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New-Onset Diabetes after Transplant (NODAT)

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Abstract

New onset diabetes mellitus after transplantation (NODAT) is a well known complication following solid organ transplantation and has been reported to occur in 4% to 25% of renal transplant recipients, 2.5% to 25% of liver transplant recipients, hepatitis C virus (HCV) infection between 40% and 60% and 2% to 53% of all solid organ transplants. This variation in the reported incidence may be because of lack of a universal agreement on the definition of NODAT, the duration of follow-up, and the presence of modifiable and non-modifiable risks factors. Moreover, reduced patient survival and accelerated graft loss have been reported with NODAT. So in this article I tried to presents an overview of the literature on the current diagnostic criteria for NODAT and discuss suggested risk factors for the development of NODAT, its potential pathogenic mechanisms, and its impact on post-transplant outcomes after solid organ transplantation.

Keywords: NODAT; Diabetes; Transplantation

Introduction

New-onset diabetes after transplantation (NODAT) refers to diabetes that occurs in previously nondiabetic persons after solid-organ transplantation as well as bone marrow and hematopoietic stem cells [1,2]. It is also called as Secondary type of diabetes mellitus since it develops secondary to use of immunosuppressants. Since In Nepal also the number of transplants patients is increasing, so it is necessary to known in details about NODAT.

Definition of NODAT

The concept of NODAT was not well known for last fifty years and was called as post transplantation diabetes mellitus. The most commonly used clinical definition was the requirement of insulin post transplantation (minimum of 30 days). Now International Consensus Guidelines on NODAT 2003 recommended that the diagnosis of NODAT should be based on the American Diabetes Association (ADA) criteria for type 2 diabetes [3,4], which are as follows:

1. Fasting plasma glucose (FPG) =7.0 mmol / L (126 mg / dL) with no calorie intake for at least 8 hours and / or
2. A 2 hour plasma glucose during an OGTT (2 hr PG) =11.1mmol / L (200 mg / dL), or
3. A casual plasma glucose =11.1 mmol / L (200 mg / dL), on 3 or more occasions.

HbA1C assay is not used because end stage renal disease (ESRD) patients and newly transplanted kidney patients are frequently associated with anemia (due to surgical blood loss, iron deficiency, immunosuppressive drugs, graft dysfunction, and abrupt discontinuation of erythropoietin administration) which leads to spurious A1C results [5,6].

Natural History and Incidence of NODAT

The first cases of NODAT were described in 1964 after a liver transplant by Thomas Starz [7] , which occurs mainly during the first 6 months post transplantation during treatment with high doses of immunosuppressant. After 6 months, the annual incidence of diabetes is similar to that observed in patients on the waiting list i.e., 6% per year [7].

The incidence of NODAT varies among the recipients of different organ transplants and over different post transplant intervals as shown in table1 below. The most accurate incidence of NODAT under calcineurin inhibitor (CNI) therapy according to the prospective study of Vincenti et al. [8] 20.5% within the first 6 months post renal transplantation. In some patients the risk of developing NODAT has been seen up to 15 years after transplantation [9].

Risk Factors of NODAT

The risk factors of NODAT are classified as *non-modifiable, modifiable or potentially modifiable*; the former helps to facilitate the identification of high risk individuals, and the latter two helps to optimize the management of NODAT.

Non Modifiable Risk Factors

Age

As per United States Renal Data System (USRDS) and the Organ Procurement Transplant Network/United Network of Organ Sharing (OPTN/UNOS) there was 90% increase of relative risk (RR) in renal transplant patients aged 45–59 yrs and a 160% increase in ≥ 60 years of age (versus 18-44 years) [11]. So, older age is a strong independent risk factor of NODAT.

Types of Transplantation	Overall Incidence %
New onset diabetes after transplantation [10]	2-53%
Renal transplant [11]	4-25%
Liver transplant [12]	2.5-25%
Heart transplant [13]	4-40%
Lung transplant [14]	30-35%
HCV infected liver transplant [15]	40-60%

Table1: Overall incidence of NODAT among various types of Transplants Recipients

Race/ethnicity

There has been little literature suggesting that African Americans and Hispanics are at increased risk for developing NODAT compared to whites. The RR of NODAT is increased by 32–68% in black patients and by 35% in Hispanic patients in comparison with white patients [16].

Family history of diabetes mellitus

There is strong evidence suggesting that individuals with a family history of diabetes among first-degree relatives have sevenfold increased risk of developing NODAT [10].

Other non-modifiable risk factors include

1. Recipient male gender
2. Presence of certain human leukocyte antigens (HLA) such as HLA A30, B27, and B42
3. Increasing HLA mismatches
4. Donor-recipient (DR) mismatch; deceased donor kidneys; male donor; and acute rejection history [17].
5. Polycystic kidney disease has been suggested to confer an increased risk of developing diabetes after renal transplantation in some studies but not in others [18–21].

