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Diabetes Mellitus after Transplantation

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Abstract

Diabetes mellitus after transplantation is a serious and frequent metabolic complication after transplantation of solid organs. The current definition of post-transplantation diabetes mellitus is based on the criteria of the American Diabetes Association and the World Health Organization for type 2 diabetes mellitus and pre-diabetic conditions. Currently, we are able to define the non-specific and specific risk factors for transplantation. The knowledge of such risk factors is important for preventive strategies, stratification of risk, and preparation of the immunosuppressive protocol. The group with the highest risk for development of post-transplantation diabetes mellitus is patients who develop hyperglycemia in the early post-transplantation period. Post-transplantation diabetes mellitus affects the survival of both the graft and the patient. With growing obesity of the patients on the waiting list, the number of patients with post-transplantation diabetes mellitus also grows. In the event of successful reduction of occurrence of post-transplantation diabetes mellitus, we may expect an improved quality of life of patients after kidney transplantation(as well as any other solid organs), to reduce morbidity and mortality of patients after transplantation, thus also reducing the costs of care of patients after transplantation.

Keywords: Transplantation; Risk factors; Post-transplant diabetes mellitus

Introduction

Diabetes mellitus after transplantation (PTDM) is a serious and frequent metabolic complication after transplantation of solid organs [1]. More clear definition of PTDM has developed over the past 50 years as a result of the increased incidence. Currently, the modern-immunosuppressive treatments also allows us to transplant highly immunized patients, to perform AB0 and HLA incompatible transplantations, and to eliminate the occurrence of rejections in the post-transplantation period, which has resulted in the significantly prolonged survival of grafts. In view of that these changes, the survival of grafts and patients is negatively affected mainly by malignacies and cardiovascular diseases [1].

The results of several studies suggest that hyperglycemia after transplantation is, from the aspect of long-term monitoring, risky for development of micro vascular and macro vascular complications. PTDM increases the cardiovascular mortality and morbidity of the transplanted patients.

Definition and diagnostics

The definition of post-transplant diabetes mellitus (PTDM) had been developed for some time until 2003, when the Instructions for Diagnostics and Management of PTDM were published [2]. Until that time, no consensus existed in definition of diabetes mellitus after transplantation. Most frequently, a clinical definition was used in practice, which was based on the post transplantation period (more than 30 days after organ transplantation) and the necessity of insulin therapy. However, that definition allowed diagnostics of only the most severe cases, whereas the patients with pre diabetes condition were excluded from that diagnostics [3]. The current definition of PTDM is based on the criteria of the American Diabetes Association (ADA) and the World Health Organization (WHO) for diabetes mellitus type 2 and pre diabetes conditions – impaired fasting glycemia and impaired glucose tolerance (Table 1) [4,5].

In 2009, it was recommended to use the standardized test for glycated hemoglobin (HbA1c) ≥ 6.5%. However, the use of this test is limited in patients with chronical kidney disease and in patients after kidney transplantation, due to possible anemia resulting from (surgical loss of blood, lack of iron, immunosuppressive therapy, sudden break in administering erythropoietin in the post-operative period, dysfunction of the graft) [4]. Therefore, after kidney transplantation, it is

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Table 1: Diagnostic criteria for diabetes mellitus.

Diagnostic criteria for diabetes mellitus:
Symptoms of diabetes mellitus: polyuria, polydipsia, inexplicable reduction on weight or Glycaemia in fasting state ≥ 7 mmol/l or Glycaemia in the 2nd hour oGTT ≥ 11.1 mmol/l

recommended not to use the standardized HbA1c test for a minimum of the first 3 months after transplantation [3,5].

Incidence and prevalence

The incidence and prevalence of PTDM has changed in connection with the used immunosuppressive protocol and particularly with the diagnostic criteria for PTDM. In the era of administering high dosages of gluco corticoids, the incidence of PTDM was 50% [6]. Calcineurin inhibitors are included in the therapy, in combination with low dosages of gluco corticoids, the incidence fluctuates by as much as 2% to 53%. In the case of liver transplantation, the incidence of PTDM is around 40% [7], in heart transplantation it is 29% [8], and in lung transplantation it is 32% [9]. The great differences in the incidence of PTDM may be assigned particularly to the different timing and frequency of diagnostic tests for PTDM [1].

