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Original Scientific Paper

NEW-ONSET DIABETES AFTER KIDNEY TRANSPLANTATION: DIAGNOSIS, RISK FACTORS, AND MANAGEMENT

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SUMMARY – New-onset diabetes after transplantation (NODAT) is a frequent and severe complication after renal transplantation. It is diagnosed according to standard criteria for type 2 diabetes. Risk factors for NODAT are non-modifiable (non-white ethnicity, older age, genetic predisposition, previous glucose intolerance, steroid therapy, male donor, and others) and modifiable (obesity, viral infections, and immunosuppressive therapy). Glucose control is needed immediately after renal transplantation and after 3, 6, and 12 months and annual glucose control is needed after that period. When NODAT is diagnosed, the primary goal includes lifestyle modification, like a diet with weight loss and exercise, and obtaining optimal glucose control to reduce micro- and macrovascular complications of diabetes. In order to obtain better glucose control, modification of immunosuppressant therapy is also needed, like a reduction of corticosteroid and calcineurin inhibitors and also a conversion of tacrolimus to a less glucotoxic agent. Pharmacotherapy includes oral hypoglycemic agents (in most cases metformin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors) and insulin (in most cases biphasic insulin several times daily or intensive insulin therapy). Finally, metabolic risk factors like dyslipidemia and hypertension should also be treated, and a regular annual screening should be performed for micro- and macrovascular complications of diabetes.

Key words: *new-onset diabetes after transplantation (NODAT), immunosuppressive drugs, diabetes management, kidney*

Definition

New-onset diabetes after transplantation (NODAT) is a severe and frequent complication after renal transplantation. Approximately 15-30% of patients with kidney transplants without previous diabetes develop NODAT during the first year after transplantation[1-3]. Many more patients after organ transplantation develop glucose intolerance. Before 2003, diabetes developed after organ transplantation was usually termed as a "posttransplantation diabetes mellitus" because there was no consensus regarding its definition. The requirement of insulin treatment shortly after transplantation (usually 30 days) was the clinical definition of "posttransplantation diabetes mellitus". However, only patients with severe cases of diabetes were identified, while patients with other glucose metabolism disorders were not involved. Finally, in 2003, the International Consensus Guidelines advised that the diagnosis of NODAT should be made according to the American Diabetes Association (ADA) criteria for type 2 diabetes[4,5]

Furthermore, in patients with a kidney transplant, the plasma glucose level for diagnosing impaired fast-

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ing glucose was set to 5.5 mmol/L[6]. Although hemoglobin A1c level ≥ 6.5% is recommended for diagnosing diabetes, it cannot be used as a diagnostic tool in the posttransplant period because that period is frequently associated with anemia resulting in false hemoglobin A1c results[7-9]. However, it should be stressed that the diagnosis of NODAT does not include patients with diabetes before transplantation and patients with transitory hyperglycemia that normalized after discharge from the hospital.

Epidemiology

Incidence of NODAT in patients after kidney transplantation depends on diagnostic criteria, immunosuppression therapy, and length of follow-up. It is usually diagnosed in the first months after transplantation, accompanied by immunosuppression therapy in high doses and reaching an incidence of 20%[10,11]. After that period, the incidence of NODAT decreases with incidence stabilizing at around 6% per year, similar to patients in the pretransplant period[3]. Moreover, if diabetes is diagnosed later in patients after kidney transplantation, it can be genuine type 2 diabetes rather than NODAT.

The prevalence of NODAT after kidney transplantation is up to 50% and depends on diagnostic criteria, immunosuppression regimen, and length of follow-up[12-13]. Wide variation in prevalence resulted from a different criterion for the diagnosis of NODAT until ADA and World Health Organization (WHO) announced Consensus Guidelines in 2003[4]. Most studies reporting a low incidence of NODAT do not include oral glucose tolerance test (OGTT) as a diagnostic criterion resulting in a significant underestimation of incidence[14]. In addition, hemoglobin A1c testing may also modify the incidence of NODAT since it cannot be used as a diagnostic tool in the posttransplant period. For example, in a prospective study that included 122 patients with a renal transplant that had normal fasting plasma glucose for over 6 months after transplantation, after OGTT testing in the same group of patients, 18% had impaired fasting glucose, 9% had impaired glucose tolerance, and even 10% had diabetes mellitus, all defined by WHO criteria[15].

