Original Research Article

Association of Genetic Risk Factors and Underlying Mechanism in the Development of New-Onset Diabetes after Transplantation

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New-onset diabetes after transplantation (NODAT) is a serious and common complication following solid organ transplantation and has been reported to occur in 2 to 53 % of all solid organ transplants. Various risk factors are associated with NODAT, however, the pathogenic mechanisms are still not very clear. In addition to the traditional risk factors for type 2 diabetes mellitus (T2DM) such as age, family history, obesity, ethnicity etc, exposure to immunosuppressive agents often leads to the occurrence of NODAT. Renal transplant patients who develop NODAT are at higher risk of cardiovascular events, infections, graft loss and patient loss. The incidence of NODAT has been reported to be high in early transplant period due to the exposure to the high doses of corticosteroids and calcineurin inhibitors and decreased physical activity during that period. Besides the traditional risk factors, genetic factors also play a major role in the development of NODAT. Knowledge of these factors at the earlier stage may help in identifying the high risk patients and implementing the preventive measures to reduce the development of NODAT. In the present article we reviewed the literature on the occurrence, traditional and genetic risk factors and the diagnostic criteria in the development of NODAT. Assessment of β-cell function and analysis of genetic factors would help in the control and management of NODAT in near future.

Keywords: NODAT, Transplantation, Genetic factors, HCV, CMV, Calcineurin inhibitors.

INTRODUCTION

New-onset diabetes after transplantation (NODAT) refers to the occurrence of diabetes in previously non-diabetic persons after solid organ transplantation as well as bone marrow and hematopoietic stem cells [1,2]. Kidney transplantation is the best therapy for end-stage renal disease (ESRD) with increased survival rates and better quality of life as compared with dialysis patients [3]. But NODAT is among one of the leading obstacles to long-term allograft and recipient survival [4]. According to data from the US renal data system (USRDS), 40% of kidney transplant recipients (KTRs) have probability to develop NODAT by their third year post transplantation [5].

This number is distressing because NODAT is a major risk factor for cardiovascular disease [6] and mortality [7-10] as well as associated with adverse impact on graft survival, graft rejection and graft loss [11,12], rate of infections [13-15] and increased health care costs [16].

According to International Consensus Guidelines on NODAT which were published in 2003, NODAT should be diagnosed based on the American diabetes Association (ADA) criteria for type 2 diabetes published in 2003 [17,18]. The 2003 ADA diagnostic criteria for diabetes cohere with the WHOs diagnostic criteria of 1999. The NODAT guidelines recommend fasting plasma glucose (FPG) to be the desired test for the diagnosis of NODAT, but studies have indicated that a two hour post glucose (2hrPG) after an oral glucose tolerance test (OGTT) might be more sensitive for the detection of NODAT.

The definition of diabetes mellitus which was prevailing in the clinical practice was FPG ≥ 7.0 mmol/dl (126 mg/dl) and 2hrPG ≥ 11.1 mmol/dl (200 mg/dl). And later FPG limit was modified to 110 mg/dl from 126 mg/dl which corresponds to impaired fasting glucose (IFG) by the International Expert Committee, based on epidemiologic prognostic data [19].

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Since 2009, International Expert Committee recommended the use of standardized HbA1c (≥ 6.5%) assay for the diagnosis of diabetes which was approved by ADA in 2010 [20]. The Expert Committee also stated that HbA1c assay cannot be used in the condition that change red cell turnover, which is the case of end-stage renal disease (ESRD) patients and newly transplanted kidney recipients. These patients are usually anemic (due to surgical blood loss, iron deficiency, immunosuppressive drugs, graft dysfunction and instantaneous discontinuation of erythropoietin administration) which may lead to spurious HbA1c results [21,22].

Even though there is more prevalence of diabetes in the general population and increasing number of NODAT in kidney transplant recipients (KTRs), there are very few studies on NODAT from India. Owing to this, we have undertaken to review the occurrence, traditional risk factors, transplant specific factors and genetic risk factors of NODAT. Understanding the root causes of the disease is important as it will help to prevent the development of post-transplant diabetes. Though the underlying pathogenic mechanisms of NODAT are still unclear, the knowledge of these risk factors is of greater importance to identify the higher risk patients and to adapt the therapeutic strategies accordingly for the prevention of disease.

The purpose of this review is to focus on the genetic risk factors of NODAT, since there was limited understanding of genetic role in the development of NODAT. Moreover, knowing the genetic risk factors at earlier stage might help the transplant recipients to take precautionary measures to avoid the occurrence of NODAT, which will help them to lead a healthy and better quality of life.

