Also, the incidence of NODAT in ADPKD patients increased in a retrospective study comparing ADPKD and non-ADPKD groups (13.4% versus 5.2%, respectively) [27]. In a multivariate analysis, ADPKD was a strong risk factor for the development of NODAT (OR: 2.41; \( P = 0.035 \), after correction for covariates); the median time to onset of NODAT in the ADPKD group was 53 days compared with 250 days in the non-ADPKD group [27]. However, the underlying mechanism was unclear. Interestingly, one study showed that ADPKD patients with normal kidney function were associated with increased insulin resistance [28].

3.5. Genetic factors

NODAT may reflect a genetic predisposition to diabetes influenced by multiple environmental factors. In kidney-transplant patients, Sumrani et al. [29] found that 26% of patients with a family history of diabetes developed NODAT, while only 14% of patients without a family history of diabetes did so. Such an association suggests that genetic variants linked to type 2 diabetes are also most likely associated with NODAT. A recent pilot study demonstrated an increased risk of NODAT among patients with a positive family history [30]. In that study, a positive, but not significant, association of eight known type-2 diabetes-associated genetic polymorphisms were predictive of NODAT, suggesting a genetic predisposition to the disorder.

However, only a few of the genetic polymorphisms associated with type 2 diabetes (such as SLC30A8, TCF7L2, IL-6 promoter polymorphism −174, and calpain-10) have been studied in detail in transplant patients. Two studies from one centre examined the genetic influence of polymorphisms in the development of NODAT in a renal-transplant cohort [31,32]. Zinc is believed to be an important modulator of insulin secretion [33]. The R325W (rs13266634) non-synonymous polymorphism in the islet-specific zinc transporter protein gene SLC30A8 has been reported to be associated with type 2 diabetes and also possibly with a defect in insulin secretion [34,35].

One study by Kang et al. [32] investigated the association between genetic variations in the SLC30A8 gene and NODAT in renal-transplant recipients. A total of 624 unrelated renal-allograft recipients with no previously diagnosed diabetes were enrolled in the study. The prevalence of NODAT was 33.8% in patients with the R/R genotype, 26.8% in those with the R/W genotype, and 19.8% in those with the W/W genotype. There was a strong association between the number of W alleles and NODAT risk reduction (trend \( P = 0.007 \)). Patients with at least one W allele showed a lower risk of NODAT compared with those with the R/R genotype (R/W RR: 0.78, \( P = 0.126 \); W/W RR: 0.52, \( P = 0.007 \)). The effect of the SLC30A8 genotype remained significant even after adjusting for age, gender, body weight gain, and type of immunosuppressant (R/W hazard ratio [HR]: 0.77, \( P = 0.114 \); W/W HR: 0.58, \( P = 0.026 \)). The authors concluded that the SLC30A8 rs13266634 gene variation was associated with protection against the development of NODAT in renal-allograft recipients.

TCF7L2, a new type 2 diabetes susceptibility gene, can lead up to a twofold increase in the risk of diabetes [36–38]. In addition, in another study, Kang et al. [31] suggested that the TCF7L2 rs7903146 genetic variation was significantly associated with an increased risk of developing NODAT in renal-allograft recipients.

The IL-6 gene promoter polymorphism at position −174 (G→C) appears to predict type 2 diabetes [39], so a study by Bamoulid et al. [40] tested whether the IL-6 gene promoter polymorphism at position −174 can predict NODAT. They found...
that the risk of NODAT was significantly higher in homozygous (GG) wild-type patients than in homozygous (CC) mutant patients, independent of age, BMI, and ADPKD (HR: 0.15 in the CC group, 95% CI: 0.03–0.99). In patients without NODAT, insulin sensitivity, as evaluated by the homoeostatic model assessment for insulin resistance (HOMA-IR) index, was lower in homozygous GG patients than in homozygous CC patients, suggesting a role for IL-6 in insulin resistance.

In addition, a study by Kurzawski et al. [41] found a significant association between NODAT and the calpain-10 gene polymorphism, an association previously shown in type 2 diabetes.