Etiology and pathophysiology

Metabolic risk factors involved in the pathogenesis of type 2 diabetes development also increase the risk of NODAT development in renal transplant recipients. Table 1summarizes several risk factors for the development of NODAT that can be divided into two major categories: those that cannot be modified and those that can be potentially modified. The most important risk factors that cannot be modified are age over 40 years, non-white ethnicity, family history of diabetes, previously diagnosed glucose intolerance, the presence of some specific human leukocyte antigen (HLA) class like HLA B42, B27, and A30, history of acute rejection of renal graft, male donor and polycystic kidneys[16]. As observed in patients with type 2 diabetes, age over 45 years is the most substantial risk factor for NODAT, and risk for NODAT incidence in older age increases by almost 50% for every decade increase in age[17-19]. Besides, the relative risk of NODAT increases by 90% in patients with renal transplant aged 45-59 and by 160% in patients with renal transplant aged over 60 years compared to the reference (18-44 years). Compared to white patients, the relative risk of NODAT is also increased in a specific race, like Hispanic patients (35% increased risk) and in black patients (32-68% increased risk)[20-21]. The most important modifiable risk factors are obesity and other obesity-related components of the metabolic syndrome, co-infection with cytomegalovirus and hepatitis C, and immunosuppressive therapy (calcineurin-inhibitors (particularly tacrolimus), corticosteroids, and sirolimus)[16]. In overweight patients (BMI > 30 kg/m^2), the risk of developing NODAT in renal transplant patients doubles. Positive hepatitis C virus and cytomegalovirus, even in those with asymptomatic infection, are independent risk factors of NODAT in renal transplant patients[20-22]. Among modifiable risk factors, the contribution of immunosuppressive agents to NODAT development is predominant[4,16,23]. The role of corticosteroids in the development of NODAT is dose-dependent, which was first described in 1964 in patients with renal transplant[24].

The etiology of NODAT is complex and not fully understood, but insulin deficiency, insulin resistance, and impaired beta cell insulin secretion are key underlying metabolic abnormalities[25]. Insulin resistance and secretion are suppressed by immunosuppressive medications, particularly calcineurin inhibitors and glucocorticoids[26]. Besides inhibition of T lymphocyte activation via a connection with intracellular target proteins, immunosuppressive medications also cause a

defect in beta cell insulin secretion and increase peripheral insulin resistance[25]. Corticosteroids are basic post-transplant immunosuppressive medication and a part of the majority of the therapies scheme. In renal transplant recipients treated with corticosteroids, the risk of NODAT is related both to the duration of therapy and used dose[17]. The most important effect of corticosteroids is the increase in peripheral insulin resistance. Consequently, corticosteroids increase hepatic gluconeogenesis and glucose secretion and increase insulin resistace[27,28]. Corticosteroids also suppress beta-cell insulin secretion and decrease glycogenesis, increase fasting and postprandial glucose level and induce islet cell apoptosis at higher doses[29-31]. High doses of corticosteroids during the first year after renal transplantation, particularly in patients with acute graft rejection, significantly increase the risk of development of NODAT. For example, in patients treated with corticosteroids, a 0.01 mg/kg higher prednisolone daily dose increase risk of developing NODAT by 5%[32]. In contrast, a progressive decrease in prednisolone dose during the first 12 months after renal transplantation significantly improves glucose control[33].