HISTORY AND INCIDENCE OF NODAT

The first cases of NODAT were illustrated by Thomas Starz after a liver transplant in 1964, which occurred mainly during the first 6 months post transplantation during treatment with high doses of immunosuppressant. The annual incidence of diabetes after 6 months is similar to that observed in patients on the waiting list i.e. 6% per year [16].

The incidence of NODAT among different types of transplant recipients is shown in Table 1. It has been reported that NODAT occurs in 2% to 53 % of all solid organ transplants [17], 4% to 25 % of renal transplant recipients [8], 4% to 40% of heart transplant recipients [23], 30% to 35% of lung transplant recipients [24], 2.5% to 25% of liver transplant recipients [25] and 40% to 60% of hepatitis C virus (HCV)-infected liver transplant recipients [26]. The variation in the reported NODAT incidence may be explained by the differences in the study plan, transplant populations, the type of organ transplants, and the duration of follow-up and also the lack of standard definition of the condition.

The prospective study of Vincenti et al [27] provided the most accurate incidence of NODAT under calcineurin inhibitor (CNI) therapy, reporting an incidence of 20.5% within the first 6 months post renal transplantation. In some patients the risk of developing NODAT has been observed up to 15 years post transplantation [28].

RISK FACTORS FOR NODAT

Various risk factors associated with the development of NODAT are non-modifiable, modifiable or potentially modifiable risk factors; the former category helps in the identification of high risk individuals, and the latter two categories help in optimizing the management of NODAT.

NON-MODIFIABLE RISK FACTORS

Older age is considered to be an important risk factor for the development of NODAT. Transplant recipients of age more than 45 years were 2.2 times more likely to develop NODAT than those of younger recipients [28]. Kasiske et al [8] showed a strong association between older age and NODAT in an analysis of the US Renal Data System (USRDS) consisting of over 11,000 Medicare beneficiaries who received primary kidney transplants between 1996 and 2000. When compared to a reference range of 18-44 years of age, transplant recipients between the age of 45-59 years were found to have a relative risk of 1.9 for NODAT($P < 0.0001$), whereas recipients who were ≥60 years of age had a relative risk of 2.09 ($P < 0.0001$) [28]. Gourishankar et al [29] reported that there is 1.5 fold increased risk for NODAT for every 10 year increase in age.

Race/ethnicity also plays a role in the development of NODAT. According to data from USRDS, NODAT was more common among African Americans (RR = 1.68, $P < 0.0001$) and Hispanics (RR = 1.35, $P < 0.0001$) as compared to Caucasians. The difference in the incidence of NODAT in patients of different ethnicity has been observed due to the differential pharmacokinetics and diabetogenic effects of immunosuppressive drugs [30]. Davidson et al [17] reported that tacrolimus has potent diabetogenic effects in African Americans as compared to whites.

Recipients with a family history of diabetes among first-degree relatives are at greater risk for the development of NODAT, with one study reporting a seven fold increase in the condition [17]. Other non-modifiable risk factors include male gender recipient, the presence of certain human leukocyte antigens (HLA) such as HLA A30, B27, and B42, increasing HLA mismatches, deceased donor kidneys, male donor and acute rejection history [31]. Polycystic kidney disease also has been suggested to increase the risk for developing diabetes after renal transplantation in few studies but was contradicted by others [32-35].

MODIFIABLE RISK FACTORS

Starlz described the contributory role of corticosteroids on NODAT in 1964 in renal transplant recipients [28,36]. The diabetogenic effect of corticosteroids depends on the dose given to the recipients. Single-center studies have suggested that oral prednisolone dose reduction to 5 mg daily considerably improves glucose tolerance during the first year of transplantation [37] while a 0.01 mg/kg/day increase in prednisolone dose increases the risk to 5% for developing NODAT [38].

Tacrolimus (Tac) has been reported to have a greater diabetogenic effect as compared to cyclosporine A (CSA) among renal and non-renal transplant recipients. In a meta-analysis regarding incidence of NODAT, Heisal et al [39] reported a higher incidence of insulin dependent diabetes mellitus (IDDM) in Tac- versus CSA-treated liver, heart, and lung transplant recipients. IDDM occurred in 9.8% of Tac-treated versus. 2.7% of CSA-treated patients ($P < 0.00001$) in renal transplant recipients. Similar trends were reported among non-renal transplant recipients (11.1% versus 6.2%, respectively ($P < 0.003$).

