New Onset Diabetes after Transplantation [NODAT] Risks Factors Outcome and Possible Role of Diabetes Educators

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Abstract

New-onset diabetes after transplantation [NODAT] is well known complication after organ transplantation especially after solid organ transplantation, bone marrow and hematopoietic stem cells. The incidence of NODAT was observed to be different over post-transplant intervals. It has many risk factors and adverse clinical outcomes include allograft dysfunction, infections, cardiovascular morbidities, and increased mortalities among renal transplant patients. Its management should start before transplantation with special stress on risk factors, modulation of immunosuppressive agents and role of diabetes education before during and after transplantation.

Keywords: Diabetes education; Renal transplant; NODAT

Introduction

Patients with operative stress are likely to be associated with acute hyperglycemia. After one month of transplantation, most of patients recover from transplant wound especially in the absence of delayed graft function, rejection, or surgical complications. Nearly 50% of transplant patients with new onset diabetes after transplantation [NODAT] showed improvement in glucose tolerance after reduction of dosage of the immunosuppressive agents. Complete remission from NODAT is difficult to predict, however some patient with NODAT within the first year post-transplant may show partial remission [1,2].

It is not known why some patients develop early-onset (within 1-year after transplantation), late-onset (1-year after transplantation), or transient diabetes mellitus i.e. NODAT diagnosed within the first year post-transplantation, with recovery to normal glucose tolerance status [3].

Prevalence

New-onset diabetes after transplantation [NODAT] is a well-recognized complication of organ transplantation especially after solid organ transplantation with different post-transplant intervals. After one year or longer of transplantation, NODAT was diagnosed in 20-50% of kidney transplants, 28-30% of heart transplants, 6-45% of lung transplants, 9-30% of liver transplants, and approximately 15% for bone marrow transplants [1,4-14] (Figure 1).

The variation in the reported NODAT frequencies may be explained by the differences in study design, transplant populations, timing of testing, in addition to the use of non-standardized diagnostic criteria. However, since 2003 the adoption of the International Consensus Guidelines on New-Onset Diabetes after Transplantation [14] has standardized the diagnosis of NODAT.

The time of screening for diabetes can affect prevalence of NODAT. Among renal transplant recipients, the peak of NODAT developed within 12 months (up to 15%); and falls to 6% later [15]. In contrast, its incidence increases by time in lung transplants [20.8% at 1 yr, and 33.5% at 5 yr post-transplant] [16]. Its cumulative incidence among cardiac transplants is nearly 30%/5 yr [17] and up to 30% within 24 months in bone marrow transplant recipients [12].
Complications of NODAT

NODAT might unfavorably affect clinical outcomes of transplant recipients. This can be through renal allograft loss, precipitation of infections, cardiovascular co-morbidities, and even increased mortality among renal transplant recipients [18,19]. The renal hyper filtration associated with diabetes, and even high risk patients, is believed to unenthusiastically affect allograft survival. Moreover, patients with NODAT might develop micro-angiopathies faster than patients with non-transplant-related diabetes [20,21]. In liver transplant recipients with NODAT showed increased cardiovascular morbidity and mortality, more fatal infections, more neuropsychiatric complications, higher rejection rates, and poorer graft survival [22,23]. In lung transplants with NODAT, cytomegalovirus (CMV) infection and acute rejection episodes were observed more often [24]. Moreover, heart-lung and lung showed that NODAT might be associated with higher risk for cardiac allograft vasculopathy [17].

Risk Factors for NODAT

The classical diabetes risk factors are also true in the post-transplant population [1,13,25]. Moreover, exposure to immunosuppressive agents especially steroids post-transplant patients [1,4,15,25,26] (Figure 2).

![Figure 2: Showed risk factors for NODAT](image)

Hepatitis C infection [HCV] and HLA-B13 locus had shown to be associated with higher risk of NODAT in liver or kidney transplant recipients [27,28]. HCV might induce diabetes through many mechanisms as pro-inflammatory cytokines, oxygen free radicals, and change of signal transduction by viral proteins, in addition to other mechanisms [29]. Other viruses like CMV infection have been associated with a 4-fold rise in the risk of NODAT possibly due to impairment of insulin secretion [30].