3.6. Hepatitis C virus (HCV) infection

In the general population, diabetes is reported to be more common in patients with hepatitis C than other types of liver disease [42,43]. Several studies have also reported an increased prevalence of NODAT after kidney and liver transplantation in patients with HCV [44]. In a meta-analysis by Fabrizi et al. [45], HCV seropositive status was associated with a 3.75-fold increased risk of NODAT in kidney transplantation. Postulated mechanisms included a direct cytopathic effect on beta cells, increased insulin resistance mediated by post-insulin-receptor defects, and decreased hepatic glucose uptake and glycogenesis [14,45]. In a study by Baid et al. [14] in liver-transplant patients, the prevalence of pretransplant diabetes was similar in patients with (+) and without (−) HCV infection, whereas the prevalence of NODAT was significantly higher in the HCV+ than HCV− patients (64% versus 28%, respectively). Using multivariate analyses, HCV infection was found to be an independent risk factor for the development of NODAT (HR: 2.5, \( P = 0.001 \)). Delgado-Borrego et al. [46] showed that, in 39 HCV+ and 60 HCV− orthotopic liver-transplant recipients, HCV infection was associated with a 35% increase in insulin resistance. Moreover, there was no difference in beta-cell function or hepatic insulin extraction between the HCV+ and HCV− groups. The presence of HCV infection and a 10-fold increase in HCV RNA were associated with increases of 62% and 8%, respectively, in insulin resistance. In another study of kidney-transplant, candidates infected with HCV, pretransplant treatment with interferon reduced the risk of NODAT, suggesting that successful pretransplant treatment of hepatitis C may potentially treat NODAT [47]. In patients infected with HCV and treated with interferon, a sustained viral response caused a two-thirds reduction in the risk of diabetes, which was also seen in the subgroup with cirrhosis, again suggesting that pretransplant treatment of HCV, wherever feasible, might also reduce the risk of developing NODAT [48].

3.7. CMV infection

CMV has also been incriminated as a risk factor for NODAT in kidney- and liver-transplant patients, and several studies suggest that asymptomatic CMV infection and CMV disease are independent risk factors of NODAT. Postulated mechanisms include impaired insulin secretion and the CMV-induced release of proinflammatory cytokines potentially leading to apoptosis and beta-cell dysfunction [49–51]. In kidney-transplant recipients, normal glucose tolerance was achieved in two patients with CMV-induced NODAT after an eight-week therapeutic course of oral valganciclovir [52].

3.8. Immunosuppression

Some immunosuppressant drugs have significant effects on glucose metabolism and, therefore, have a role of paramount importance in the pathophysiology of NODAT (Fig. 1).

4. Corticosteroids

Glucose intolerance is a well-known complication of corticosteroid therapy. These compounds induce a state of insulin resistance, and also lead to increased hepatic gluconeogenesis [53]. The diabetogenic effects appear to be dose-related [54]. In recent years, given the progressive reduction of steroid dosages in transplantation, a reduction of NODAT incidence has been seen [13,55]. Several studies have demonstrated short-term improvements in glucose intolerance and even a cure of diabetes with corticosteroid dose reduction [56–59]. However, even after improvements in glucose intolerance, patients can have later relapses, reflecting their genetic predisposition to
diabetes. Thus, whether elimination of chronic low-dose steroids improves glucose metabolism remains controversial. The effect of complete corticosteroid avoidance or its early withdrawal on the development of NODAT has been described in the Astellas Corticosteroid Withdrawal study, the FREEDOM trial and the CARMEN study [60–62]. In each of these studies, there were no statistically significant differences in the overall incidence of NODAT in steroid-free versus steroid-treated patients, although there was a trend towards a reduced need for insulin treatment. However, Midvedt et al. [63] showed that lowering daily prednisolone to 5 mg/day had beneficial effects on insulin action after renal transplantation, although complete withdrawal of 5-mg prednisolone may have no significant effects on insulin sensitivity. Furthermore, decreasing the diabetogenic effect of immunosuppressant therapy must be weighed against the risk of allograft rejection, which would require restitution of steroid therapy. Pulsed high-dose steroids for acute rejection also appear to be a strong risk factor for NODAT [64].