Tacrolimus and cyclosporine are calcineurin-inhibitor drugs that are widely used in patients with renal transplantation and in most cases, patients are treated with one or the other drug as part of their immunosuppressive combination. Both drugs impair insulin release and insulin sensitivity, which are the most important mechanisms for calcineurin-inhibitor induced NODAT. However, the risk of NODAT development is about 50% higher with tacrolimus compared to cyclosporine and, compared to corticosteroids, it seems that the effect on NODAT is not related to used dose[2,3,34-36]. Tacrolimus is the preferred calcineurin-inhibitor drug because it has superior efficacy and safety[37]. The main pathophysiological disorders that cause hyperglycemia in patients with renal transplantation are apoptosis of beta-cell and insulin resistance. In a beta-cell, calcineurin is a calmodulin-dependent serine/threonine phosphatase that consists of two subunits, both of which are required for its function. In addition, calcium influx activates calcineurin and interacts with proteins that are involved in beta-cell function, proliferation, and maturation[38]. Treatment with calcineurin-inhibitor drugs reversibly suppresses the secretion of insulin, attacking insulin mRNA transcription[39]. At peripheral muscles, calcineurin is involved in gene transcription that improves insulin sensitivity, and calcineurin deficiency increases insulin resistance in muscles. In addition, calcineurin-inhibitors also reduce glucose transporter type 4 (GLUT-4) receptor molecules at the cell membrane of peripheral tissues (muscle and adipose tissue), blocking glucose entry into the cell cytoplasm[40,41]. Tacrolimus also suppresses glucose-induced insulin release from beta-cell via reduced glucokinase activity[42]. At the microscopic level, treatment with calcineurin-inhibitors results in cytoplasmic swelling, altered insulin staining, and vacuolization[43]. In a prospective study that included over 8000 patients with renal transplantation, treatment with tacrolimus was associated with a significantly higher incidence of NODAT compared to cyclosporin[44]. Moreover, the risk for NODAT is increased more than two-fold at the highest dosages of tacrolimus, and even at the lowest dosages of tacrolimus, the risk for NODAT is increased by over 28%. The diabetogenic effect of tacrolimus is further potentiated with increasing steroid dosages, so the patients who receive >0.75 mg/kg per day have the highest risk for NODAT. Compared to tacrolimus, a higher steroid dose does not increase the risk for NODAT in patients treated with cyclosporine.

Sirolimus is an immunosuppressive agent also used in patients with renal transplantation that increases the risk of NODAT. However, it seems that the risk of NODAT in patients on sirolimus therapy is mainly due to its combination with calcineurin-inhibitors, although extensive database studies and single-center reviews suggest that sirolimus itself is also a risk factor for NODAT[45,46]. The diabetogenic activity of sirolimus is mediated by hypertriglyceridemia and insulin resistance[47]. Since sirolimus is neutral with respect to NODAT compared to calcineurin-inhibitors, conversion from calcineurin-inhibitors to sirolimus may decrease the risk of NODAT[17,48].

In order to improve glucose control in patients with established NODAT, but also to decrease the risk for NODAT development, ADA suggests an algorithm for immunosuppression management in patients with renal transplantation[10]. In patients with a high risk of NODAT development but with low immunological risk, the first choice might be the cyclosporine-glucocorticoid combination, and in the case of NODAT development or inadequate glucose control, a switch to belatacept is indicated with glucocorticoid

Table 1: New-onset diabetes after kidney transplantation: risk factors

Non-modifiable risk factors	Modifiable risk factors
- Older age - Non-white race - Genetic predisposition (HLA A28, A30, B27, Bw42) - Polycystic kidney disease - Previous glucose intolerance - Previous steroid therapy - Male donor - Deceased donor - Diabetes in parents and/or relatives	- Obesity and metabolic syndrome - Low physical activity - Viral infection (hepatitis C, cytomegalovirus) - Corticosteroids: ↑ gluconeogenesis, ↑ insulin resistance, ↓ secretion, ↓ beta-cell function - Calcineurin-inhibitors: ↓ insulin release, ↓ insulin sensitivity, ↓ glucose uptake, ↓ beta-cell function, ↓ beta-cell proliferation, ↓ beta-cell maturation - Sirolimus: ↑ triglyceridemia, ↑ insulin resistance

reduction. In patients with high immunological risk, the first choice is tacrolimus-glucocorticoid combination[37,49]. In the case of NODAT development or inadequate glucose control, a reduction of tacrolimus and glucocorticoid should be made. Finally, if there is no improvement in glucose control 6 months after transplantation and 3 months of minimal glucocorticoid dose, a switch to cyclosporine is considered in patients with high immunological risk, and in patients with low immunological risk, a therapy with belatacept should be considered.

