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Diabetes in patients after kidney transplant

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Abstract:

Diabetes is a group of metabolic diseases characterized by hyperglycaemia associated with inadequate insulin secretion or poor cells response to insulin. It can affect a large proportion of patients after a kidney transplant. New onset diabetes after transplantation (NODAT) is often associated with the use of immunosuppressive drugs including steroids. However, a significantly greater number of risk factors affect the development of the disease. The occurrence of diabetes after renal transplantation is associated with some limitations in society function and significantly impairs the proper conduct of such patients in outpatient departments. Frequent drug modifications may result in much faster impairment of the grafted

kidney function and eventually loss of graft. This work aims to show the essence of the disease, to assess the risk factors of its development, and to show the role of diabetes education to help patient affected by the disease.

Keywords: kidney transplant, diabetes, owerweight, immunosupression.

Introduction:

Diabetes is one of the main complications in patients after kidney transplant. It is estimated that it affects about 25% of all transplant recipients who had previously had no carbohydrate disturbances. The disease is called new onset diabetes after transplantation (NODAT). And it is closely related to the use of immunosuppressants, in particular steroids. Therefore, it is sometimes mistakenly called ‘’postherapy diabetes’’. The incidence depends to a large extent on the period of observation, diagnostic criteria and immunosuppressive therapy. Most often, the disease develops within the first 6 months after surgery, when patients are treated with high doses of immunosuppression. After this period, the incidence of patients with diabetes is similar to that of people waiting for a transplant (1). Thus, late diagnosis of NODAT can be difficult to distinguish from normal type 2 diabetes. In people with NODAT, similar complications of the disease will develop as in the case of type 2 diabetes, but this will happen much earlier. (2). Adding NODAT is associated with worse results after kidney transplantation and an increased risk of developing cardiovascular complications, kidney failure and death due to graft failure. (3). In addition, it is associated with a significant increase in the cost of treating patients. Regardless of the type (type 1, type 2, NODAT) it is a significant burden for the patient and is a potential possibility of losing the transplanted kidney. (4).

Risk factors:

New onset diabetes after transplantation (NODAT) can develop spontaneously and insidiously in the first 6 months after kidney transplantation. During this period, patients may be exposed to hyperglycaemia without apparent clinical symptoms as is the case with type 2 diabetes. Reports from large US studies such as the United States Renal Data System and the Organization Procurement Transplant Network / United Network of Body Sharing have identified several independent risk factors for the development of NODAT. As in the case of type 2 diabetes, older age is a strong predisposing factor for the development of NODAT. The existence of a 90% increase in the risk of disease in patients aged 45-59 and over 160% in patients over 60 years of post-transplant diabetes, than in the population of recipients under 45, which was considered a reference group. In addition, the incidence of NODAT in Afroamericans and Spanish is much higher than in Caucasian (5). Overweight is considered a major risk factor for type 2 diabetes as it is associated with increased insulin resistance of peripheral tissues. It is also extremely important in the development of NODAT in the early and late post-transplant period. It is estimated that BMI over 30 kg / m2 is a two times more increase in the risk of post-transplant diabetes. The tendency to increase body weight after

