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Review

Risk assessment and management of post-transplant diabetes mellitus

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ARTICLE INFO

Article history:
Received 25 May 2016
Accepted 21 July 2016

Keywords:
Diabetes mellitus
Organ transplantation
Risk factors
Management

ABSTRACT

The success rate of organ transplantation has been increasing with advances in surgical and pharmacological techniques. However, the number of solid organ transplant recipients who require metabolic disease management is also growing. Post-transplant diabetes mellitus (PTDM) is a common complication after solid organ transplantation and is associated with risks of graft loss, cardiovascular morbidity, and mortality. Other risk factors for PTDM include older age, genetic background, obesity, hepatitis C virus infection, hypomagnesemia, and use of immunosuppressant agents (corticosteroids, calcineurin inhibitors, and mammalian target of rapamycin inhibitor). Management of PTDM should be started before the transplantation plan to properly screen high-risk patients. Even though PTDM management is similar to that of general type 2 diabetes, therapeutic approaches must be made with consideration of drug interactions between immunosuppressive agents, glucose-lowering medications, and graft rejection and function.

1. Introduction

The number of solid organ transplantation recipients and survivors continues to increase over time due to advances in surgical techniques and the use of immunosuppressants [1]. As the life expectancy of organ transplantation recipients extends, the incidence of metabolic diseases (diabetes, dyslipidemia, obesity, and metabolic syndrome) is expected to grow [2–5]. The ultimate value of metabolic disease management in post-transplantation survivors is the reduction of long-term morbidity and mortality, as well as prevention or delay of cardiovascular diseases that are related to metabolic diseases [6,7].

Research regarding the occurrence of diabetes following solid organ transplantation has progressed since the first report in 1964 of diabetes following kidney transplantation [8]. Transplant recipients with no prior history of diabetes who develop diabetes either have unrecognized diabetes prior to transplantation or diabetes that develops after transplantation. The latter is the true definition of diabetes after transplantation and is referred to as new-onset diabetes after transplantation (NODAT). There is a recommendation, however, to describe diabetes after transplantation as post-transplantation diabetes mellitus (PTDM), as the evaluation of diabetes before transplantation has frequently been insufficient and many cases of diabetes after transplantation are not truly new-onset [9]. PTDM is a common complication after organ transplantation and increases the risks of cardiovascular morbidity, mortality and allograft organ function loss

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http://dx.doi.org/10.1016/j.metabol.2016.07.011
0026-0495/

[10–14]. Compared to nondiabetic recipients, patients with PTDM have approximately a three-fold increased risk of cardiovascular diseases [15]. Therefore, identification of risk factors, early diagnosis, and prompt management of PTDM are critical issues. In addition, as regular physical activity and body weight reduction have been found to prevent type 2 diabetes (T2DM) [16], these could be also applied to decrease PTDM risk. This review outlines the risk factors, diagnosis, and current therapeutic approaches for patients with PTDM.

2. Risk Factors and Pathogenesis of PTDM

In general, PTDM and T2DM mellitus are both explained by insulin resistance [17,18]. Insufficient insulin secretion to target tissues caused by pancreatic beta cell dysfunction and use of immunosuppressive agents are additional factors that contribute to PTDM development [19,20]. Insulin resistance causes postprandial hyperglycemia, and impaired insulin secretion and insulin sensitivity both lead to a poor prognosis for patients with PTDM [17]. The risk factors associated with PTDM are shown in Fig. 1.

2.1. Age

Similar to the increased risk of T2DM in older populations, older age is a risk factor for PTDM. In particular, the age of the patient at the time of the transplantation is a critical factor. The risk of PTDM starts to increase at the age of 45 [21], with a 160% increase in patients ≥60 years of age compared to patients aged 18–44 years [22]. Moreover, persistent hyperglycemia is associated with PTDM patients who are >40 years old [23].

