Transplant Immunology 30 (2014) 52–58

Contents lists available at ScienceDirect

Transplant Immunology

journal homepage: www.elsevier.com/locate/trim

Review

New onset of diabetes after transplantation — An overview of epidemiology, mechanism of development and diagnosis

Sailaja Kesiraju [a,c,*], Purna Paritala [b], Uma Maheswara Rao Ch [b], S. Sahariah [a,b]

[a] Department of Biochemistry and Immunology, Transimmun, Hyderabad, India
[b] Department of Kidney Transplant, Krishna Institute of Medical Sciences, Hyderabad, India
[c] Department of Immunology, Bhagwan Mahavir Medical Research Center, Hyderabad, India

ARTICLE INFO

Article history:
Received 26 September 2013
Received in revised form 21 October 2013
Accepted 21 October 2013

Keywords:
NODAT
Renal transplantation
Epidemiology
β-cell function
OGTT

ABSTRACT

New onset of diabetes after transplantation (NODAT) is a serious and common complication following solid organ transplantation. NODAT has been reported to occur in 2% to 53% of renal transplant recipients. Several risk factors are associated with NODAT, however the mechanisms underlying were unclear. Renal transplant recipients who develop NODAT are reported to be at increased risk of infections, cardiovascular events, graft loss and patient loss. It has been reported that the incidence of NODAT is high in the early transplant period due to the exposure to the high doses of corticosteroids, calcineurin inhibitors and the physical inactivity during that period. In addition to these risk factors the traditional risk factors also play a major role in developing NODAT. Early detection is crucial in the management and control of NODAT which can be achieved through pretransplant screening there by identifying high risk patients and implementing the measures to reduce the development of NODAT. In the present article we reviewed the literature on the epidemiology, risk factors, mechanisms involved and the diagnostic criteria in the development of NODAT. Development of diagnostic tools for the assessment of β-cell function and determination of the role of glycemic control would include future area of research.

Contents

1. Introduction

New-onset diabetes after transplantation (NODAT) refers to the occurrence of diabetes in previously non-diabetic persons after organ transplantation. The incidence rates of NODAT vary by organ transplanted and post-transplant interval. The estimated incidence rates at 12 months post-transplant are 2–52% for kidney transplants, 9–21% for liver transplants, and approximately 20% for lung transplants. NODAT, an unavoidable consequence of the transplant and immunosuppressive process, has been labeled as type 2 diabetes mellitus (T2DM). Besides the traditional risk factors for T2DM (age, family history, obesity, and ethnicity), exposure to immunosuppressive agents often leads to the occurrence of NODAT. NODAT is characterized not only by abnormal glucose homeostasis but also by deterioration in the lipid profile, higher BP, and elevated inflammatory markers.

Transplantation is a cost effective treatment offering best quality of life when compared to other modalities available to end-stage renal disease patients. With the increase in the number of kidney transplant

* Corresponding author at: Bhagwan Mahavir Medical Research Center, A.C. Gaurds, Masabtank, Hyderabad 500004, India. Tel.: +91 40 23497303.
E-mail address: kesirajusailaja@gmail.com (S. Kesiraju).

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http://dx.doi.org/10.1016/j.trim.2013.10.006

recipients (KTR) worldwide there is a relative increase in the number of individuals with new onset of diabetes after transplantation. New onset of diabetes after transplantation associated with adverse impact on patient survival, graft rejection and graft loss as well as high risk of cardiovascular disease [1], rate of infections [2–4] leading to graft failure [5,6] and mortality[7–10]. The wide variations in the incidence of NODAT reported were may be due to the wide variations in the criteria for the diagnosis of diabetes, diverse population and different protocols followed for immunosuppression.

International Consensus Guidelines on NODAT were published in 2003, recommending that NODAT should be diagnosed based on the American Diabetes Association (ADA) criteria for type 2 diabetes published in 2003 [11,12]. The 2003 ADA criteria for the diagnosis of diabetes, coheres with the WHOs criteria of 1999. The NODAT guidelines recommend that fasting plasma glucose (FPG) is the preferred test for diagnosing NODAT, but studies have indicated that a two hour glucose (2hrPG) after an oral glucose tolerance test (OGTT) may be more sensitive for the identification of NODAT. The definition of diabetes mellitus in clinical practice, was fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), two-hours post-glucose ≥ 11.1 mmol/dL (200 mg/dL). And later the fasting plasma glucose limit was revised to 110 mg/dl from 126 mg/dl which corresponds to impaired fasting glucose (IFG) by the International Expert Committee, based on epidemiologic predictive data [13]. International Expert Committee also recommended the use of standardized HbA1c (≥6.5%) assay for the diagnosis of diabetes which has been approved by ADA in 2010 [14].

Owing to the high prevalence of diabetes in general population, and very few studies from India on NODAT, which is a prominent long-term problem for the success of both patient and graft survival, we have undertaken to review the epidemiology, development, mechanism, risk factors and prevention of NODAT and to compare the differences if any in Indian population, from other population. If the goal is to understand the root causes of the epidemic, it is important to first review the literature to understand the timing and origin of the epidemic. This type of epidemiologic analysis may provide insights into the potential etiologies that can then be used in the experimental setting. In this review we will not discuss the treatment or the management of NODAT which was well reviewed. The intent of this review is to focus on the underlying patho-physiological mechanism of NODAT, since there was limited understanding of the exact mechanism of events leading to NODAT.

