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Phenotypic risk factors for new-onset diabetes mellitus (NODAT) in renal transplant recipients

Fenotypowe czynniki rozwoju cukrzycy po przeszczepie nerki

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Summary

New-onset diabetes mellitus after transplantation (NODAT) is defined as diabetes which developed after organ transplantation. NODAT occurs in approximately 16-20% of recipients one year after kidney transplantation and is the main factor for the increased mortality and morbidity, increased medical costs, progressive graft failure and decreased patients' quality of life. Determination of phenotypic risk factors allows to define the scale of the risk of NODAT and can be helpful in detecting patients at risk of post-transplant diabetes. Overweight and obesity are well-known phenotypic risk factors that can be modified by lifestyle-change intervention. Adequate education about the principles of healthy lifestyle is one of the most important prevention factors. The medical staff should organize health education which should begin long before the planned transplantation, even at the stage of predialysis treatment or dialysis and be continued after transplantation. Early assessment of the risk of developing glucose metabolism disorders also allows the selection of immunosuppressive therapy less likely to affect carbohydrate metabolism. The article presents examples of simple risk scores and also principles of prevention and treatment of NODAT.

The article presents the definition of NODAT, risk factors, especially overweight or obesity, risk scores and also principles of prevention and treatment of NODAT.

Keywords: NODAT • kidney transplantation • diabetes mellitus

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Abbreviations: **ADA** - American Diabetes Association, **BMI** - body mass index, **CMV** - cytomegalovirus, **CS** - corticosteroids, **CsA** - cyclosporine A, **GFR** - glomerular filtration rate, **HbA1c** - glycated hemoglobin, **HCV** - hepatitis C virus, **HD** - hemodialysis, **HLA A26** - human leukocyte antigen encoded by the A locus in the major histocompatibility complex, **HLA B27** - human leukocyte antigen encoded by the B locus in the major histocompatibility complex, **IFG** - impaired fasting glucose, **IGT** - impaired glucose tolerance, **IS** - immunosuppressive, **KTx** - kidney transplantation, **LDL** - low-density lipoprotein, **MMF** - mycophenolate mofetil, **NODAT** - new-onset diabetes mellitus after kidney transplantation, **OGTT** - oral glucose tolerance test, **SIR** - sirolimus, **TAC** - tacrolimus, **WHO** - World Health Organization.

INTRODUCTION

Kidney transplantation is the most effective method of renal replacement therapy. In Poland 1113 kidney transplants (KTx) were performed in 2013 [27]. Patients after renal transplantation require immunosuppressive (IS) therapy. Complication of this treatment can be glucose metabolism disorders, which is an important clinical problem. New-onset diabetes mellitus (NODAT) is defined as diabetes which developed after organ transplantation [11]. NODAT occurs in approximately 16-20% of recipients one year after transplantation and 17-24% after 3 years from the KTx [10,17,21].

Similar data were obtained in our own study encompassing 377 consecutive renal transplant recipients in whom the incidence of NODAT at 3, 6 and 12 months after KTx was 15.9%, 22.1% and 23.4% respectively. The mean interval from transplantation to the onset of the NODAT was 3.08 ± 2.73 months [23]. NODAT is the main factor for the development of cardiovascular disease, largely associated with the increased mortality and morbidity and increased medical costs, and consequently, a decrease in patients' quality of life [33]. It has also been associated with progressive graft failure and decreased patient survival [9,32]. Known risk factors of NODAT are: positive family history of type 2 diabetes in parents or siblings, past gestational diabetes, birth of a baby with weight over 4 kg, polycystic ovarian syndrome, ethnicity predisposed to have diabetes (black race, Hispanics), HCV and CMV infection, presence of HLA A26 or B27, low physical activity, overweight ($BMI > 25 \text{ kg/m}^2$) and obesity ($BMI > 30 \text{ kg/m}^2$), hypertension, previously diagnosed glucose metabolism disorders (impaired glucose tolerance - IGT or impaired fasting glucose - IFG), lipid disorders, age over 40 years, polycystic kidney disease as a cause of chronic kidney disease, use of the immunosuppressive drugs. Also there were indicated factors lowering the incidence of NODAT, which include: younger age of the recipient, use of the mycophenolate mofetil (MMF) or azathioprine, chronic glomerulonephritis as a cause of renal failure, a higher level of education of transplant recipient [5,12,14]. Among these, overweight and obesity can be modified by lifestyle-change intervention, including diet modifications and exercise [21,32].

Factors predisposing to the development of NODAT were also examined in our study. The multivariate analysis revealed that the independent significant predictors of NODAT existing before transplantation were positive family history of diabetes and treatment by peritoneal dialysis; from the

elements operating after transplantation exclusively had a significant impact older donor age. Our finding, not reported in previous literature, was the observation of significantly higher rate of NODAT in the peritoneal dialysis treated patients compared with the hemodialysis group (35.4% versus 21.2%) [23].