5. Calcineurin inhibitors

Direct evidence of the diabetogenic effect of calcineurin inhibitors (CNIs) comes from studies in animals [65–67]. Cyclosporine administration, for example, is reported to be associated with decreased pancreatic insulin content and decreased beta-cell volume [65–67], whereas pancreatic islet-cell toxicity in dogs and impaired release of insulin from cultured human pancreatic islet cells have been reported with cyclosporine [68,69]. Cyclosporine might also induce a state of insulin resistance as high levels of insulin in rats [70] and of C-peptide in humans [71] have been reported.

Tacrolimus has been reported to cause NODAT through decreased insulin secretion of pancreatic beta cells in animal models with inhibition of mRNA transcription of insulin [72–74]. Human studies have also suggested that insulin resistance might be implicated [75,76].

Diabetogenicity is particularly enhanced by tacrolimus compared with cyclosporine in kidney [2,8,77,78], liver [79] and heart [80] transplantation. Kasikse et al. [2] found that the incidence of NODAT was 70% higher in the first 2 years post-transplant with versus without tacrolimus treatment. In the DIRECT study, a randomized trial of kidney-transplant recipients comparing cyclosporine- and tacrolimus-based regimens in addition to basiliximab, mycophenolic acid, and steroids, the incidence of NODAT or IFG was significantly higher in the tacrolimus group (33.6% versus 26% in the cyclosporine group) [61].

Hypomagnesaemia is a common problem in the post-transplantation period and is particularly associated with CNI use [81]. It has also been suggested that hypomagnesaemia is associated with decreased insulin sensitivity [82]. Observational and interventional studies in healthy subjects and diabetic patients have shown that higher magnesium intakes can reduce the risk of IGT [83–88]. In a recent retrospective study, Van Laecke et al. [89] showed that hypomagnesaemia with any immunosuppressant drug regimen was an independent predictor of NODAT in renal-transplant patients. After adjusting for magnesium levels, the association between CNI use and NODAT disappeared, suggesting that the diabetogenic effect of these drugs could be at least partly due to hypomagnesaemia [89]. Further studies are needed to address the impact of magnesium supplementation in the prevention of NODAT.

6. Sirolimus

Sirolimus has so far not been well studied, but it is increasingly being recognized as a possible diabetogenic, as several observational studies have found that sirolimus use was associated with an increased incidence of NODAT [90–92]. Johnston et al. [90], drawing from the USRDS, reported in a study of 16,861 patients that, comparing those treated with cyclosporine and either mycophenolate mofetil (MMF) or azathioprine, the sirolimus-treated patients had an increased risk of NODAT whether taken in combination with cyclosporine (adjusted HR: 1.61, 95% CI: 1.36–1.90), tacrolimus (HR: 1.66; 95% CI: 1.42–1.93) or an antimetabolite (HR: 1.36, 95% CI: 1.09–1.69). On the other hand, some multicentre trials of sirolimus failed to demonstrate any association between sirolimus and NODAT [93–95]. However, the controls in these studies received corticosteroids and CNIs and, therefore, any potential association between sirolimus and NODAT may have been missed. Pathogenically speaking, sirolimus promotes hepatic insulin resistance [96] and beta-cell toxicity [97–99]. The mechanisms that explain why sirolimus may lead to NODAT include impaired insulin-mediated suppression of hepatic glucose production [96], and insulin resistance due to ectopic triglyceride deposition or direct beta-cell toxicity [97,98]. In contrast, there is no evidence that either azathioprine or MMF causes NODAT [2,100].