Role of Immunosuppressive Agents

Posttransplant patients who do not develop NODAT are as likely to be treated with immunosuppressive agents as are patients who develop NODAT. Therefore, those who develop NODAT probably have individual vulnerability factors that are enhanced by the posttransplant environment, including exposure to immunosuppressive agents.

Glucocorticoids that are commonly consumed by transplant recipients [31] induce insulin resistance, enhance lipolysis, and increase hepatic glycogenolysis and gluconeogenesis thus increased blood sugar. Moreover, such drugs inhibit insulin secretion and stimulate glucagon release [32,33]. These effects can induce hyperglycemia in susceptible patients.

Risk factors for the development of NODAT included traditional T2DM risk factors, as older age, ethnicity (African American, Hispanic, and Native American), family history of T2DM, and obesity, in addition to other risk factors unique to post-transplantation environment such as immunosuppression, cytomegalovirus infection, hepatitis C seropositivity, and weight gain after transplantation. In addition, immunosuppression drugs commonly used have been implicated to be diabetogenic, including calcineurin inhibitors (tacrolimus and cyclosporine), corticosteroids, and mammalian target of rapamycin inhibitors (sirolimus and everolimus) [34], although earlier studies had raised the possibility that rapamycin inhibition of mammalian target of rapamycin may reduce the risk of diabetes [35]. The diabetogenic effects of calcineurin inhibitors are partially attributed to pancreatic A-cell apoptosis and impaired insulin secretion [36,37] additionally, there is sparse literature describing calcineurin inhibitory induced insulin resistance [15,17]. In this review, we will provide a hypothesis-driven discussion describing recent advances in our understanding of potential mechanisms involved in the diabetogenicity of calcineurin inhibitors focusing on its contribution to increased insulin resistance.

Diagnosis of NODAT

The International Consensus Guidelines on New-Onset Diabetes after Transplantation recommended that the diagnosis of NODAT be based on the American Diabetes Association criteria for the diagnosis of diabetes. Accordingly, NODAT is diagnosed by finding two fasting plasma glucose (FPG) values (measured on different days) higher than 126 mg/dl; a plasma glucose level higher than 200 mg/dl at 2 h during a 75-g oral glucose tolerance test (OGTT) a random plasma glucose level higher than 200 mg/dl in a patient with typical diabetes clinical manifestations or A1C more than 6.5%. If two different tests are available in an individual and the results are discordant, the test whose result is above the diagnostic cut point should be repeated, and the diagnosis is made on the basis of the confirmed test (American Diabetes Association Standards of medical care in diabetes-2011) [38]. In addition to the known pitfalls of the HbA1c test [39] blood transfusion will make results of HbA1c to be unreliable.

Management of NODAT

Solid organ transplantation is now the standard of care for end-stage organ failure, and primary care physicians are frequently involved in the follow-up care of transplant recipients. New-onset diabetes after transplantation [NODAT] has emerged as an increasingly important determinant of outcomes and survival in transplant recipients. Patient education and self-management are crucial for ensuring successful outcome post transplantation [40] (Figure 3).
C) Post transplant monitoring

Patients discharged without hyperglycemia should have FPG evaluation weekly during the first month, then every 3rd month for 1 yr, and then annually. If IFG is detected at any time, an OGTT should be done to increase diagnostic succumb; persons identified as having IFG or IGT should receive lifestyle counseling preferably by diabetes educators [14], with special stress on diet and exercise as tolerated. Persons with NODAT, the severity of hyperglycemia is ranging from mild hyperglycemia that responds to dietary modification alone to severe elevation requiring combined therapy including insulin. All patients with NODAT should receive diabetes self-management education, including diet and exercise counseling, sick day management, and self-blood glucose monitoring. Once a diagnosis of NODAT has been confirmed in a patient who is more than 3 months posttransplant, the HbA1c can be used to monitor glycemic control [14].

D) Anti-diabetes medications

If drug therapy to control diabetes is indicated, it is wise to select agents that are suitable for the patient’s underlying conditions. In transplant recipients with NODAT but with normal or adequate renal, hepatic, and cardiac function, most of the available classes of medications (including insulin sensitizers, insulin secretagogues, and incretins) can be used before considering insulin therapy. Careful attention must be considered to avoid the adverse effects of anti-diabetes agents in the transplant population. Metformin should be cautiously used when used in renal transplant patients with graft dysfunction because of the risk of developing lactic acidosis.