NODAT

The diagnosis of diabetes mellitus after kidney transplantation is based on the general clinical and biochemical criteria defined by the World Health Organization (WHO) and the American Diabetes Association (ADA) in 2003 [26]. These criteria are consistent with the general principles of diagnosis of diabetes mellitus:

- Casual plasma glucose $\geq 200 \text{ mg/dl}$ ($\geq 11.1 \text{ mmol/l}$) and the declaration of the typical symptoms of hyperglycemia (polyuria, polydipsia and unexplained weight loss),
- Twice identified fasting plasma glucose $\geq 126 \text{ mg/dl}$ ($\geq 7.0 \text{ mmol/l}$); fasting is defined as no caloric intake for at least eight hours,
- Glycemia in 120 minutes of oral glucose tolerance test - (OGTT 75 g) $\geq 200 \text{ mg/dl}$ ($\geq 11.1 \text{ mmol/l}$) [1].
- Currently Polish Diabetes Association does not recommend use of glycated hemoglobin (HbA1c) for the diagnosis of diabetes [15].

NODAT occurs frequently in the 1st year after transplantation (incidence 15-25%) but NODAT can occur at any time after kidney transplantation and it may stay subclinical for a long time [7]. It is reasonable to assess blood glucose at each visit and at least every three months in the first year after renal transplantation [13].

Factors significantly contributing to development of NODAT are immunosuppressive (IS) drugs used after transplantation: calcineurin inhibitors, especially tacrolimus, but also cyclosporin A and corticosteroids (CS). A meta-analysis showed that insulin-treated NODAT occurred in 9.8% of renal transplant recipients on tacrolimus versus 2.7% of those on cyclosporine-based regimens [16].

The possible mechanisms that may cause NODAT are: impaired insulin-mediated suppression of hepatic glucose production, insulin resistance induction or direct pancreatic beta cell toxicity [4,20,22].

Hyperglycemia occurs often in the postoperative period because of high corticoids dosage after KTx and it may correlate with the future development of NODAT. Identification of

postoperative hyperglycemia may have clinically significant implications for long-term patient and graft survival [6].

RISK FACTORS FOR NODAT

Chakkerla et al. in a single-center retrospective cohort study used pre-transplant clinical and laboratory measurements to construct a risk score for NODAT [7]. They suggested a simple risk score using the sum of seven risk factors. A score of 0–7 is calculated from: pre-transplant age (age > 50 y.), family history of type 2 diabetes mellitus, BMI - defined as the weight in kilograms divided by the square of the height in meters (kg/m^2), pretransplant fasting glucose (≥ 100 mg/dl) and triglycerides, use of gout medicine, and predicted use of corticosteroids pre-transplant (non-transplant indications or immunologic indications). The risk score predicted incidence of NODAT at 1 year after transplantation. The risk of NODAT ranged from 7%, for a score of 0, to 56%, for a score of ≥ 4 [7].

Mathew et al. in cohort study showed that malnutrition at the start of dialysis was common [25]. In this study two markers of nutritional status were used – BMI and its evolution over time on dialysis prior to kidney transplantation. They showed negative correlation to the level of BMI at the start of HD. A higher rate of increase in BMI pre-transplant was seen in NODAT patients [25].

Relation of weight gain to the development of diabetes mellitus is known. Resnick et al. showed that each kilogram of weight gained annually in 10 years increase a risk of developing diabetes in the subsequent 10 years for about 49% [28]. This study implicates that malnutrition before HD and KTx may be another significant risk factor of developing NODAT [28].

Marrero et al. in a large multi-center study showed relationship between baseline pre-transplant BMI and NODAT development, but no relationship between post-transplant BMI gain and NODAT [24]. In this study 24% of patients who developed NODAT were obese at the time of transplantation. The risk of NODAT increased by 13% for each increase of one unit of BMI.

In a study by Marrero there was an increase of 8.2% of basal weight at 1 year after transplantation [24], but weight gain in the first year after transplantation was not an independent predictor for NODAT in multivariate analysis [24]. Cosio et al. found a correlation between pre-transplant weight and NODAT, but not with weight gain, in patients who received cyclosporine-based immunosuppression [10]. In the general population, an association was found between duration of obesity and the risk of non-insulin-dependent diabetes mellitus [29]. It is possible that another risk factor of NODAT is duration of overweight and obesity before transplantation.

PREVENTION OF DIABETES

A patient characterized by an increased risk of development of NODAT should be learned about the benefits associated

with normal weight and regular physical activity. It is also important to identify a group of patients that need diabetes screening. Patients characterized by the presence of pre-diabetic state (IFG or IGT) should be advised to lose weight, maintain normal BMI, cease cigarette smoking and increase physical activity. This group can be also recommended to be treated with CsA rather than TAC and with low dose of corticosteroids (CS).

Early steroid withdrawal on postoperative day 6 significantly reduced the incidence of developing NODAT 5% vs 21% in steroid treated patients ($p=0.015$) but the regimen require induction with polyclonal antibody or IL-2 receptor antibody [19].

The CS dose should be decreased as soon as possible to 5 mg/day prednisolone, but completely CS withdrawal is not recommended [11].