7. Anti-CD25 monoclonal antibodies

Basiliximab is an antibody directed against an interleukin (IL)–2 receptor (CD25) that also suppresses CD25 CD4 T lymphocytes. Despite smaller dosages of steroids and cyclosporine, non-diabetic kidney-transplant recipients, given basiliximab as an induction therapy, experienced an increased incidence of early (10 weeks after kidney transplantation) NODAT, IFG or IGT [101]. This trend had been previously suggested in a 2007 study by Bayes et al. [102], in which patients treated with anti-CD25 monoclonal antibodies had a greater incidence of NODAT. Suppression of regulatory T lymphocytes may have a negative impact on beta cells [103], and it may also be that basiliximab can interfere with beta cells through its effects on T lymphocytes. However, the underlying mechanism remains unknown, and further studies are needed to confirm these findings.

8. NODAT, transplant-associated hyperglycaemia (TAH) and post-transplant outcomes

In the general population, the link between diabetes and cardiovascular disease is strong [104], and has been explained by multiple mechanisms, such as the detrimental effects of hyperglycaemia [105], dyslipidaemia [106], hypertension [107], and
insulin resistance \[108\], or the combination \[109\] of all of these risk factors, on vessels. In the transplant setting, NODAT is recognized as a serious complication, but is still the subject of ongoing debate. Clinical studies evaluating graft and patient survival after SOT have yielded variable results, and are summarized in Table 1.

8.1. Kidney-patient survival

A number of studies indicate that NODAT is associated with reduced patient survival \[2,110,111\]. Using the Kaplan–Meier method, Revanur et al. \[111\] demonstrated a statistically significant difference in patient survival between those who developed NODAT and those who did not. The mean survival of patients with NODAT, insulin-dependent diabetes, non-insulin-dependent diabetes and coexistent diabetes was 10.3, 8.4, 3.7 and 8.6 years, respectively. In contrast, patients without NODAT or preexisting diabetes had a mean survival of 12.8 years. The 10-year patient survival in non-diabetics was 75% compared with 49% in those with NODAT and 39% in those with insulin-dependent diabetes \[111\]. In addition, the mortality rate did not increase in NODAT patients until 8 years post-transplant, which is consistent with the time lag between diabetes onset and cardiovascular complications. This observation reinforces the importance of addressing cardiovascular risk factors in patients with NODAT.

In the study by Kasiske et al. \[2\], the development of NODAT, regardless of aetiology, was associated with an 87% higher rate of mortality in US transplant recipients. Cosio et al. \[110\], using Cox regression, found that NODAT correlated with reduced patient survival (HR). Although part of the increased mortality with hyperglycaemia can be attributed to a greater infection risk \[2,112\], more and more studies now point to an increased cardiovascular disease (CVD) risk \[9,113,114\]. CVD is now the main cause (1.88, 95% CI: 1.07–3.3) of death with a functioning graft. Matas et al. \[112\] and Meier-Kriesche et al. \[115\] showed that CVD explained 30.1–47.6% of deaths, while sepsis explained 11.7–18.6% and malignancy explained 10.1–11.6% of deaths. Lentine et al. \[114\], using the USRDS registry, demonstrated that both preexisting diabetes (HR: 1.13; \(P = 0.05\)) and NODAT (HR: 1.6; \(P < 0.0001\)) were independent risk factors of myocardial infarction within the first 36 months of transplantation. On the other hand, in the study by Hjelmesaeth et al. \[116\], NODAT was a predictor of major cardiac events, but not of all-cause mortality, during the first 8 years after renal transplantation (HR: 3.27, 95% CI: 1.22–8.8; \(P = 0.019\)).