NODAT in patients with renal transplantation negatively affects the survival of graft and patient. In patients with renal transplantation but without diabetes, the risk of cardiovascular disease is increased twofold compared to the general population, and that risk is additionally increased after the development of NODAT[50,51]. Therefore, patients with renal transplantation and NODAT have a significantly increased risk of developing the cardiovascular disease but also decreased survival rate compared to patients without NODAT[52]. Patients with renal transplantation and NODAT have several risk factors that increase the risk of cardiovascular disease like hyperinsulinemia, glucose intolerance, hypertension, dyslipidemia, and insulin resistance. Besides increased cardiovascular risk, patients with renal transplantation and NODAT have an increased risk of infections and sepsis. After organ transplantation, the survival rate of patients with NODAT is reduced by 3 years compared to patients without NODAT[53]. NODAT in renal transplant recipients also has adverse effects on graft function and survival[54]. Proposed mechanisms include a higher risk of microvascular complication (particularly diabetic nephropathy), hypertension, increased risk of urinary infections, and low immunosuppressant doses[4].

Diagnosis

A precise incidence of NODAT has been difficult to estimate in years before 2003 because of different definitions and diagnostic criteria of NODAT. De novo diabetes after organ transplantation was usually termed as a "posttransplantation diabetes mellitus" and diagnosed as random plasma glucose over 11.1 mmol/L, or fasting plasma glucose over 7.7 mmol/L or treatment of hyperglycemia with oral agent or insulin in the period after organ transplantation. Finally, in 2003, International Consensus Guidelines and ADA declare that the diagnosis of NODAT should be the same as the criteria for diagnosing type 2 diabetes[4,5]. All patients in the pre-transplant baseline evaluation should perform standard OGTT according to WHO procedures with 75 g of glucose melted in water[4]. In addition, in the pretransplant management and evaluation period, medical documentation of patients and family glucose history should be included[55]. Patients with abnormal OGTT before transplantation indicating impair glucose tolerance should be screened once a year[4]. Patients with OGTT suggesting glucose intolerance or overt diabetes before transplantation must be educated about diet and weight control, lifestyle modifications with exercise, and also treated with adequate therapy (oral hypoglycemic agents or insulin therapy). After renal transplantation, patients must control fasting plasma glucose at regular periods (0, 3, 6, and 12 months after transplantation). After that time, one-yearly testing of fasting plasma glucose should be performed (Figure 1)[4]. If fasting plasma glucose suggests glucose intolerance or overt diabetes test is repeated two times, it is important that the sample be measured after an overnight fast (8-12 hour). However, the most sensitive test for diagnosis of diabetes is a standard