Bloom et al [40] reported that among the HCV positive patients, NODAT development was more in the Tac- compared with the CSA- treated patients (57.8% versus 7.7%, P, 0.0001).

Table 1. Overall incidence of NODAT among different types of Transplant Recipients

Types of Transplantation	Overall incidence (%)
New-onset diabetes after transplantation	2-53 %
Renal transplant	4-25 %
Heart transplant	4-40 %
Lung transplant	30-35 %
Liver transplant	2.5-25 %
HCV infected liver transplant	40-60 %

In one single-center study, tacrolimus in combination with sirolimus was found to be associated with a higher incidence of NODAT than tacrolimus alone [41].

Obesity (BMI ≥ 30 kg/m^2) has been observed to be associated with the development of NODAT and according to the analysis of USRDS database, it is considered to be one of the strongest risk factors for NODAT (RR of 1.73, P < 0.0001) [42]. The pattern of body fat distribution also has been suggested to play a contributory role. It is hypothesized that intra-abdominal fat or waist-to-hip ratio could be more significant risk factors for NODAT development than total body weight or BMI [17].

Earlier studies have suggested that the greater number of metabolic syndrome components is associated with greater risk for NODAT development [43]. However, multivariate analysis, including the individual metabolic syndrome components as covariates demonstrated by Bayer et al [44], showed that only low density lipoprotein (LDL) was independently associated with the development of NODAT among all the pre-transplant metabolic syndrome components.

In a single-center retrospective analysis comprising of 254 renal transplant recipients, Van Laecke et al [45] reported that hypomagnesemia during the first-month post transplantation was associated with NODAT development, independent of the immunosuppressive regimen used. Whether Mg supplementation and adjustment of Mg deficiency would reduce the incidence of insulin resistance or NODAT has to be studied.

POTENTIALLY MODIFIABLE RISK FACTORS

In a study composing of 490 kidney transplant recipients, Cosio et al [46] reported that higher pretransplant glucose is a risk factor for the development of NODAT at one year. Compared to patients with pretransplant FPG levels between 90-100 as the reference group, patients with plasma glucose <90mg/dl have lower risk of NODAT (OR = 0.46, P = 0.01). Whereas, the risk for developing NODAT increases as the pretransplant FPG levels increases (FPG = 101-109, OR = 1.5; FPG = 110-125, OR = 7.6, P < 0.0001).

It has been suggested that Hepatitis C virus (HCV) infection is associated with IFG or the development of type 2 diabetes mellitus in the general population. Bloom et al [47] reported that the 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 β cells.

Studies suggested that asymptomatic CMV infection and CMV disease, both are independently associated with the development of NODAT. Hjelmesaeth et al [48] reported that asymptomatic CMV infection was associated with a four-fold increased risk of NODAT, in a study comprising of 160 non-diabetic renal transplant recipients who were monitored for CMV infection during the first 3 months after transplantation.