8.2. Kidney-graft survival

NODAT adversely affects graft survival, as it is associated with a 63% increase in kidney graft failure \[2\]. Similarly, Roth et al. \[117\] reported that a kidney-transplant patient with NODAT had a significantly lower rate of graft survival at 4 years compared with non-diabetic subjects (54% versus 82%, respectively). The 12-year graft survival in diabetic patients was 48% compared with 70% in control patients (\(P = 0.04\)), and Cox regression analysis revealed that diabetes was a significant predictor of graft loss (RR: 3.72; \(P = 0.04\), independent of age,
gender, and race. Renal function at 5 years, as assessed by serum creatinine levels, was poorer in diabetic patients compared with controls (2.9 ± 2.6 mg/dL versus 2.0 ± 0.07 mg/dL, respectively) [118]. Several authors have compared the impact of acute rejection and NODAT on kidney-graft survival [119,120] and, not surprisingly, the worst outcome was in those with both acute rejection and NODAT. Interestingly, in the study by Matas et al. [120], graft survival was identical in patients with NODAT and no acute rejection compared with those with neither acute rejection nor NODAT for up to 9 years post-transplant. After 9 years, graft survival began to decrease in the NODAT group, which is consistent with the time lag between the onset of diabetes and the development of complications. In the same study, death-censored graft survival was also identical in patients without acute rejection and with or without NODAT, thereby confirming the hypothesis that differences in graft survival might be explained by cardiovascular death despite functioning grafts. This hypothesis was also suggested in the study by Cole et al. [119], in which NODAT was associated with increased risk of death with a functioning graft, but not with death-censored graft loss.

8.3. Liver-patient survival

For liver transplantation, the data are scarce and contradictory. The overall mortality risk was increased in patients with NODAT in a study by Baid et al. [14] (HR: 3.67; P < 0.0001). In a study by John and Thuluvath [121], rates of cardiovascular or neurological events, infectious diseases, and acute rejection were increased in NODAT, but no differences were noted in mortality after 5 years.

8.4. Liver-graft survival

There is now growing recognition that NODAT confers an increased risk of post-transplant fibrosis in patients transplanted for HCV infection, and the recurrence of such infection following liver transplantation is of major importance, as it is seen in nearly 100% of cases and brings a 20% greater risk of cirrhosis after 5 years [122]. NODAT has been reported to be one of the most important variables in the severity of HCV recurrence and to work in synergy with age. In addition, the combination of receiving a liver from an older donor (>55 years) and having NODAT is associated to an 8.4-fold increased risk of progression to severe fibrosis [123]. Furthermore, Veldt et al. [124] showed that patients with diabetes and prediabetes (with an elevated HOMA-IR) are at increased risk for rapid fibrosis progression after liver transplantation for hepatitis. Taken altogether, it appears that NODAT confers an increased risk of post-transplant fibrosis in liver-transplant patients.

8.5. Heart and lung transplants

In lung-transplant recipients, 5-year mortality rates are 27% higher in patients with either NODAT or preexisting diabetes [125]. Actuarial survival rates are shown to be decreased in heart transplantation, while vascular intima–media thickness is reported to be increased [126]. However, in a study by Bedanova et al. [127], although heart-transplant patients with NODAT had an increased risk of acute rejection, there was no effect on their long-term survival [127].

9. Diagnosis

Only a few studies have investigated pretransplant baseline evaluations of NODAT risk, and systematic pre- and post-transplant OGTTs were not performed in these studies, making it difficult to arrive at evidence-based conclusions regarding pretransplantation evaluations. Ramesh Prasad et al. [128] performed a case-control study of non-diabetic kidney recipients who had received a living-donor allograft, and had undergone a 75-g OGTT and random blood glucose (RBG) measurement prior to transplantation. In patients with no pretransplant glucose abnormalities, NODAT risk at six months post-transplant was >25% for those with a pretransplant RBG > 6.0 mmol/L and 50% if RBG levels were >7.2 mmol/L. Also, if the RBG was <5.0 mmol/L pretransplant, the risk of NODAT was <10%.

In a retrospective study by Joss et al. [129], risk factors for the development of NODAT were older age, heavier weight at time of transplantation, higher mean pretransplant random plasma glucose concentrations (HR: 1.54, 95% CI: 1.14–2.08; P < 0.01), higher plasma glucose within the first seven days post-transplant (HR: 1.27, 95% CI: 1.09–1.47; P < 0.01) and use of tacrolimus (HR: 3.70, 95% CI: 1.61–8.46; P < 0.01).