Sulfonylureas are associated with weight gain and hypoglycemia. Hypoglycemia can be severe, prolonged, and potentially fatal especially among elderly patients and those with limited hepatic function. On the other hand, glucagon-like peptide-1 (GLP-1) agonists and the dipeptidylpeptidase-4 (DPP-4) inhibitors are less liable to induce hypoglycemia compared with sulfonylureas. The GLP-1 agonists are linked with decreased gut motility, nausea, and occasional vomiting, which might interfere with the oral posttransplant immunosuppressive regimens. The DPP-4 inhibitors have minimal gastrointestinal adverse effects [44] and are well-tolerated by diabetic patients. However, no studies using GLP-1 agonists or DPP-4 inhibitors in the management of NODAT have been published. The thiazolidinediones -being insulin sensitizers- have less risk for inducing hypoglycemia, and used effectively in cases with NODAT [45] but adverse effect by inducing fluid retention is limiting its use.

Finally, insulin is used widely in the management of NODAT. The standard regimens (basal insulin, split-mix, and basal-bolus) are all valid in the management of NODAT. However, flexibility and originality are required to modify insulin protocols. It is usually initiated for control of severe hyperglycemia linked to an acute rejection episode that is being treated with pulse steroid. However, with decreasing the steroid dosage insulin needs will follow and close blood glucose monitoring will be essential.

Immunosuppressive Regimen

Both endocrinologists and transplant team should collaborate for proper evaluation and management of patients with NODAT to reach therapeutic decisions with possible modification of immunosuppressive agents. Certainly, in patients receiving steroid-containing protocols, the minimal daily or alternate day steroid dose
should be used if that can be done safely without endangering graft survival. This opinion was supported by that some studies that claim that steroid-sparing or steroid-free regimens were associated with decreased risk of NODAT [46,47], but with more controversy and more need for further evidence. Some studies involving relatively small numbers of patients have shown glycemic improvement [with occasional conversion of tacrolimus to cyclosporine [48,49] which could be explained by the more potent inhibitory effect of tacrolimus on insulin secretion [35]. Thus, the emerging data suggest that the preferential use of cyclosporine (CsA) for transplant-related immunosuppression might be a rational approach to diabetes risk reduction, assuming graft protection is similar to that achieved using tacrolimus and other agents [5,48,49]. Currently, there is no agreement concerning which immunosuppressive regimen capable of preventing NODAT; however, studies aimed at CNI minimalization in patients receiving potent induction therapy are enduring [50].

The gold standard of transplant management is optimal immunosuppression without untoward adverse effects through cautious use of these agents. Aiming for the lowest effective steroid dose after transplantation decreased the risk of NODAT [48,51]. Compared to CsA, tacrolimus reduces the risk of acute rejection and improves graft survival during the first year of transplantation. Low-dose tacrolimus minimizes the risk of NODAT compared to higher doses of tacrolimus. However, further studies are needed to define the best possible immunosuppressive regimen taking in consideration risks for organ rejection and NODAT [52].

Co-morbid Conditions

Attention given to diabetes co-morbid conditions should be extended to cases with NODAT as well. Thus, dyslipidemia should be managed using lifestyle modification, statin, and other possible medications. CNI are known to increase cholesterol levels, so patients may require adjustment of statin dose post-transplantation [53]. However, CNI inhibit CYP3A4; therefore, patients may receive higher exposure to statins metabolized by this enzyme [e.g. simvastatin, atorvastatin, and lovastatin]. Pravastatin and fluvastatin, which are not metabolized by CYP3A4, tends to be used preferentially in transplant patients with dyslipidemia. Fibrates may be needed for management of sirolimus and glucocorticoids associated hypertriglyceridemia and if it is severe the risk of pancreatitis is there. But the risk of rhabdomyolysis is also there especially if combined with statins, therefore fish oil can be used as an alternative.