2. Epidemiology

Renal transplant recipients with NODAT exhibit similar complications as those seen in the general population with type 2 diabetes, but at an accelerated rate [15]. There is a nine fold risk of diabetes in solid organ transplant recipients than their age matched controls [16]. Most of the studies reported cumulative frequencies of the incidence of NODAT while few reports were on sequential basis, differentiating the early, late and transient incidence of diabetes [17,18]. It was observed that the higher rate of incidence occurred in the first 6 months after transplantation. The few Indian studies present, highlighted only the risk factors for the incidence of NODAT [19–24]. Madhav et al. [19] in their retrospective study of 218 post-transplant patients, reported cumulative rates of 14.01% and 19.8% at 3 and 12 months respectively and observed an incremental incidence of 14.97% during the first post-transplant year. They also stated that the earliest incidence of NODAT was at 9 days after transplant and the risk factors were recipient age (≥36 years), Hepatitis C virus infection, HLA-B13, family history of DM, body mass index (≥30), and calcineurin inhibitor therapy. They also noted that NODAT had no influence on biochemical parameters. Jayant.T. Mathew et al. [20] in their prospective study of non-diabetic ESRD patients who were followed over 2 years after transplantation found persistent abnormal glucose tolerance in 45% patients and observed that pre-transplant factors like greater age, abnormal glucose tolerance parameters, and rapid gain in dry weight on hemodialysis (HD), along with higher prednisolone and cyclosporine (CsA) doses early post-transplant were important factors associated with the development of NODAT. Sharma R.K et al. [24] in their retrospective analysis of 1023 Indian transplanted patients between 1989 and 2000 showed no association between cytomegalovirus (CMV) and NODAT.

Epidemiological studies globally reported, using the United States Renal Data System (USRDS) records indicated that 40% of kidney transplant recipients will have developed NODAT by third year post-transplantation [25]; Kasiske et al. [8] reported a cumulative incidence rate of 9.1% at three months, 16% at 12 months and 24% at 36 months post-transplantation; Hur et al. [17] differentiated between persistent, transient and late onset of NODAT. They reported an overall incidence of NODAT of 39% at one year and 35.1% at seven years respectively for NODAT and defined persistent NODAT (23.4%) who had hyperglycemia within the first year of transplantation that continued unto the seventh year post-transplant. They also noted that other subgroups in their study had transient NODAT (15.6%) in which hyperglycemia started and ended within the first year, and late NODAT (11.7%) who developed hyperglycemia after the first year post-transplantation. A study from Kuwait [26] reported a cumulative prevalence of 21.2% of NODAT and in the same study they observed a higher (29.6%) incidence of NODAT in a subgroup of Arab ethnicity. A report from Warsaw [16,27] showed a 10.5% prevalence of NODAT. Gourishankar et al. [28,29] have shown 9.8% of NODAT prevalence in Canadian transplant recipients. Yagnik C.S. [30] in his report elucidated that early life malnutrition coupled with over-nutrition later might play a role in the pathogenesis of non-insulin-dependent diabetes mellitus (NIDDM) which is common in India [31].

3. Pathophysiological mechanisms and development of NODAT

The pathophysiology of NODAT is similar to that of type 2 diabetes mellitus [11] but is complicated by both transplantation specific and non-transplantation related risk factors. Multiple cellular and physiological mechanisms may be involved in the pathogenesis of NODAT. Earlier studies [32] reported that there was a high incidence of de novo hyperglycemia immediately after transplantation which can be associated with the exposure of pancreatic β-cells to several stress factors, collectively the surgical procedure, weight gain due to physical inactivity immediately after surgery (insulin sensitivity), high doses of corticosteroids and initiation of CNIs. The underlying mechanism of development of NODAT can be classified into insulin resistance and defect in insulin secretion. Surgical stress has a deleterious effect on pancreatic β-cell function such as metabolic stress, release of catabolic hormones, inhibition of insulin secretion resultant hyperglycemia and hypo-insulinemia leading to peri-operative keto-acidosis.

Early transplant hyperglycemia contributes to the reduction of glucose induced insulin secretion (GIIS) and β-cell hypertrophy. Glucotoxicity may result from oxidative stress due to the presence of reactive oxygen species within the β-cell from the mitochondrial electron transport chain [33]. It is well established that chronic hyperglycemia leads to β-cell degranulation and reduction of GIIS [34]. Progressive β-cell failure, reduction in β-cell mass and increase in β-cell apoptosis could be one of the pathophysiological mechanisms behind the development of NODAT (Fig. 1).

It is even observed [35] that absence of hepatic glucose production has no effect on the fasting plasma glucose concentration and compensatory induction of gluconeogenesis occurs in kidney and intestine driven by glucagon, glucocorticoids and acidosis. Could this be one of the reasons associated with early post-transplant hyperglycemia? Control of gluconeogenesis is mediated by glucagon. Whether estimating the levels of glucagon would help in finding any mechanism in NODAT? Shalev favors the theory that any excessive demand on beta cells to produce insulin to counteract elevated blood sugar eventually stresses the β-cells, which become less able to make enough insulin to meet the