Iida et al. [130] performed pretransplant OGTTs in tacrolimus-treated, living-donor kidney-transplant patients with no known pretransplant diabetes. There were no statistically significant differences between patients with normal pretransplant OGTTs and those with IFG or IGT, although the odds ratios (OR) tended to be higher in those with IGT/IGT. Although OGTT did not predict NODAT, the authors concluded that IGT appeared to be a threshold influencing NODAT. Patients with diabetes according to their pretransplant OGTT had the highest risk of NODAT. However, the problem with this study was the lack of post-transplant OGTTs, and that NODAT was defined as morning fasting blood glucose or RBG > 11.1 mmol/L on more than one occasion, thus underestimating the incidence of NODAT [130,131].

In spite of the lack of specific studies on this topic, the 2004 updated International Consensus Guidelines for NODAT suggest that a pretransplant baseline evaluation should include a complete medical and family history, and that FPG should be tested regularly while on the waiting list and that an OGTT be done in patients with normal FPG [132]. This recommendation is based on the fact that an OGTT is a better predictor of increased cardiovascular risk and mortality than FPG, especially in patients with IGT [131]. For this reason, we also agree that patients with a normal FPG should have an OGTT, whereas patients with an abnormal FPG or abnormal OGTT should be counselled for lifestyle modifications (weight, diet, exercise) while awaiting their transplant. If applicable, HCV infection treatment should be considered in patients with any glucose anomaly. In addition, given the increased risk of NODAT, the immunosuppressant regimen should be chosen by weighing the
risk of NODAT against the risk of organ dysfunction or acute rejection.

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, it is recommended that all non-diabetic kidney-transplant recipients be screened by FPG, OGTT, and/or HbA1c at least once a week for four weeks, every three months for 1 year and once a year thereafter (all recommendation level 2D). It is also suggested to screen for NODAT with FPG, OGTT, and/or HbA1c after starting, or substantially increasing the dosages of, CNIs, mammalian target of rapamycin (mTOR) inhibitors or corticosteroids (recommendation level 2D) [133]. It is not uncommon to observe, even with small doses of steroids, normal FPG and a late-afternoon or early-evening peak in blood glucose concentration. In a study by Valderhaug et al. [134], an OGTT done 10 weeks after transplantation in 1571 kidney-transplant patients without pretransplant diabetes found NODAT in 14%. Of these, 51% were identified by OGTT only, 17% by fasting glucose, and 32% by OGTT and FPG together. As OGTTs are cumbersome, the purpose of the study was to assess the accuracy of FPG and HbA1c in selecting patients who should undergo a diagnostic OGTT 10 weeks after renal transplantation. Receiver operating characteristic (ROC) curves with a sensitivity level of 80% revealed that patients with an FPG of 5.3–6.9 mmol/L or an HbA1c ≥ 5.8% or, alternatively, an FPG ≥ 5.0 mmol/L combined with an HbA1c ≥ 5.7% in the early post-transplant period, should undergo an OGTT for evaluation of NODAT. Therefore, it should be taken into account that normal FPG levels are probably lower in steroid-treated patients and should not be the only screening test for NODAT. HbA1c should also be part of the screening tests to evaluate who should undergo an OGTT.

10. Management

Management of NODAT includes pretransplant identification of high-risk patients, regular screening of all patients, consideration of immunosuppressant medication modification, and treatment of diabetes [3]. The goals of managing NODAT are to prevent the symptoms of uncontrolled hyperglycaemia and the vascular complications associated with diabetes. The management strategy for NODAT has mostly been extrapolated from diabetic populations without SOT and follows a stepwise approach. Self-monitoring of blood glucose is an essential component in the management of diet, hypoglycaemia or insulin-treated diabetes. HbA1c should be measured every three months, aiming for a target value <7% [3,135], but avoiding ≤6% if hypoglycaemic reactions occur [133].

Modifiable risk factors also need to be addressed. In such a population, obesity and immunosuppressant drugs are key contributors. Where NODAT or IGT/IFG have been diagnosed, lifestyle changes should be emphasized, including appropriate diet, weight loss if necessary, and increased physical activity to delay and/or prevent diabetes or to improve glucose control [136]. In kidney transplantation, Sharif et al. [137] showed that lifestyle modifications can benefit high-risk transplant recipients with glucose intolerance, and can attenuate and, in some cases, even reverse the development of diabetes or glycaemic dysregulation.