Patients with active CMV infection had considerably lower median insulin release when compared with their CMV negative counterparts, suggesting that the potential mechanism for the diabetogenic effect of CMV infection might include impaired insulin release from pancreatic β cells. It is suggested that CMV-induced release of proinflammatory cytokines might lead to apoptosis and functional disturbances of pancreatic β cells [49].
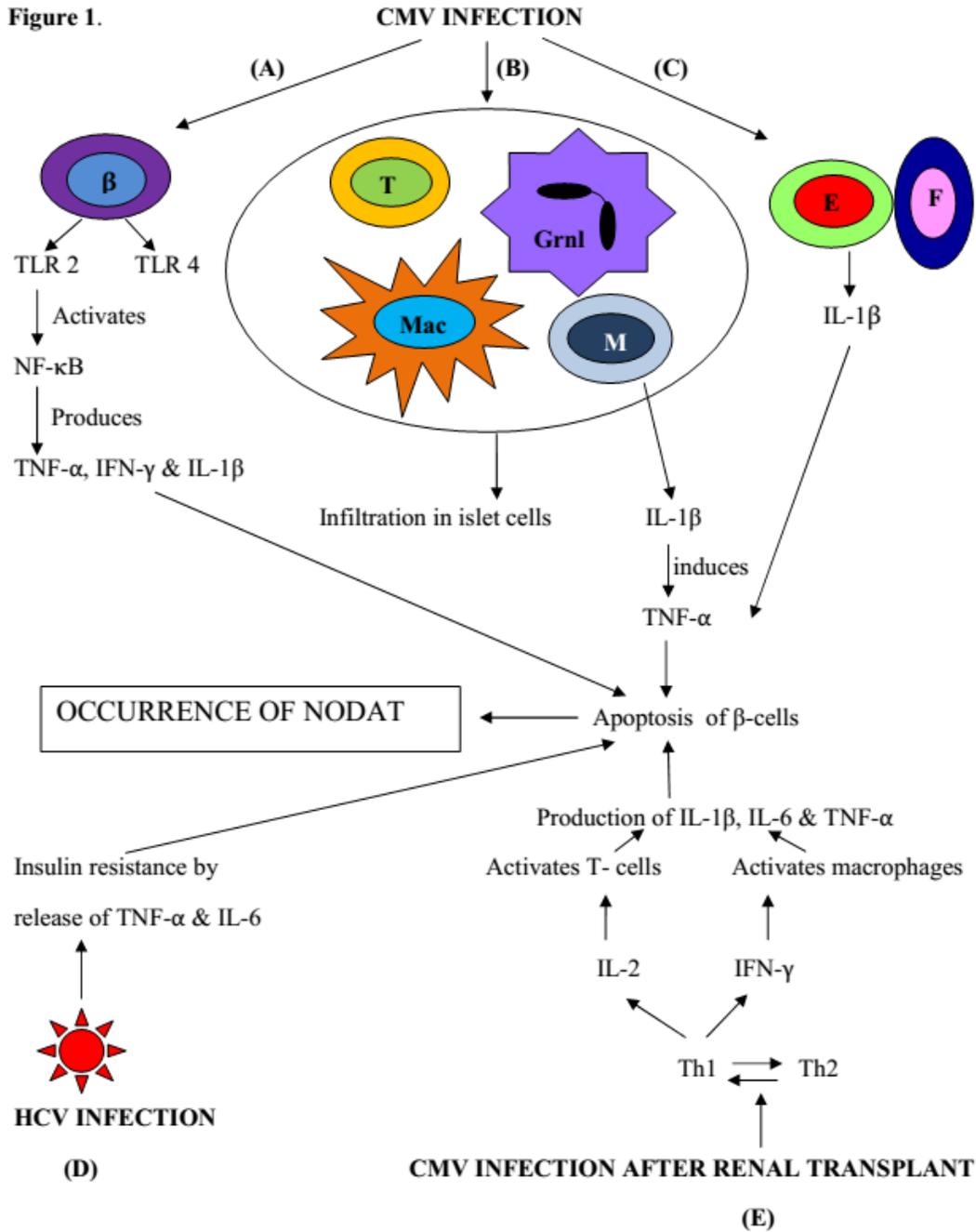
PROBABLE MECHANISMS OF B-CELL DAMAGE AFTER HCV AND CMV INFECTION LEADING TO NODAT

Proinflammatory cytokines may play a major role in the pathogenesis of both type 1 [50] and type 2 diabetes [51]. Tumour necrosis factor (TNF)-α, interferon (IFN)-γ and interleukin (IL)-1 have detrimental effects on pancreatic β-cells, and TNF-α and IL-6 induce insulin resistance. The detrimental effect of cytokines on β-cell could be due to the induction of apoptosis [52], or toxic effects caused by reactive oxygen or nitrogen species, or elevated free fatty acids and by insulin resistance in the β-cell itself [51]. Probable mechanisms for HCV and CMV-induced β-cell damage leading to NODAT are demonstrated in Figure 1.

Hepatitis C virus (HCV) has become one of the important risk factors of T2DM and NODAT by elevating the levels of proinflammatory cytokines such as TNF-α and IL-6 leading to insulin resistance [53]. This may induce the apoptosis of β-cells and occurrence of diabetes after renal transplantation in HCV positive patients.

During CMV infection also, various types of cells produce proinflammatory cytokines. Firstly, β-cells express toll-like receptors such as TLR 2 and TLR4 [54], TLR2 is involved in binding of CMV to target cells [55]. Activated TLR2 in β-cells leads to activation of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) following the production of low levels of proinflammatory cytokines leading to apoptosis of β-cells which may further develop NODAT [54].

Secondly, infiltration of T-cells, granulocytes, monocytes and macrophages inside the islet cells due to CMV infection, may lead to local production of proinflammatory cytokines causing β-cell dysfunction [56]. Binding of CMV to monocytes induces IL-1β production and release [57], which further activates TNF-α production in human pancreatic duct cells leading to apoptosis of β-cells [58]. Thirdly, CMV infection may also infect the neighbouring pancreatic cells (endothelial cells and fibroblasts) leading to the production of cytokines. Endothelial cells produce increased levels of IL-1β due to CMV infection with subsequent induction of apoptosis of β-cells [59].