2.2. Genetic Background

A retrospective study reported an approximately seven-fold increase in the risk of PTDM and a higher incidence in patients with one parent who had diabetes compared to patients without a family history of diabetes [24,25].

African American and Hispanic patients carry a higher risk of PTDM than Caucasian patients [11,22,26]. According to an analysis of the US Renal Data System, there is a 68% increase in the relative risk in African American patients and a 35% increase in Hispanic patients compared with that in Caucasian patients [22]. In addition, a recent study reported a higher incidence of PTDM in South Asians than in Caucasians (5-year cumulative incidence 35% vs 10%, subhazard ratio 4.2, 95% CI 2.4–8.5) [27]. This difference implies differences in the pathophysiological development or aggravation of diabetes among ethnicities [28].

In addition to ethnicity, more specific genes or single nucleotide polymorphisms (SNPs) are also related to PTDM. Our group previously showed that mutations in *TCF7L2, SLC30A8, HHEX, CDKAL1, CDKM2A/B,* and *KCNQ1*, which are contributing factors to T2DM, were also associated with PTDM [29–32]. Other mutations with established associations to T2DM have been reported in patients with PTDM; such as, *ADIPOQ* rs1501299 [33] and *CAPN10* rs5030952 [34]. SNPs in *IRS1* and *HNF4* increased the risk of diabetes in Hispanic kidney recipients by approximately two fold [35]. Angiotensinogen-encoding SNP was also associated an increased risk of PTDM [36]. The calcineurin inhibitor (CNI) target gene, which is the transcription factor for nuclear factor of activated T cells, regulates insulin production and could influence PTDM development in CNI users [37]. We also found an association between the *SLC30A8* rs13266634 mutation, which encodes the pancreatic beta cell specific zinc transporter-8 (ZnT-8), and susceptibility to PTDM. The polymorphic residue at position 325 of the ZnT-8 variant has resistance to the dampening of insulin granule fusion by cyclosporine and thus, remains unaffected by PTDM [38]. Moreover, an interleukin-6 promotor polymorphism was also reported to have a protective effect on the development of PTDM [39] (Table 1).

2.3. Obesity

Obesity is a well-known risk factor for T2DM that also raises PTDM risk [40]. Transplant recipients were reported to gain 10%–20% of their body weight within the first year [41] or the

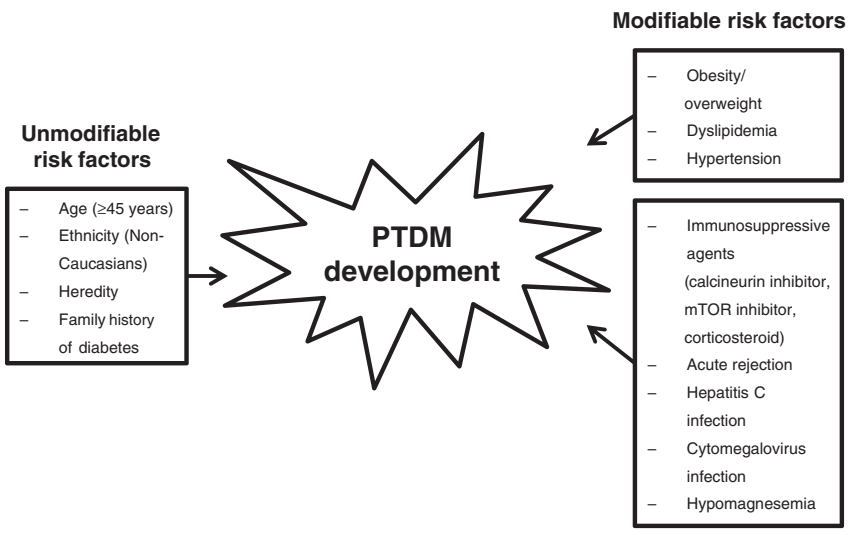

Fig. 1 – Risk factors for post-transplant diabetes mellitus.