kidney transplantation may result from compensating for unsatisfactory nutritional status occurring in some patients during conservative treatment as well as dialysis renal failure. Decreased appetite as a consequence of chronic endotoxin poisoning and increased catabolism may lead to malnutrition. However, in the examined patients, the underweight before renal transplantation was found only in about 4%, and after the kidney transplantation, the percentage of underweight patients remained unchanged. However, a significant increase in the number of overweight and obese people was noted up to 75% (50% overweight, 25% obesity), which should be associated with improper feeding. Patients undergoing dialysis are advised to have a high-energy diet to prevent catabolism and wasting. Maintaining this diet after kidney transplantation along with the improvement of appetite resulting from the reduced severity of renal failure and the use of steroid therapy that increases appetite and insulin resistance leads to a rapid increase in body weight, especially at low physical activity. Recent reports have demonstrated that HCV serology is also one of the important risk factors, especially when tacrolimus has been used in immunosuppression. (6). Male sex also increases the risk of developing the disease. It is difficult to recognize a positive family history of diabetes as an important risk factor for developing NODAT due to insufficient reports. Population studies show that about 20% of people with type 2 diabetes have a positive family history of diabetes (7). This difference indicates that the appearance of diabetes mellitus after kidney transplantation is significantly influenced by factors in the post-transplantation period, favoring the development of diabetes in people burdened with less "diabetogenic genotype'' than in the general population. This is understandable in the situation of transplantation of factors causing a significant increase in insulin resistance of tissues and disorders of insulin secretion (especially immunosuppressive drugs with a diabetogenic effect). However, family history of type 2 diabetes was found to be an important factor in the development of NODAT in the analysis of several studies (8,9). In retrospective studies, a higher frequency of development of NODAT was demonstrated in patients with metabolic syndrome and a several-fold increase in risk with all symptoms. (10). A characteristic feature of the lipoprotein metabolism disturbances associated with insulin resistance is high triglycerides and low HDL cholesterol (11). Among patients who develop NODAT after a kidney transplant, reduced HDL levels (<40 mg / dl) and / or high triglycerides (> 250 mg / dl) occur before transplantation in about 30% of patients. Such a metabolic profile may indicate the presence of significant insulin resistance and a high risk of developing diabetes in the conditions of the activation of additional diabetogenic factors.

Recently, hypomagnesaemia after transplantation has been found to be an independent prognostic factor for the development of NODAT, both after kidney and liver transplantation. (12). This is related to the general population, where hiomagnezemia is associated with increased insulin resistance in obese children and adults with type 2 diabetes. However, these studies do not prove a causal relationship, and hypomagnesemia may be considered only as a marker of insulin resistance or epithelial damage degree of renal tubules in accordance with the population of people with type 2 diabetes. Although magnesium supplementation has already shown a beneficial effect on insulin resistance in the general population, randomized, controlled studies assess the effect of early post-transplant magnesium supplementation on glucose metabolism that is under way, with the hope of shedding light on this still a controversial problem (13).

In addition to the less documented risk factors, we can include: deceased donor transplant, pregnant diabetes, birth of a child weighing more than 4 kg, polycystic ovarian syndrome, and cardiovascular disease (14).

Immunosupression:

The diabetic effect of glucocorticoids, mainly as a result of insulin resistance, is dependent on both impaired glucose absorption by insulin in peripheral tissues and increased hepatic gluconeogenesis. The healing regimens for high doses of steroids in the 1970s were the reason for the high incidence of so-called postherapy diabetes, which decreased after the introduction of ciclosporin as a ‘’new immunosuppressive drug’' in the 1980s. (15). The steroid pulses currently used to treat acute rejection are still a direct factor in the development of NODAT. In recent reports, it has been found that the temporary interruption of the use of steroids does not significantly reduce the frequency of NODAT, while eliminating them from the immunotherapy regimen reduces the incidence of diabetes significantly. However, both strategies for conserving steroids are associated with higher rates of acute rejection and a higher risk of graft loss. (16). Therefore, in patients at high risk for NODAT, the glucocorticoid minimization strategy should be balanced with the immunological risk profile to avoid acute rejection and loss of the graft.

Calcineurin inhibitor (CNI) is diabetogenic by causing a defect in insulin secretion by interfering with the nuclear factor of activated T cell signaling in pancreatic β cells. Tacrolimus induces reversible suppression of insulin secretion at the level of mRNA insulin transcription followed by inhibition of calcineurin in β (17) cells. The high level of FK506-12 binding protein present in pancreatic β cells may explain why tacrolimus is more potent in suppressing insulin than ciclosporin. Meta-analyzes show a significantly higher incidence of NODAT development in patients using tacrolimus than in patients receiving cyclosporine. It is obvious that the risk of developing diabetes is associated with the dose of tacrolimus, and its high serum levels significantly increase the risk of developing the disease especially in the early post-transplant period (18).