Figure 1.   **CMV INFECTION**

Figure 1. Probable mechanisms of β- cell damage after CMV and HCV infection leading to NODAT. (A). CMV infection inducing β- cells to produce proinflammatory cytokines, leading to the apoptosis of the cells. (B). Production of proinflammatory cytokines due to CMV infection by infiltration of T- cells, granulocytes, monocytes and macrophages in islet cells, leading to apoptosis of β-cells. (C). CMV induced apoptosis of β-cells by production of proinflammatory cytokines in other islet cells (endothelial cells and fibroblasts). (D). Insulin resistance by release of proinflammatory cytokines due to HCV infection, leading to apoptosis of β-cells. (E). Balance between Th1and Th2 lymphocytes during CMV infection after renal transplantation, leading to β-cell destruction with predominant Th1 response. **Abbreviations:** β- β-cells, T- T-cells, Grnl- granulocytes, Mac- macrophages, M- monocytes, E- endothelial cells, F- fibroblasts,

During CMV infection after renal transplantation, the immune response may depend upon the balance between T helper 1 (Th1) and T helper 2 (Th2) lymphocytes with a predominant Th1 response leading to β-cell dysfunction [52]. Among Th1 cytokines, IL-2 activates T cytotoxic lymphocytes, while IFN-γ induces macrophages to produce proinflammatory cytokines like IL-1β, IL-6 and TNF-α, which may induce the apoptosis of β-cells.

ASSOCIATION OF NODAT WITH IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive agents also play a major role in the development of NODAT. Immunosuppressive drugs account for 74% of the risk for NODAT development [30]. The association between corticosteroids and NODAT has been established clearly and is mostly dependent on the cumulative dosages and therapy duration [17,60]. In the early years of transplantation, higher dosages of corticosteroids were used, which was responsible for higher NODAT incidence as 46%.

Later, the progressive reduction in corticosteroids dosages resulted in a parallel reduction in the incidence of NODAT [39]. It has been reported by large, prospective, multicenter trial that steroid withdrawal at 3 months did not reduce the incidence of NODAT significantly, whereas, corticosteroid avoidance from the first day resulted in a significant reduction of NODAT [61,62].

Even though cyclosporine therapies permitted for reduction in steroid dosages with subsequent reduction of NODAT incidence, calcineurin inhibitors (CNI) also have been found to be associated with glucose metabolism impairment [17]. It has been demonstrated in both animal models and human studies that calcineurin inhibitors exhibit their diabetogenic effect by inhibiting insulin secretion [63,64]. Probable pathway of calcineurin inhibitors leading to NODAT are demonstrated in **Figure 2**. Analysis of USRDS reported that the risk for developing NODAT was 53% more in patients who were treated with tacrolimus, and also the rate of NODAT diagnosis during the second year was greater [8,16].

In a review consisting of 4102 renal transplant recipients, it was found that the RR for NODAT at 1 and 3 year were 1.86(95% CI 1.11 to 3.09) and 3.86(95% CI 2.01 to 7.41) higher with tacrolimus, respectively [65]. A similar NODAT risk was also found in non renal transplants [39]. Cyclosporine and tacrolimus trough blood levels were not related to the appearance of NODAT at discharge; 3 and 6 months; and 1,3 and 5 year after transplantation. However, early post transplantation levels are associated with NODAT development. It has been reported that the tacrolimus trough levels >15ng/ml during first month are associated with the development of NODAT [66]. Boots et al [67] reported that a 33% reduction in tacrolimus level resulted in a 36% improvement in pancreatic β-cell secretion capacity. Tacrolimus has been considered to be associated with a higher rate of NODAT but not with a reduced risk for graft failure [8].

The use of azathioprine and mycophenolate mofetil has been associated with a lower risk for NODAT, probably because it may allow the clinicians to reduce the dosages of more diabetogenic immunosuppressive agents. Patients who were on azathioprine and mycophenolate mofetil therapy were found to have a 16% and 22% lower incidence of NODAT, respectively, yet it has not been confirmed in a meta-analysis [8,65]. The role of sirolimus in glucose metabolism is controversial. However, a higher incidence of NODAT in black patients was noticed who received sirolimus in combination with tacrolimus, suggesting the possibility of sirolimus association with impaired glucose metabolism [68].