Many organ transplant recipients are hypertensive, and posttransplant immunosuppressive agents may also increase blood pressure and the need for more antihypertensives. The National Kidney Foundation recommended controlling blood pressure below 130/80 mm Hg in renal transplant patients [54]. Beta-blockers and calcium channel blockers appear to be well tolerated and effective [55]. Angiotensin-converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARB) are associated with reduction in glomerular filtration rate and risk of hyperkalemia and therefore should be used cautiously in renal transplant recipients. Moreover, ACE inhibitors when combined with sirolimus increased the risk of angioedema [56]. In patients with transplant renal artery stenosis (usually develops within the first 2 yr), ACE inhibitors and ARB may induce an acute kidney injury [55]. Despite these adverse effects, ACE inhibitors and ARB might be valuable for some patients especially in presence of proteinuria; congestive heart failure; and other appropriate indications.

The interpretation of microalbuminuria becomes complicated in diabetic kidney Transplant recipients patients. In native kidneys, albuminuria is a useful marker of diabetic nephropathy; however after kidney transplantation it is associated with glomerular injury and systemic inflammation from different causes beside diabetic nephropathy. Moreover, it is a forecaster of patient and graft survival [57].

Hyperuricemia, a feature of uremia, can be provoked after transplantation by CNI especially cyclosporine. In addition to the risk of gout, it is associated with cardiovascular disease, inflammation, insulin resistance, and decreased renal graft survival [58].

Debates and Areas of Indistinctness

Primary prevention of NODAT

The use of lifestyle intervention is possible by identifying high-risk recipients during the pretransplant period [11,14]. Once identified, we have to manipulate lifestyle by intervention aiming at decreasing obesity by increasing physical activity and appropriate nutrition. Lifestyle approaches customized to the transplant patients need to be developed and tested for efficacy regarding the prevention of NODAT. The approach used in the Diabetes Prevention Program [59] was effective in otherwise healthy subjects with IGT. We think that diabetes educators will have an important role in this issue. The use of medications to prevent type 2 diabetes has been well documented in the general population [60], but not yet in transplant recipients. An ideal drug for prevention of NODAT must correct or improve the gluco-regulatory defects underlying NODAT. Such a drug should have a low risk of hypoglycemia and have minimal interactions with associated post-transplant medications. In preclinical studies, exendin-4 restored the expression of insulin receptor substrate-2 in tacrolimus-treated rodent and human islets [61]. Recent areas of investigation include clinical validation of NODAT risk score engines, validity of primary prevention of NODAT, the development of less diabetogenic immunosuppressive regimens, and potential protective effect on cardiovascular outcomes [62]. However, till now there are no data from clinical studies regarding medications for prevention of NODAT.

Optimal glycemic management

NODAT has been identified as a risk factor for graft rejection, long-term graft failure, and decreased patient survival; however the mechanisms concerning hyperglycemia to these adverse outcomes remain to be dogged. Controlled diabetes in liver transplant recipients is associated with reduction of infections [63]. Once NODAT has been diagnosed, specific anti-hyperglycemic therapy is essential to reach a tight glycemic control, which contributes to significantly reduce posttransplant mortality and morbidity [64].

As already noted, hepatic, renal, and cardiac dysfunction compel limitations to drug selection for glycemic control. Moreover, hypoglycemia can induce seizure and arrhythmia, which would be undesirable in cardiac transplant patients. Hypoglycemia also triggers adrenergic discharge and the expression of pro-inflammatory cytokines [65-73] is associated with adverse outcomes in high-risk patients. Thus, future studies are needed to determine whether recurrent hypoglycemia increases the risk of acute graft rejection and chronic graft dysfunction.
Role of diabetes educators

Muhlhauser and Berger [74] recommended that patients should receive evidence-based information regarding their disease to assist them in making informed decisions regarding management of their diabetes.

Higher risk of Diabetic Retinopathy [DR] is associated with longer duration of diabetes, insulin therapy, higher HbA1c level, male gender, and lower level of education, whereas higher risk of DR is also associated with lower compliance to diet control and exercise, which suggest that lower level of diabetic self-management increased the risk of DR [75].