Modifiable Risk Factors

Obesity

Overweight or obese patients have a higher risk of developing NODAT, with an RR of 1.4 for patients with a BMI between 25 and 30 kg/m^2 and an RR of 1.7–1.8 for patients with a BMI >30 kg/m^2 [22]. The pattern of body fat distribution especially intra-abdominal fat or waist-to-hip ratio have been found to be important risk factors for NODAT than total body weight or BMI [17].

Hypertriglyceridemia/hypertension

Multivariate analysis has shown that among all the pre-transplant metabolic syndrome components, only low density lipoprotein was independently associated with the development of NODAT [23].

Proteinuria

A single-center study has shown an association between proteinuria five days after transplantation and the development of NODAT [24]. But, these findings have been challenged because proteinuria on day five may just reflect the highly concentrated urine associated with hyperglycemia induced osmotic diuresis from the early post transplant, use of high dose corticosteroids or residual native kidney proteinuria. Moreover it has been shown that immediate post transplant proteinuria generally resolves several weeks after transplantation [25].

Hypomagnesemia

The post transplantation hypomagnesemia was found to be an independent predictor of NODAT in both renal and liver transplant especially induced by CNIs (more common with tacrolimus) , due to renal magnesium wasting occurring through transcriptional inhibition of the renal magnesium transporter in the distal collecting tubule.

Impaired glucose tolerance before transplantation

Cosio et al. [9] demonstrated that higher pretransplant glucose is a risk factor for NODAT at one year. Among patients with IFG pretransplant, 70% had hyperglycemia at one year (IFG 43% and NODAT 27%).

Potentially Modifiable Risk Factors

HCV-associated NODAT

The association between HCV infection and IFG, or the development of overt type 2 diabetes mellitus in the general population, has long been suggested. Potential mechanisms for the diabetogenic effect of HCV infection include insulin resistance; decreased hepatic glucose uptake and glycogenesis; and direct cytopathic effect of the virus on pancreatic cells [26]. Baid et al. [27] have shown that the presence of HCV infection was independently associated with a 62% increase in insulin resistance ($P = 0.0005$).

Cytomegalovirus-associated NODAT

The link between cytomegalovirus (CMV) infection and the development of NODAT was first reported in 1985 in a renal transplant recipient [28]. Patients with active CMV infection had a significantly lower median insulin release compared to their CMV negative counterparts, suggesting that impaired pancreatic β cell insulin release may be involved in the pathogenic mechanism of CMV-associated NODAT. It is speculated that CMV-induced release of proinflammatory cytokines may lead to apoptosis and functional disturbances of pancreatic β-cells [29].

Also diseases like chronic renal failure, hypovitaminosis D, hyperparathyroidism, multiple transplants, and repeated interventions for transplant rejections may create a putative diabetogenic environment in some posttransplant patients [30].

Known risk factors for NODAT following liver transplant were reported: donor liver steatosis, fasting plasma glucose; protective factors: use of IL-2R antagonist. Lower survival death by pulmonary infection and multisystem failure [31], other risk factors include tacrolimus use, hepatitis C virus infection [32]. Many factors yet to be studied [33].

Pathogenesis of NODAT

Starlz was the first to describe the role of corticosteroids in NODAT in 1964 in renal transplant recipients [34]. The diabetogenic effect of glucocorticoids is mainly due to insulin resistance, mediated by both impaired insulin-dependent glucose uptake in the peripheral tissues and enhanced gluconeogenesis in the liver. High-dose glucocorticoid regimens used during the 1970s were associated with a very high incidence of so-called "steroid diabetes," which declined when cyclosporine was introduced as an immunosuppressant in the 1980s. A 0.01 mg/kg/d increase in prednisolone dose was associated with a 5% risk of developing NODAT [35].

CNIs are diabetogenic by inducing a defect in insulin secretion [36] by interfering with the nuclear factor of activated T-cell signaling in pancreatic β cells. This pathway triggers the expression of genes critical for β cell function, including at least six genes mutated in hereditary forms of monogenic diabetes.

Tacrolimus induces a reversible suppression of insulin secretion at the level of insulin mRNA transcription, mediated by the binding of the drug to FK506 binding protein-12 and a subsequent inhibition of calcineurin in the β-cells [37]. Maes et al. [38] showed that a high tacrolimus trough level, particularly a level of greater than 15 ng/mL in the first month after transplant, was a significant risk factor for persistent IFG or diabetes mellitus beyond the first year after transplantation.

Potential mechanisms of the diabetogenic effect of HCV infection include insulin resistance, decreased hepatic glucose uptake and glycogenesis, and a direct cytopathic effect of the virus on pancreatic beta cells [39].