Ciclosporin damages insulin-producing pancreatic islets, inhibits insulin synthesis and secretion dependent glucose. Ciclosporin increases the duration of steroids in the patient's body and influences the development of NODAT (19). Only a systematic examination of the blood cyclosporin concentration and individual selection of the therapeutic dose can, in a sense, protect the patient from the onset of diabetes.

There is now strong evidence that m-TOR inhibitors (m-TORIs) cause changes in glucose metabolism. This diabetogenic effect is probably due to the combination of insulin secretion defect (toxicity with β cells) and insulin resistance. Sirolimus, based on cohort US studies, poses a risk of developing NODAT, especially in combination with CNI (20). Discontinuation of CNI therapy and replacement of m-TORIs is not associated with an improvement in insulin resistance and in many cases aggravates the impaired insulin response.

Diagnosis:

In recent years, the concept of recognizing NODAT has significantly improved. Before 2003, de novo-recognized diabetes in patients after transplantation suffered from a lack of precise definition and was simply called " diabetes after transplantation ". Most often, the definition was based on the need to use subcutaneous insulin injections in patients during immunosuppression for 30 days after surgery, which significantly excluded patients with glucose disorder without clinical symptoms. International guidelines on NODAT were published in 2003 and recommended that the diagnosis be based on guidelines for the diagnosis of type 2 diabetes. In addition, it has been recommended since 2009 to use standardized indications in a limit of fasting plasma glucose (FPG) up to 100 mg / dL. HbA1c in the diagnosis of diabetes (A1C level ≥ 6.5%), which this position was approved by the American Diabetes Association (ADA). (22). The Committee of Experts stated that the HbA1c test can not be used in conditions changing the turnover of red blood cells. This applies to patients with end-stage renal disease (ESRD) and new transplanted patients. For example, post-transplantation is often associated with anemia (due to surgical loss of blood, iron deficiency, immunosuppressive drugs, graft dysfunction and sudden discontinuation of erythropoietin administration), resulting in false HbA1c results (23). Likewise, glucose levels, not HbA1c, must be used as screening for the sudden onset of diabetes with high glucocorticoid doses (24). In addition, the diagnosis is facilitated by clinical symptoms typical of diabetes, such as increased thirst, increased urine output, weakness and the appearance of purulent lesions on the skin and frequent urinary tract infections.

Patient education:

Every patient diagnosed with NODAT requires additional special training on self-care and self-control in this disease. In cases of some intellectual impairment, it becomes reasonable to include the patient's family in education. It is optimal then to use the services of experienced diabetology educators from the nearest diabetes center. Patients who need to take insulin are required to complete their training. Many kidney transplant patients treated with high doses of steroids only show intolerance to glucose without symptoms of diabetes. In this group of patients, it is very important to provide specific tips for the use of a proper diet. Obtaining knowledge about proper nutrition protects the patient against the development of full-blown diabetes. Taking into account the current possibilities of diabetes care, professional education is fully realizable. Educational nurses inform about the principles of proper nutrition, recommended and allowed physical effort, methods of self-control and some complications of diabetes. (25).

Summary:

In conclusion, it is important to detect NODAT early on the basis of the 2003 guidelines based on both blood glucose and HbA1c levels. However, the A1C test should be interpreted with caution in people with anemia. Type 2 diabetes and NODAT have many common risk factors: older age, higher BMI, African or Spanish ethnicity, family history, the presence of metabolic syndrome, positive HCV serology and hypomagnesaemia. Most cases of NODAT occur within the first 6 months after transplantation when patients are treated with high doses

of immunosuppression. Thus, immunosuppressive drugs (CNIs, glucocorticoids and m-TOR inhibitors), by causing a defect in insulin secretion and insulin resistance, are likely to act as triggers for glucose metabolism disorders in risk group patients. Late detection of NODAT and poor management of a patient with glucose level disturbances can quickly lead to a deterioration of graphene function and loss of a transplanted kidney. Therefore, it is important that every patient receives due education and support from the host center.

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