Impaired glucose homeostasis has been seen in renal transplant recipients who received basiliximab, a CD25 antibody indirectly suppressing T-cell proliferation. In the basiliximab group, 51.5% of patients were found to develop NODAT, impaired glucose tolerance, or impaired fasting glucose, versus 36.9% of patients in the group without basiliximab, but the pathogenic mechanism were unknown [69].

## ASSOCIATION OF NODAT WITH GENETIC FACTORS

There are not many reports of NODAT with respect to genetic background. Some studies showed the association between human leukocyte antigen (HLA) phenotypes and NODAT but they were conflicting. Therefore, HLA phenotype cannot be considered as a reliable risk factor for NODAT [17]. In previous studies, HLA-B42 [70] and HLA-B27 [38] has been identified as predictive factors for NODAT. Recently, HLA-B13 and HLA-B15 phenotypes have been reported as independent predictors of NODAT [71].

A study carried out in 70 kidney transplant recipients has reported that patients with vitamin D receptor TaqI t allele were at a higher risk for NODAT than the control group with the TT genotype [72]. In the general population, several genetic polymorphisms are considered to have contribution to diabetes. Previous studies reported that the IL-6 gene promoter polymorphisms at position -174 (G→C) has been associated with type 2 diabetes [73] and insulin resistance [74, 75]. Bamoulid et al [76] also demonstrated that polymorphism in IL-6 gene promoter region at position -174 (G→C) were associated with the later development of NODAT.

The risk for NODAT was found to be significantly higher in homozygous (GG) wild-type patients than in homozygous (CC) mutant patients independent of age, BMI, and other confounding factors. Moreover, the incidence of NODAT increased linearly from low to intermediate and high IL-6 production capacity. Furthermore, insulin sensitivity as assessed by HOMA-IR index was lower in homozygous wild-type GG recipients without diabetes than in homozygous CC mutant recipients without diabetes, suggesting a role for IL-6 in insulin resistance.

Various genes previously reported to be associated with T2DM susceptibility include transcription factor 7-like 2 (TCF7L2), peroxisome proliferator-activated receptor gamma (PPARG), potassium inwardly-rectifying channel, subfamily J, member 11 (KCNJ11), solute carrier family 30 (zinc transporter), member 8 (SLC30A8), cyclin-dependent kinase inhibitors CDKN2A/CDKN2B, the insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2), and others [77-79]. It has been reported that many of the genes influence diabetes risk by affecting insulin secretion [80].