The link between CMV infection and the development of NODAT was first reported in 1985 in a renal transplant recipient [40]. It is speculated that CMV-induced release of proinflammatory cytokines may lead to apoptosis and functional disturbances of pancreatic b cells [30].

Sequelae of NODAT

In addition to the risk of developing the well-known long term complications of diabetes, NODAT also identifies patients at high risk for adverse clinical outcomes: loss of the renal allograft, infections, cardiovascular events, and increased mortality among renal transplant patients [41,42].

Among liver transplant recipients, NODAT is associated with increased cardiovascular morbidity and mortality, more fatal infections more neuropsychiatric complications, higher rejection rates, and poorer graft survival [43].

Among lung transplant recipients, cytomegalovirus (CMV) infection and acute rejection episodes were observed more frequently among patients who developed NODAT compared with their normoglycemic counterparts [44].

Management of NODAT

Pretransplant Evaluation

Currently, pretransplant risk assessment should be based on the phenotype and the medical history of the patient. The following factors associated with a higher risk of NODAT should be considered:

An age >45 years old,

A familial history of type 2 diabetes,

A personal history of NODAT with previous graft or gestational diabetes,

IFG, impaired glucose tolerance, criteria for metabolic syndrome, a BMI >30 kg/m^2, and a positive hepatitis C serology

The screening should include an evaluation of the glucose metabolism status by FPG and/or OGTT. A recent large study (N=889) has underlined the low sensitivity of FPG in detecting pretransplant glucose metabolism abnormalities in patients with ESRD because of insulin resistance. An FPG screening should be performed in all candidates, followed ideally by an OGTT in patients with FPG between 92 and 125 mg/dL (± 50% of patients). This should allow the identification of >80% of pretransplant diabetes [45].

The use of A1C is not recommended for the screening given the low sensitivity of the test in ESRD patients [5]. Patients should be screened for risk factors before transplantation in order to prospectively tailor their immunosuppression and minimize the risk of NODAT.

Patients at risk should be counseled on the importance of lifestyle intervention, including weight control, diet, and physical activity; as such strategy is efficient in patients at risk for type 2 diabetes.

Post transplant monitoring

Recent guidelines recommend screening all kidney transplant recipients with FPG, OGTT, and/or A1C assay at least weekly for 4 weeks, every 3 months for 1 year, and annually thereafter [46].

The screening with FPG levels should be performed at the intervals described above, and an OGTT could be considered in patients with IFG at 3 and 6 months (as the higher risk of NODAT is present during the first 6 months after transplantation). Additionally, A1C could be assayed at 3 and 6 months, and then yearly, to improve NODAT diagnostic accuracy.

Pharmacological Management of Hyperglycemia

Currently, it is considered that patients with an A1C assay ≥ 6.5% should start glucose-lowering agents. As for type 2 diabetes, a stepwise approach should be adopted.

The first step includes dietetic recommendations (weight control, diet, and exercise).

The second step is the initiation of an oral agent in monotherapy. The choice of the drug should take into account the patient-specific factors, graft function (some drugs or active metabolites are eliminated by the kidney), specific side effects, and potential pharmacokinetic interactions with immunosuppressive drugs (mainly interaction with CNI or m-TOR through metabolization by cytochrome P450, family 3, subfamily A, polypeptide 4/5 [CYP3A4/5]). Almost all oral agents can be used, except for the first-generation sulfonylureas (because they accumulate and induce hypoglycemic episodes) and biguanides (because they induce lactic acidosis). Biguanides should be avoided if the glomerular filtration rate is <60 mL/min. Gliquidone, the most-prescribed agent for kidney transplants in our institution, is efficient, well tolerated, and has no interaction with immunosuppressive drugs.

The third step is a combination of oral agents with different mechanisms of actions. Combination therapy has not been investigated and compared in kidney allograft recipients.

The last step is the initiation of insulin with or without oral agents. If individualized goals for glucose control are not achieved within 2–4 months, lifestyle interventions should be reassessed and patients should move to the next step.

So, management similar to type 2 diabetes. Glycemic monitoring post transplant is similar as given in a review published in J Clinical Endocr Metab [47], Correction of hyperglycemia, dyslipidemia and hypertension must also be undertaken [47].

Conclusions

NODAT is associated with a higher risk of complications, such as infections and cardiovascular disease - So, representing a higher life threatening risk and a higher cost for the Health System .So, we should identify the risk factors for NODAT and with early diagnosis combined with appropriate therapy will results in the success of the procedure as far as patient survival and transplantation durability.

Future Aspect: Further studies are required to ascertain the current incidence, prevalence and natural history of NODAT in order to identify more effective strategies for prevention and management which include the development of immunosuppressive regimens with minimal diabetogenic effects, determination of the role of glycemic control on graft survival, and interventions for primary prevention of NODAT.

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