Controversy concerning the effectiveness of diabetes education in a group setting vs. individual setting is a concern to health care providers. This issue is important to address because implementation of group education programs helps to decrease overall cost and allows more individuals to be reached at once. Rickheim et al. [76] conducted a study to assess the effectiveness of diabetes education programs when delivered in a group setting vs. an individual setting. They enrolled 170 participants from which they placed 87 in group education and 83 in individual education treatments. Education material included information on carbohydrate counting, portion control, meal spacing, self-monitoring of blood glucose, physical activity, heart-healthy eating, foot care, sick day management, monitoring for diabetes complications, self-management problem solving, and information regarding the progression of type 2 diabetes. They found significant increase in knowledge scores associated with significant decrease in A1C in both treatment groups (P < 0.01), but A1C reduction was significantly lower in the individuals receiving group education compared to the individuals receiving individual treatment (2.5% vs. 1.7%, P < 0.01). Another study by Trento et al. [77] for assessment the effects of group care on the management of diabetes and the prevention of complications related to diabetes, based on their results, they conclude that diabetes education programs delivered in group settings are effective in the management of diabetes.

In the same direction, Erlich et al. [78], showed evidence that patients with diabetes who participate in a group education program have lower A1C levels, improved lipid profiles, higher quality of life scores, and improved knowledge about diabetes and problem-solving ability.

Elliott et al. [79] recommended- in an Omani study- improving knowledge transfer to people living with diabetes so that they can successfully take on more responsibility for managing their disease. They added that guidelines need to be further updated and training of providers needs to focus on improving communication skills relevant to knowledge transfer and patient education.

Improving Diabetes Self-Management and Education (DSME) has been shown effective at improving blood glucose control in multiple large scale studies [80,81]. Research has conclusively shown that effective health education should be provided with respect to the patients’ level of education and variations in their understanding of the illness [82], since patients with diabetes who had limited literacy and lower knowledge about diabetes and self-management had poorer health outcomes [83].

A meta-analysis reviewing 84 studies regarding the effect of self-management training in individuals with type 2 diabetes; Norris et al. [84] found that knowledge; frequency and accuracy of self-monitoring blood glucose, dietary habits and glycemic control were positively affected after short-term follow-up. Moreover, they added that education interventions that included patient collaboration might be more effective than didactic interventions. Thus, it seems an interactive environment in which the participants partake in the development of their diabetes management program may have additional benefits to those already seen with didactic interventions. Following ten sessions of diabetes management education program, Miller et al. [85] found that older individuals with type 2 diabetes showed significant improvements in diabetes knowledge (P < 0.0001), disease management skills (P < 0.01), and decision-making abilities (P < 0.0001).

The learning environment should be manipulated based on the communication status of the audience. Insufficient steps to control for visual impairment could result in decreased effectiveness of diabetes management programs within this population. In the hopes of addressing this issue, Bernbaum et al. [86] examined the importance of adapting diabetes education programs for individuals with visual impairments. They concluded that an education program adapted for visual impairment provided an acceptable learning environment for participants.

Increased knowledge of diabetes management has been associated with better control of blood glucose concentrations. Harwell et al. [87] conducted a telephone survey in a rural population group and found that the participants knew their last A1C value, but they could not interpret the value properly. Skeie et al. [88] found that the high-knowledge group, that included individuals who had diabetes for a longer time period, had a better understanding of A1C compared to the low-knowledge group. Evidence shows that as an individual’s knowledge of diabetes management increases the A1C values decrease. Raji [89] conducted a study to investigate the effectiveness of active and passive diabetes education on A1C values. It was determined that both educational interventions resulted in improved glycemic control based on A1C scores. A meta-analysis conducted by Norris et al. [90] reviewed 31 studies and they concluded that A1C levels are improved by diabetes self-management education, with participant contact time being identified as the only predictor of effect (23.6 hours of contact time needed for every 1% reduction in A1C levels).

In a meta-analysis done by Steinsbekk et al. [91] they concluded - based on current evidence- that interventions delivered by a single educator, delivered in less than ten months, with more than 12 hours and between 6 and 10 sessions give the best results but more research is needed to confirm this. Moreover, it can be concluded that group-based DSME in people with type 2 diabetes results in improvements in clinical, lifestyle and psychosocial outcomes.

Conclusion

Due to the importance of NODAT, diabetes education and its impact on the outcome of post-transplant morbidity and mortality become crucial point of research among organ transplant populations. Diabetes education in a group setting can be adopted for organ transplant recipients with NODAT.

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