Chakkera et al [81] analyzed 15 previously identified variants in 8 genes associated with T2DM which included rs12255372 and rs7901695 in TCF7L2, rs5219 and rs5215 in KCNJ11, rs 1801282 in PPARG, rs13266634 in SLC30A8, rs10811661 and rs564398 in CDKN2A/CDKN2B, rs4402960 and rs1470579 in IGF2BP2, rs10946398, rs7756992, rs7754840 in CDKAL1, and rs1111875 and rs5015480 in HHEX but they did not find statistically significant evidence for association between markers in any of these genes and risk of NODAT development.
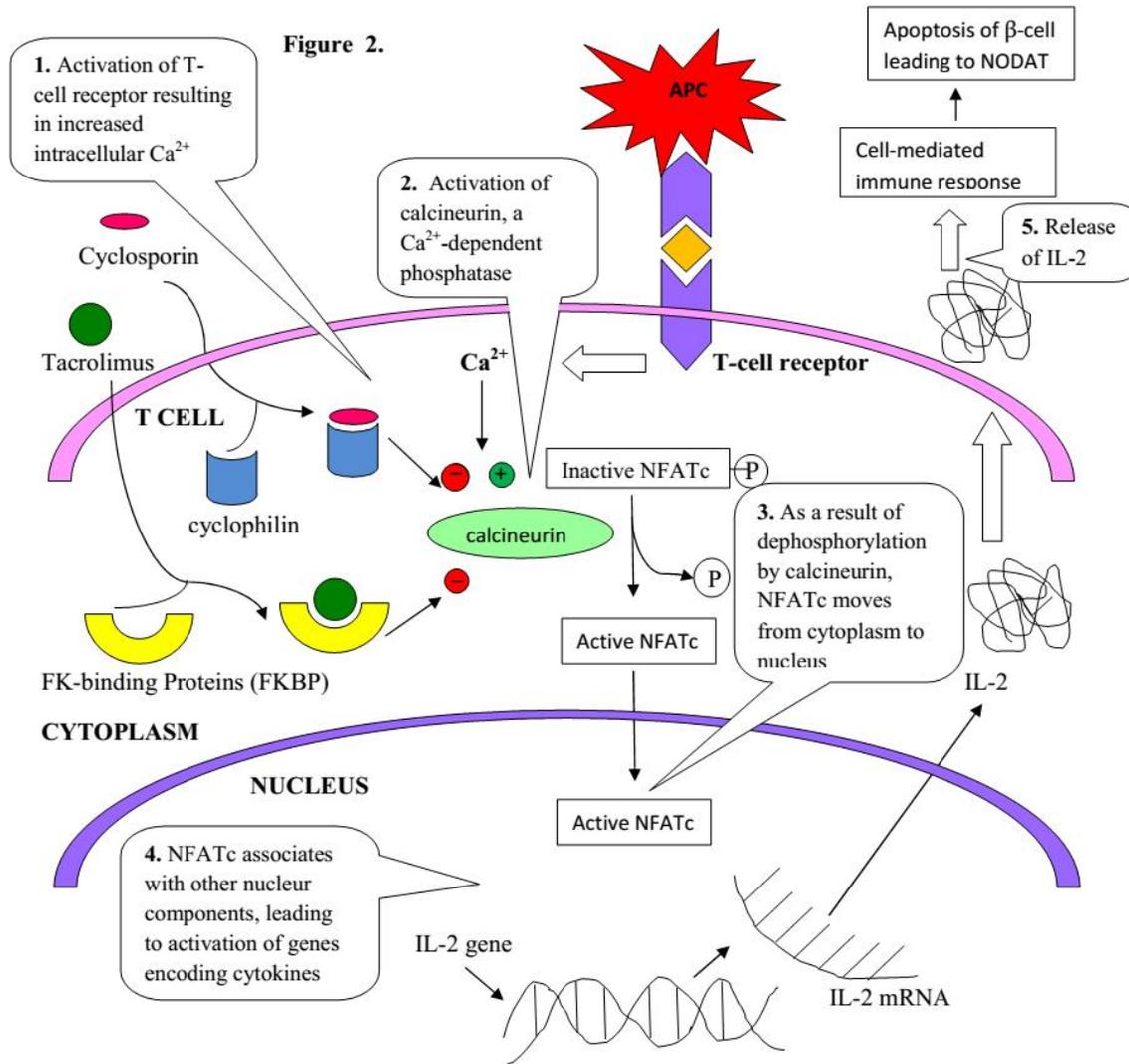
Figure 2. Probable pathway of calcineurin inhibitors leading to NODAT. (1). Cyclosporine and tacrolimus bind to specific regulatory proteins, cyclophilin A and FK506 binding protein-12, which bind to the interface of the calcineurin A/B heterodimer and prevent activation of the nuclear factorof activated T cells (NFAT). (2). Activation of T-cell receptor results in increased intracellualar calcium concentration, leading to activation of calcineurin. (3). Dephosphorylation of NFATc protein caused by calcineurin and activated NFATc translocate into nucleus from cytoplasm. (4). NFATc congregate on DNA regulatory sequences to alter gene expression. (5). Release of IL-2 preventing immune cell activation and leading to apoptosis of β-cell.

Ghisdal et al [82] analyzed 11 well-established type 2 diabetes susceptibility genes (TCF7L2, FTO, CDKAL1, KCNJ11, HHEX-IDE region, SLC30A8, CDKN2A-CDKN2B region, IGF2BP2, HNF1B, WFS1, and PPARG genes) and the occurrence of NODAT within 6 months after transplantation in a large cohort of predominantly white renal transplant patients. TCF7L2 was the only polymorphism found to be significantly associated with NODAT in the whole cohort. The risk for NODAT was found to be significantly higher in patients with CT and TT genotype as compared to CC genotype.

Yang et al [83] assessed the genetic risk factors associated with NODAT in Hispanic kidney transplant recipients. Among 14 alleles in nine genes, hepatocyte nuclear factor 4 alpha AA (rs2144908), hepatocyte nuclear factor 4 alpha TT (rs1884614), and insulin receptor substrate 1 AA+ AG

(rs1801278) were found to be significantly associated with NODAT.

Ergun et al [84] analyzed the relationship between the enzyme endothelial nitric oxide synthase gene intron 4 polymorphism and NODAT in kidney allograft recipients. This enzyme is involved in the synthesis of nitric oxide, which mediates insulin-induced uptake and metabolism of glucose in the skeletal muscle. Having a 4a allele of the endothelial nitric oxide synthase gene intron 4 polymorphism was found to be an independent risk factor for NODAT development.