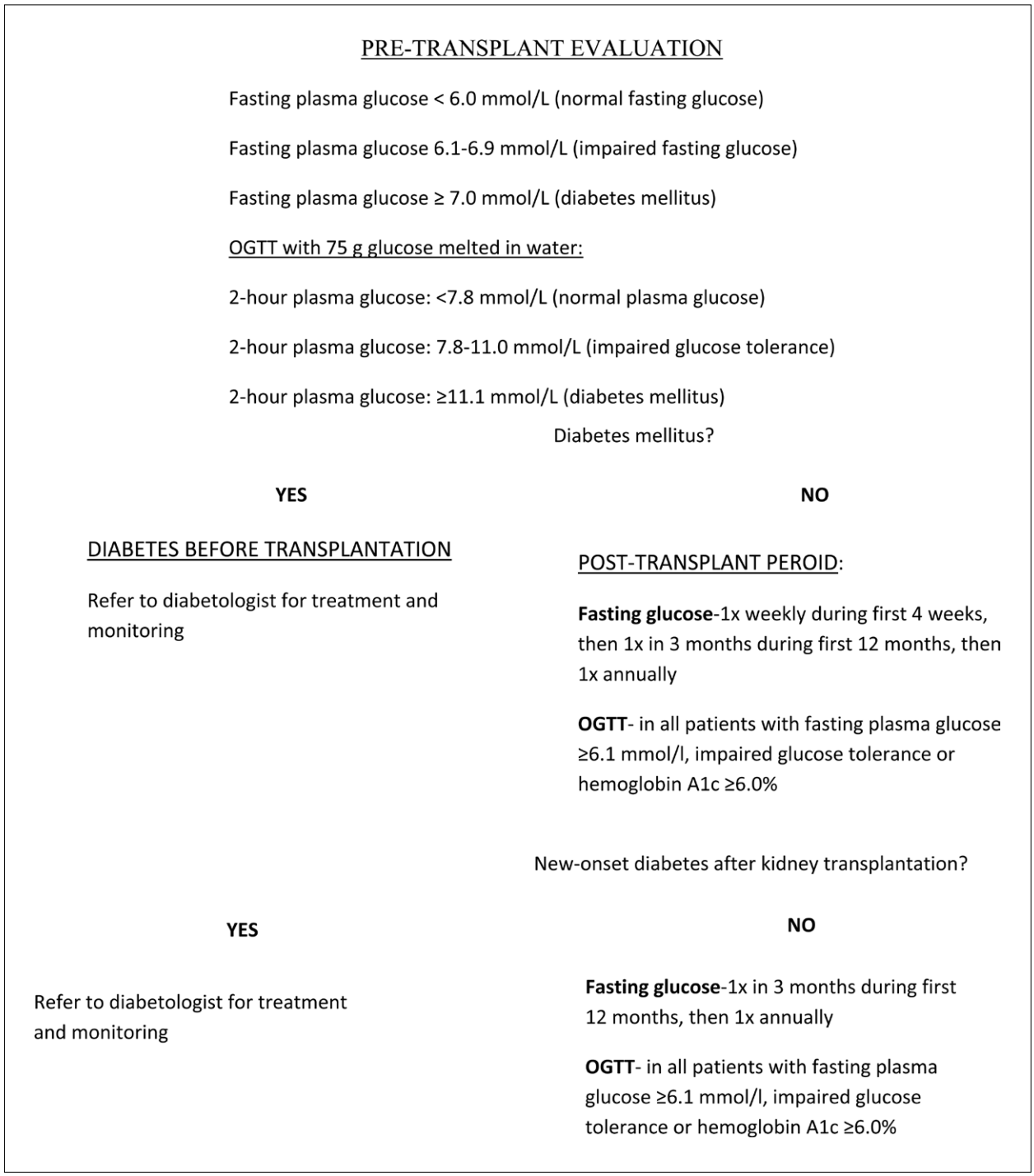

Figure 1: Algorithm for the diagnosis of diabetes in patients before and after kidney transplantation

OGTT with 75g glucose melted in water, but that is not practical for routine use[25]. The diagnosis of diabetes should not be relied on hemoglobin A1c level or capillary blood glucose in wait-listed patients as well as after transplantation because in that period anemia is a common finding resulting in misleading hemoglobin A1c results[7-9]. Urine testing may detect positive ketones that are strong evidence not only for hypergly-

cemia but also for patients that have insulin deficiency and must be treated with insulin therapy. Patients with renal transplantation and NODAT should be checked for hemoglobin A1c every 3 months and even more often fasting plasma glucose in the early posttransplant period.

After the diagnosis of NODAT, patients must be educated about diet and weight control, lifestyle modifications with exercise, and regular monitoring of blood glucose with appropriate follow-up, in order to reduce the risk of the short- and long-term complications of diabetes. In addition, strict control and treatment of other metabolic disorders associated with diabetes like hypertension and dyslipidemia are also needed[56]. Corticosteroid and calcineurin inhibitors reduction in the early posttransplant period will improve glucose control, but this decision should be made by transplant nephrologist [4,25,57]. If possible, conversion of tacrolimus to less glucotoxic agents like cyclosporin or mycophenolic acid can reduce hyperglycemia[58,59]. Patients with NODAT must be treated according to the ADA guidelines for managing patients with type 2 diabetes because there are no studies conducted specifically in patients with transplantation[4]. The primary goal and first step are maintenance of ideal body weight through dietary modification and also increased physical activity, similar to the treatment of patients with type 2 diabetes[4]. Glucose monitoring in patients with NODAT should be checked with hemoglobin A1c initially every 3 months and also with fasting plasma glucose at each visit. The hemoglobin below 7% should be considered a reasonable goal, although there is no study evaluating specific cut-off for hemoglobin A1c in NODAT patients[4]. However, the period after kidney transplantation is frequently associated with anemia resulting in misleading hemoglobin A1c results[7-9]. Besides glucose control, hypertension and dyslipidemia should also be treated because, in connection with diabetes, these are major contributors to cardiovascular disease, but also immunosuppressive therapy may further aggravate hypertension and dyslipidemia[60,61]. According to ADA guidelines, the reference range for blood pressure and serum lipids in patients with NODAT is the same as for patients with type 2 diabetes. Fluvastatin and pravastatin have the lowest drug interactions compared to other statins[62]. Antihypertensive therapy should include treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB).