Although complete steroid withdrawal can reduce the incidence of NODAT, a significantly percentage of patients suffer a rejection episode requiring reinstitution of CS therapy [18].

Late steroid withdrawal (≥ 3 months) resulted in increased rates of acute rejection and late graft lost. Rapid discontinuation of prednisone within the first week post transplantation increases risk of mild acute rejection but minimizes steroid-related complications. The IS protocols for rapid CS withdrawal requires induction therapy with polyclonal antibody or IL-2 receptor antibody but resulted in decreased 10-years rates of NODAT (6.3% in protocol with CsA/MMF, 19.3% with TAC high dose/SIR low dose and 5.5% with TAC low dose/SIR high dose). These study was conducted in the group of renal transplant recipients with grafts from living donors in 73 % of them [31].

Patients should be observed for the occurrence of other risk factors for diseases of the cardiovascular system (hypertension, lipid disorders, etc.). They also should avoid diabetogenic drugs. One of the most important prevention factors is adequate education about the principles of a healthy lifestyle [15].

NODAT TREATMENT

Self-monitoring of blood glucose is essential for diabetes monitoring. It is useful in patients taking oral antidiabetics or insulin and also in those who control diabetes only by diet therapy.

One of the most important therapeutic strategies for patients with diabetes after transplantation involves weight loss through a healthy diet and physical activity. That has been shown to decrease peripheral insulin resistance, plasma triglyceride and LDL levels. Lifestyle changes and educational elements are recommended as the first step in the treatment of diabetes.

Another step of diabetes treatment can be oral-agent monotherapy but it is important to be aware of some restrictions.

In the case of transplant recipients with impaired kidney function it is important to consider the possibility of serious adverse effects such as lactic acidosis (with metformin – not recommended if GFR<60 ml/min/1,73m²) and hypoglycemia (with long-acting sulfonylureas). Particular care is required in the selection of oral agents for elderly transplant patients and lower doses should be used. If adequate control is not obtained with a single agent then a combination of agents with different mechanisms of action could be considered. Administration of insulin may be required when use of oral agents is insufficient, not recommended or unsafe. The indications for insulin therapy initiation should be considered if blood glucose levels do not fall below 120-140 mg/dl (6.7-7.8 mmol) before meals and below 160-180 mg/dl (8.9-10 mmol) after meals, with HbA1c levels above 7.5%. Also, if at any point patient becomes metabolically decompensated, insulin injections must be administered. Patients may also be switched to insulin if therapeutic goals are not met with previous therapies. Insulin doses and number of daily injections should be adjusted to achieve target glucose levels but one should be aware of neuroglycopenia [11].

LIFESTYLE INTERVENTION

The medical staff should organize health education (nurses, dieticians). It should be focused on the exclusion or modification of these risk factors, which depend on the patient (reduction of body weight, cessation of smoking, physical activity). Education should begin long before the planned transplantation, even at the stage of predialysis treatment or dialysis and should be continued after transplantation [2]. Obese patients should be aware that most transplant centers do not perform the transplantation procedure if BMI>35 kg/m² [30].

There are two medical nutrition therapy goals that contribute specifically to glycemic management: to moderate the overall carbohydrate intake and to reduce insulin resistance by promoting weight loss in overweight or obese patients. The overall carbohydrate intake should be reduced to 130-180 g/day. Carbohydrates with a lower glycemic index are favored. In overweight or obese patients the total caloric content of food must be reduced to achieve weight

loss. The most optimal is to return to baseline BMI of the patient with exception of patients with increase in BMI due to physical activity.

Medical nutrition therapy is time consuming and specialized so dietician should take care of the patient. All the patients from a risk group of NODAT are advised medical nutrition therapy [3].

It is well known that physical activity slows the progression of diabetes and delays the onset of its complications. Physical activity lowers blood glucose levels, mobilizes stored glycogen into glucose and increases use of alternative energy sources such as free fatty acids. It promotes the body weight reduction, insulin resistance reduction and ultimately reduces the risk of NODAT. Patients should engage in a minimum of 150 min/week of exercise undertaken at moderate intensity. Any form of aerobic exercise (including walking) that uses large muscle groups and causes sustained increases in heart rate is likely to be beneficial, but patients should avoid sports, which increase the risk of injury to the transplanted kidney. Resistance gym-based training may be less effective for maintaining blood glucose control but adequate for maintaining muscle mass and strength [8]. It is well known that adherence to life style modification is difficult to obtain and require strong motivation.

CONCLUSIONS

NODAT is an important problem in the care of patients after kidney transplantation. The exact determination of high-risk groups of this complication on the basis of their phenotypic traits, and clinical data enables accurate screening and rapid implementation of treatment in case of detection of diabetes. This is accompanied by reduction in mortality, graft-loss, improved quality of life and decreased costs of treatment in this group of patients. Simple risk scales can be helpful in detecting patients at risk of post-transplant diabetes. Appropriate education, diet and physical activity before and after transplantation limit the incidence of NODAT. Early assessment of the risk of developing diabetes after transplantation also allows the selection of immunosuppressive therapy less likely to affect carbohydrate metabolism.

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