Kang et al [85] suggest an association between adiponectin gene polymorphism and NODAT. In Korean kidney transplant recipients, 276G/T single nucleotide polymorphism (SNP) of adiponectin gene (rs1501299) was found to be associated with NODAT in a gender – specific manner. Moreover, reduced pre-transplantation serum adiponectin concentrations are also found to be associated with NODAT development [86, 87]. Hence estimation of pre transplant serum adiponectin will be a useful marker in the assessment of NODAT.

Jeong et al [88] suggested that chemokine ligand 5 (CCL5) gene polymorphisms was also associated with the development of NODAT in Korean kidney transplant recipients. Elevated serum CCL5 concentrations are observed in some inflammatory conditions, including kidney transplantation [89,90] and type 2 diabetes mellitus (T2DM) [91-93].

Bruna et al [94] analyzed the association of 276G/T adiponectin gene polymorphism and rs2280789 and rs3817655 CCL5 gene polymorphisms with NODAT development in Caucasian kidney transplant recipients. The TT genotype of 276G/T adiponectin gene polymorphism was significantly more frequent in NODAT than non-NODAT patients compared with GG/GT genotypes. They did not find any association between CCL5 SNPs and NODAT. There were no differences in genotype distribution and allele frequency of rs2280789 and rs3817655 CCL5 gene polymorphisms between NODAT and non-NODAT groups.

Yu et al [95] investigated the association between adiponectin gene polymorphism at position 45 and 276, that is, SNP-45: T/G, SNP-276: G/T and the risk of post transplantation diabetes mellitus (PTDM) in Chinese renal allograft recipients. The incidence of PTDM was significantly higher in patients with the GG genotype than those with the TG and TT genotypes for both SNP-45 and SNP-276.

Laure et al [96] reported the association of single-nucleotide polymorphisms in peroxisome proliferator-activated receptor α (PPARα) and P450 oxidoreductase (POR) with the development of NODAT in kidney transplant recipients treated with tacrolimus. They assessed two variants in PPARα (rs4253728 G>A and rs4823613 A>G) and one coding variant in POR (rs1057868; POR*28; A503V) and found that PPARα rs4253728 G>A and POR*28 variant alleles were both independently associated with an increased risk for developing NODAT after kidney transplantation.

SUMMARY

NODAT is a serious complication after renal transplantation associated with graft loss and patient loss. Therefore, there is a necessity to prevent the occurrence of NODAT. Various factors are responsible for the development of NODAT, but most studies have stated that insulin impairment and insulin resistance are the primary cause for the development of NODAT. The mechanism of NODAT are still unclear, however, immunosuppressants, HCV and CMV infection play an important role in the development of NODAT.

Most of the mechanisms involved in the development of NODAT release proinflammatory cytokines, which has cytopathic effect on β-cells. Apart from traditional factors responsible for NODAT, genetic factors also play a major role in the development of NODAT. Knowledge of genetic factors can help in identifying high risk patients and implementing preventive measures to reduce NODAT development. Identifying the genetic factors at earlier stage can help the clinicians to adopt the individualized immunosuppressants, thereby avoiding the occurrence of NODAT.

Aiming at uncovering the underlying genes responsible for the development of NODAT, adopting appropriate medications and preventive measures might reduce the burden of diabetes, thereby increasing the long term allograft function and better survival rates in the organ transplant recipients.

ABBREVIATIONS

NODAT: New-Onset Diabetes After Transplantation
T2DM: Type-2 Diabetes Mellitus
ESRD: End Stage Renal Disease
USRDS: United States Renal Data System
KTR: Kidney Transplant Recipient
ADA: American Diabetes Association
OGTT: Oral Glucose Tolerance Test
FPG: Fasting Plasma Glucose
2hrPG: Two Hour Post Glucose
IFG: Impaired Fasting Glucose
HCV: Hepatitis C Virus
CMV: Cytomegalovirus
CNI: Calcineurin Inhibitots
RR: Relative Risk
OR: Odds Ratio
HLA: Human Leukocyte Antigens
Tac: Tacrolimus
CSA: Cyclosporin A
BMI: Body Mass Index
LDL: Low Density Lipoprotein
TNF: Tumour Necrosis factor
INF: Interferon
IL: Interleukin

COMPETING INTERESTS

The authors declare that they do not have competing interests.

AUTHOR'S CONTRIBUTIONS

We conceived the plan of the review, drafted the manuscript and revised it. All authors read and approved the final manuscript.

AUTHORS DETAILS

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