Adoption of lifestyle modification like diet and exercise with weight loss can improve glycemic control over 6 months[63]. If hemoglobin A1c rises over 6.5%, then pharmacotherapy must be started or changed. The choice between an appropriate oral agent or insulin depends on the severity of hyperglycemia, timing of developed hyperglycemia after transplantation, and comorbidities[23]. Early after transplantation, when patients are treated with high doses of immunosuppressant and graft function is not yet fully established, patients are usually treated with insulin therapy[48]. Biphasic insulin several times daily (premix insulin) is typically required in the early post-transplant period because corticosteroids are usually given in the morning, resulting in high glucose levels in the afternoon. In case of persistent hyperglycemia with biphasic insulin several times daily, intensive insulin therapy is needed. Treatment with a combination of long-acting insulin and oral hypoglycemic agent, often used in patients with type 2 diabetes, is not effective in patients with NODAT.

The selection of an optimal oral hypoglycemic agent is usually determined with a glomerular filtration rate. In patients with renal transplantation and NODAT, no oral hypoglycemic agent is contraindicated and all oral hypoglycemic agents can combine with immunosuppressive drugs, according to glomerular filtration rate. Metformin, the first choice and gold standard treatment in patients with type 2 diabetes, is usually prescribed as a first-line option in renal transplant recipients with NODAT because metformin improves insulin sensitivity often present in patients with NODAT and can be safely used if glomerular filtration rate is over 45 ml/min[64]. Sulfonylureas are also widely used in renal transplant recipients with NODAT because they are the most powerful oral hypoglycemic agent in reducing hemoglobin A1c. In addition, newer and mostly used sulfonylurea gliclazide can be safely used even in those with chronic kidney disease. However, they may exacerbate weight gain in the period after renal transplantation and may increase the serum concentration of cyclosporine, and the risk of hypoglycemia is also increased[14]. Besides long-acting sulfonylureas like gliclazide, short-acting sulfonylurea repaglinide can be safely used in patients with renal transplantation and NODAT[65]. Thiazolidinediones like metformin improve insulin sensitivity often present in patients with NODAT and improve glucose

Table 2: Recommendations for assessment and management of new-onset diabetes after kidney transplantation

Recommendations for assessment and management of new-onset diabetes after kidney transplantation
- all patients in the baseline evaluation before transplantation should perform a standard oral glucose tolerance test according to the World Health Organization, with 75g glucose melted in water - diagnosis of new-onset diabetes after kidney transplantation should be the same as for type 2 diabetes, according to the American Diabetes Association - in patients with diagnosed new-onset diabetes after kidney transplantation, the aim of management strategies include a diet with weight control, exercise (lifestyle modification), and optimal glucose control with the aim to reduce the risk of short- and long-term complications of diabetes - lower doses of immunosuppressant (corticosteroid and calcineurin inhibitors) are required in order to achieve better glucose control. Conversion of tacrolimus to less glucotoxic immunosuppressant like cyclosporin or mycophenolic acid is recommended if possible - majority of the oral hypoglycemic agents can be used: metformin (caution is required according to the level of renal function), sulfonylureas (risk of hypoglycemia and weight gain, increases cyclosporin level), thiazolidinediones (increases the risk of heart failure and usually not used in renal transplant recipients), dipeptidyl peptidase-4 (DPP-4) inhibitors (shown to be safe and efficacious in renal transplant recipients), sodium-glucose cotransporter (SGLT) 2 inhibitors (increased risk of urinary and genital infections, caution is required according to the level of renal function, usually not used in renal transplant recipients) - in the early period after renal transplantation, when doses of immunosuppressant are high and graft function is not fully achieved, insulin therapy is usually administered. Biphasic insulin (premix insulin) administered several times daily is the preferred therapy in most patients. If optimal glucose control is not achieved with biphasic insulin, intensive insulin therapy is needed. - optimal management of other metabolic disorders associated with diabetes like hypertension and dyslipidemia are also needed as well as annual screening for chronic complications of diabetes: retinopathy, nephropathy, neuropathy, peripheral arterial disease, and cardiovascular disease