A recent meta-analysis by Knight et al. [138] reviewed the data for steroid avoidance or withdrawal after renal transplantation and concluded that it is associated with a small increase in the risk of acute rejection (RR: 1.56, 95% CI: 1.31–1.87) in comparison with protocols including steroids. However, the effect on graft function was small, with no effect on graft or patient survival. With steroid-avoidance protocols, several benefits were observed in cardiovascular risk profiles, including reduced incidences of hypertension, NODAT (RR: 0.64, 95% CI: 0.5–0.83), and hypercholesterolaemia.

The options for drug treatment of NODAT are multiple, although it must be borne in mind that safety and efficacy data for antidiabetic treatments for transplant patients are lacking. Glucocorticoid-induced diabetes is characterized by normal or slightly increased fasting blood sugars, as well as increased postprandial blood glucose and insulin resistance [139].

10.1. Oral hypoglycaemic agents

The traditional approach of using oral hypoglycaemic agents as first-line drugs is recommended. However, in transplant cases, when choosing a drug treatment, any potential interactions with the immunosuppressant regimen, lower glomerular filtration rates and transplant-associated osteoporosis have to be considered (Table 2). This means that, in transplant recipients who have impaired renal function, metformin should be used with caution. According to the Compendium of Pharmaceuticals and Specialties, renal impairment (serum creatinine > 136 μmol/L in men and >124 μmol/L in women) or abnormal creatinine clearance (<60 mL/min) are contraindications for the use of metformin because of the small possibility of an increased risk of lactic acidosis [140]. However, metformin therapy has also been associated with major benefits related to macrovascular endpoints that outweigh the minimal risk of lactic acidosis. Thus, in transplant patients with stable kidney function >45 mL/min, metformin can be used as long as kidney function is checked regularly. Also, as suggested by McCormack et al. [141], in patients with creatinine clearance <60 mL/min, reducing the maximum dose by about 50% would be a reasonable approach (Table 2).
In patients with impaired renal function, glipizide, glimepiride, and gliclazide [142] should be preferred over glyburide and the first-generation sulphonylureas [142]. Meglitinides, such as nateglinide and repaglinide, are not contraindicated in patients with renal or liver failure, and also appear to have no adverse drug interactions. Repaglinide has been used with good results in kidney-transplant patients [143,144]. However, it must be remembered that cyclosporine raises plasma concentrations of repaglinide and, thus, may enhance the blood glucose-lowering effect of repaglinide and increase the risk of hypoglycaemia [145]. Alpha-glucosidase inhibitors, such as acarbose, decrease both carbohydrate absorption and postprandial glucose levels. However, they are not particularly powerful and, although they have gastrointestinal side-effects, the risk of hypoglycaemia and drug interactions is very low. These agents should be avoided in those with creatinine clearance <25 mL/min/1.73 m² [146].

Thiazolidinediones (TZDs) are peroxisome proliferator-activated receptor agonists that increase peripheral glucose uptake and suppress hepatic glucose production. No interactions have been reported between CNIs and either rosiglitazone or pioglitazone [147,148]. However, these drugs are often associated with oedema, and are contraindicated in those with decreased left ventricular ejection. Furthermore, there is a growing body of evidence suggesting that TZDs decrease bone density and so increase the risk of fractures, particularly in women [149]. They should, therefore, be used with caution in transplant cases. However, a review of TZD use in NODAT suggested that TZDs can be used as long as special attention is paid to any potential side-effects that may be more common in such a population [150].

Exenatide is a glucagon-like peptide 1 (GLP-1) analogue that is administered subcutaneously. It is approved in the US by its Food and Drug Administration (FDA) for the treatment of type 2 diabetes that is not sufficiently controlled by oral agents. However, the use of GLP-1 agonists has yet to be tested in transplant recipients. Similarly, dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin) may also be used although, as yet, no data are available in transplant recipients. In one study, the area under the curve (AUC) and Cmax of sitagliptin were increased by 29% and 68%, respectively, in healthy subjects given a single 100-mg dose of sitagliptin together with a single 600-mg dose of cyclosporine. These changes were not considered clinically significant and, therefore, dose adjustment is not recommended when combining cyclosporine and sitagliptin. However, the combination has not been specifically studied in transplant patients [151].