Risk factors

The occurrence of PTDM depends on the factors specific to both the donor and recipient [1]. Diabetes mellitus after kidney transplantation represents a frequent complication and has negative effects on the function of the transplanted kidney. Currently, we are able to define the non-specific and specific risk factors for transplantation. The knowledge of such risk factors is important for preventive strategies, stratification of risk, and management of the immunosuppressive protocol [10].

Gluco corticoids have through regulation of gene transcription potent immunosuppressive and anti-inflammatory properties. It is well known that gluco corticoids also have severe metabolic side effects. Calcineurin inhibitors cause a reversible suppression of insulin secretion at the level of transcription of them RNA of insulin binding to the FK506 – binding protein 12 and subsequent inhibition of calcineurin B – cells in the pancreas. Mono therapy rapamycin respectively combined immunosuppressive therapy (calcineurin inhibitors and rapamycin) is associated with insulin resistance and a higher incidence of PTDM. It is widely known that adipose tissue produces hormones that control is multi factorial. Several studies it has been confirmed that the formation of adipose tissue hormones (mainly adiponectin) also influenced by genetic factors, gluco corticoids and body fat distribution [8].

The screening of the risk factors for development of PTDM should be done prior to including the patient onto the waiting list, and it is even recommended toper form oGTT (oral glucose tolerance test) also in patients with physiological levels of glycaemia in the fasting state. Any pre-transplantation impaired glucose tolerance or impaired fasting hyper glycaemia is connected with more than a 2.5 times higher risk of development of PTDM compared with the "normoglycemic" patients [11].

The reports from extensive databases (e.g. United States Renal Data System – USRDS, Organ Procurement Transplant Network – OPTN, United Network of Organ Sharing - UNOS) which analyze the information on patients with chronical kidney disease, on organ donors, and on patients after kidney transplantation, identified several independent risk factors for PTDM (Table 2) [3].

Identification of risk patients for PTDM

Screening of patients in the waiting list: The pre-transplantation risk of development of PTDM should be based on the patient´s history and phenotype. In addition, it is important to account for age (>45 years), positive family history of type 2 diabetes mellitus, gestation diabetes, pre diabetes, and metabolic syndrome, BMI of more than 30 kg/sqm. The screening of patients on the waiting list should contain an assessment of the metabolism of glucose by oGTT. That test should be carried out in all patients waiting for transplantation. However, minimum in patients with the above risk factors, [12] the use of HbA1c is not recommended for screening due to the low sensitivity of the test in patients with failure of kidneys [13].

Screening of patients after transplantation: The screening for PTDM or pre diabetes after transplantation is recommended to be performed in all patients. It is appropriate to determine HbA1c 1 week after transplantation in the first 4 weeks after transplantation, then every 3 months for the period of 1 year from transplantation, then once a year. O GTT should be done in the 3rd and 6th month after transplantation [14].

New approaches in the treatment and diagnostics of post-transplantation diabetes mellitus

The improved knowledge of PTDM and pre diabetic conditions has led to the creation of recommendations for the therapy and diagnostics of PTDM, which are based on the recommendations for treatment of type 2 diabetes mellitus [15]. The published ADA recommendations for the diagnostics and management of PTDM stress the clinical importance of PTDM with the necessity of proactive and multidisciplinary approach [4,13]. However, the idea that PTDM is similar to type 2 diabetes mellitus is misleading, and under such "similarity", adequate initial therapy in the early post-transplantation period may be postponed due to the "adjustment" of immunosuppression in the patient who developed PTDM. The group with the highest risk for development PTDM is patients who develop hyperglycemia in the early post-transplantation period (2-7 days after transplantation), and that is 60% to 90% patients after transplantation without the presence of diabetes mellitus before transplantation. Of this group, 40% will develop PTDM within 3 years from the kidney transplantation. In these patients, the dominant problem is decreased insulin secretion due to application of calcineurin inhibitors – tacrolimus. According to the latest discoveries which are also confirmed by small studies, an early preventive intervention by exogenous insulin in the event of hyperglycemia in the immediate post-transplantation period may reduce the risk of development of PTDM. In that case, insulin acts as a protective factor for the B-cells of the pancreas [15].

Under the latest discoveries, a conference was held in Vienna in 2013, the aim of which was to update the previous recommendations, as well as to discuss the "gaps" in the then current clinical knowledge [4,13,16]. The outcome of the conference is the following recommendations (the strength of the evidence is stated in brackets):

Table 2: Risk factors for development of PTDM.