tolerance and endothelial function[66]. However, since treatment with thiazolidinediones increases the risk for heart failure and cyclosporine may promote sodium retention and many patients after renal transplantation are already at high risk of heart failure, thiazolidinediones are usually avoided in the majority of patients with NODAT. Dipeptidyl peptidase-4 (DPP-4) inhibitors are safe and effective in patients with renal transplantation and NODAT[67,68]. These drugs inhibit the DPP-4 enzyme and consequently increase pancreatic insulin secretion and decrease pancreatic glucagon secretion. There is no risk of weight gain and hypoglycemia. Sodium-glucose cotransporter (SGLT) 2 inhibitors inhibit renal glucose reabsorption in the proximal tubule increasing glucosuria. Besides, better glucose control therapy with SGLT-2 inhibitors also results in weight loss without risk of hypoglycemia. However, SGLT-2 inhibitors cannot be used in case of reduced renal function. In addition, since the risk of urinary and genital infection is significantly increased, SGLT-2 inhibitors are usually not used in patients with renal transplantation and NODAT[69]. If glucose control is inadequate with a single oral hypoglycemic agent, a combination of two or three drugs with different mechanisms of action are reasonable before starting with insulin therapy. In patients with marked hyperglycemia, infection, and impaired graft function or with high doses of immunosuppressive drugs, initiation of insulin therapy should not be delayed. Moreover, early initiation of insulin therapy in the period after transplantation can preserve beta-cell function and decreases NODAT incidence after renal transplantation[70].

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Sažetak

NOVONASTALA ŠEĆERNA BOLEST NAKON TRANSPLANTACIJE BUBREGA: DIJAGNOZA, RIZIČNI FAKTORI I LIJEČENJE

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Šećerna bolest nakon transplantacije (NODAT) je česta i ozbiljna komplikacija nakon transplantacije bubrega. Dijagnosticira se na temelju kriterija za dijagnozu šećerne bolesti tipa 2. Rizične faktore za razvoj NODAT-a dijelimo na one na koje ne možemo utjecati (dob, nebijela rasa, genetska predispozicija, prethodna intolerancija glukoze ili terapija kortikosteroidima, muški donor i ostali) i one na koje možemo utjecati (debljina, virusna infekcija, imunosupresivna terapija). Nakon transplantacije bubrega glikemija natašte se treba određivati svaka tri mjeseca tijekom prve godine, a nakon toga jedanput godišnje. Ukoliko se dijagnosticira NODAT potrebna je promjena životnih navika (kontrola težine, dijeta, tjelovježba), i redovita kontrola glikemije s ciljem sprječavanja nastanka komplikacija šećerne bolesti. Smanjenje doze kortikosteroida smanjuje hiperglikemiju kao i smanjenje doze kalcineurinskih inhibitora i konverzija takrolimusa u druge imunosupresivne lijekove. Farmakoterapija uključuje liječenje oralnim hipoglikemijskim lijekovima (najčešće metformin, preparati sulfonilureje te inhibitori dipeptidil peptidaze-4 (DPP-4)) te inzulinom (najčešće predmiješanim inzulinom u više dnevnih doza ili intenziviranom inzulinskom terapijom). Potrebno je liječenje i ostalih poremećaja u sklopu šećerne bolesti kao što su hipertenzija i hiperlipidemija te godišnji uvid u kronične komplikacije šećerne bolesti (retinopatija, nefropatija, neuropatija, periferna arterijska bolest te kardiovaskularna bolest) s ciljem očuvanja kvalitete života.

Ključne riječi: *novonastala šećerna bolest nakon transplantacije organa (NODAT), transplantacija bubrega, imunosupresivni lijekovi, liječenje šećerne bolesti*