The metabolic syndrome has also proved to be a strong risk factor for graft failure in kidney transplantation and so must be addressed [152]. Aggressive management of cardiovascular risk factors such as hypertension and dyslipidaemia is necessary. However, there are only a few randomized controlled trials examining the safety and efficacy of strategies to reduce CVD in transplant recipients, and it is unclear whether clinicians are prepared to apply guidelines aimed at the general population to transplant recipients. Patients with NODAT who are at increased CVD risk should also be prescribed aspirin as primary and secondary prevention of CVD, albeit while carefully assessing the risks (bleeding) and benefits (ischaemic events), although the evidence that the benefits of aspirin outweigh the harm is not strong in transplant cases.

Table 2
Hypoglycaemic agents and their interactions in solid-organ transplantation.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Interactions</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation sulphonylureas [142,157]</td>
<td>Glipizide</td>
<td>↑ CsA levels</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>Gliclazide</td>
<td>↑ CsA levels</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>Glyburide (glibenclamide)</td>
<td>↑ CsA levels</td>
<td>Avoid if GFR is &lt;50 mL/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>Glimepiride</td>
<td>↑ CsA levels</td>
<td>Start at 1 mg/day</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose</td>
<td></td>
<td>Avoid if GFR is &lt;25 mL/min/1.73 m² [146]</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td></td>
<td>According to CPS: contraindicated if SCR is &gt;136 μmol/L in men and &gt;124 μmol/L in women [146]; avoid if GFR is &lt;45 mL/min/1.73 m²; ↓ 50% if GFR is 45–60 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>↑ repaglinide levels with CsA [145]</td>
<td>Start with 0.5 mg with meals and titrate carefully if renal function is impaired</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td></td>
<td>Titrated carefully if renal function is impaired</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Pioglitazone</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td></td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Incretin mimetics</td>
<td>Exenatide</td>
<td></td>
<td>Avoid if GFR is &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>Pramlintide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin</td>
<td>Hepatically metabolized by CYP3A4</td>
<td>↓ 50% if GFR is 30–50 mL/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td></td>
<td>↓ 75% if GFR is &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td></td>
<td>Vildagliptin</td>
<td></td>
<td>Avoid if advanced CKD on haemodialysis</td>
</tr>
</tbody>
</table>

CsA: cyclosporin A; GFR: glomerular filtration rate; CPS: Compendium of Pharmaceuticals and Specialties; SCr: serum creatinine; CKD: chronic kidney disease.
10.2. Insulin

Many patients eventually need to take insulin. Even with only small daily doses of steroids taken in the morning, a late-afternoon or early-evening peak in blood glucose concentration may be seen. Medium-acting neutral protamine Hagedorn (NPH) insulin in the morning is especially useful for controlling late-afternoon or early-evening glucose levels. If postprandial glucose is not controlled with this strategy, then the short-acting insulin aspart (Novolog) premeal or lispro (Humalog) can be added to the regimen. If morning blood glucose is increased, then medium-acting NPH, glargine or detemir can be given in addition at night [153].

11. Conclusion

As long-term post-transplant survival continues to improve, chronic complications such as NODAT are becoming the obstacle to optimal survival and can lead to increased CVD mortality. For this reason, all efforts should be directed towards preventing this complication by: (1) identifying patients at risk of developing the disease and introducing interventions on modifiable risk factors such as obesity, immunosuppressant regimen and HCV infection; (2) performing early and repetitive screening for the disease; (3) aggressively treating patients with NODAT; and (4) aggressively treating other cardiovascular risk factors. In future, further research needs to focus on the effects of NODAT prevention and treatment on hard endpoints such as mortality, graft survival, and cardiovascular events.

Conflict of interest statement

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