Non-modifiable risk factors	Modifiable risk factors
age	Corticosteroids
population (afro Americans, Hispanic)	Inhibitors of calcineurin
family history of DM2	Obesity
males	Hypertriacyl glycerolemia
HLA A30, B27, B42	arterial hypertension
Higher number of HLA discrepancies donor/recipient	Hypomagnezemia
Polycystic kidney disease	prediabetes before transplantation
Extended criteria donor	hepatitis C
	cytomegalovirus infection
	proteinuria

- **Change of terminology from "new onset diabetes mellitus" to diabetes mellitus after transplantation.** The term post transplantation diabetes mellitus addresses these shortcomings by simply describing newly diagnosed diabetes mellitus in the post transplantation setting (irrespective of timing or whether it was present but undetected prior to transplantation or not). The term PTDM should be utilized for clinically stable patients who have developed persistent post transplantation hyper glycemia. The term pre diabetes should be utilized for patients with post transplantation hyper glycemia not reaching diagnostic thresholds for PTDM (impaired fasting glucose and/or impaired glucose tolerance) [17].

- **Exclusion of transient hyperglycemia after transplantation from the diagnostics of PTDM.** Hyperglycemia is extremely frequent in the early post-transplantation period and develops in approximately 90% of patients after kidney transplantation. The diagnostics of hyperglycemia in the post-transplantation period is very important because it is a significant risk factor for PTDM. However, upon stabilizing the patient´s condition and the function of the graft, hyperglycemia will cease, and therefore, the diagnosis of PTDM should be reserved for those patients in whom hyperglycemia survives, in spite of good function of the graft at maintaining immunosuppression in the late post-transplantation period [17].

- **Diagnostics of PTDM based on oGTT.** Currently, oGTT is considered as a golden standard for the diagnostics of PTDM. In the event of applying oGTT, the incidence of PTDM is significantly higher compared to the postprandial monitoring of glycaemia or applying HbA1c. oGTT allows diagnosing the disorder of glucose tolerance, which is a significant risk factor for development of PTDM [17].

- **Identification of risk patients for PTDM.** The risk factors for PTDM are known and are described in detail in Chapter 4. The aim of the recommendations is always to identify the risk patients – particularly the patients with metabolic syndrome, and to affect the risk factors before transplantation itself [17].

- **Immunosuppression, stressing the best result for survival of the patient and the graft regardless of the risk of PTDM.** Immunosuppression is one of the most important risk factors for PTDM. However, the review meta-analyses confirm that discontinuation of corticosteroids in the therapy between the 3rd and 6th month after kidney transplantation has no significant effect on incidence of PTDM. However, the number of rejection episodes significantly increases. On the other hand, discontinuation of corticosteroids after several days of therapy resulted in reduced incidence of PTDM, but the significant reduction of incidence of PTDM was recorded only in cases when cyclosporine A (not tacrolimus) was used in the immunosuppressive protocol. However, the immunosuppressive protocol using cyclosporine A as calcineurin inhibitor without corticosteroids may be applied only in the event of low immunologic risk of the recipient [15,17].

- **Apply preventive strategies, not modifications of immunosuppression.** Prevention of PTDM should be recommended to all potential recipients with risk factors for development of PTDM. Prevention should include both non-pharmacologic procedures (weight reduction, change of life style) and pharmacologic therapy [17].

Conclusion

Kidney transplantation is the best treatment of terminal kidney failure. However, development of PTDM affects the survival of the graft and the patient. With growing obesity of the patients on the waiting list, the number of patients with PTDM grows. Obesity is the key risk factor for incidence and development of PTDM. Therefore, it is important to apply the measures which are able to eliminate the incidence of PTDM. Several analyzes suggest that preventive measures in cases of type 2 diabetes mellitus may be also effective in the prevention of PTDM. According to the latest analyses and recommendations, a change in lifestyle and effective therapy of the post-transplant hyperglycemia by insulin (as a protective factor for B-cells) is the method of choice in prevention of PTDM. In the event of successful reduction in incidence of PTDM, we may expect an improved quality of patients' lives after transplantation of kidneys (as well as any other solid organs), to decrease the morbidity and mortality of patients after transplantation, with resulting decreased costs on care for the patients after transplantation [18,19].

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