

DESENVOLVIMENTO DE DIABETES MELITTUS APÓS TRANSPLANTE RENAL – RELATO DE CASO

DEVELOPMENT OF DIABETES MELITTUS AFTER KIDNEY TRANSPLANTATION – CASE REPORT

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RESUMO

O Diabetes Mellitus é uma complicação bem conhecida da terapia imunossupressora que condiciona aumento da morbimortalidade cardiovascular e diminuição da sobrevida do enxerto. Essa condição foi, inicialmente, reconhecida em receptores de transplante renal por Starzl em 1964, e, a partir de então, tem sido citada. O relato mostra a abertura da doença em uma paciente recentemente transplantada com um quadro clássico de cetoacidose diabética – situação descrita poucas vezes na literatura devido a sua raridade.

PALAVRAS-CHAVE: Transplante renal. Tacrolimus. Cetoacidose. Diabetes mellitus.

ABSTRACT

Diabetes Mellitus is a well-known complication of immunosuppressive therapy that causes an increase in cardiovascular morbidity and mortality and a decrease in graft survival. This condition was initially recognized in recipients of renal transplantation by Starzl in 1964, and has since been cited. The report shows the opening of the disease in a recently transplanted patient with a classic case of diabetic ketoacidosis - a situation rarely described in the literature due to its rarity.

KEYWORDS: Renal transplantation. Tacrolimus. Ketoacidosis. Diabetes Mellitus.

INTRODUCTION

Diabetes mellitus is a common and well known pos-transplant immunosuppressive therapy complication. This condition was at first reported by

Starzl in 1964, in kidney transplant recipients. It was demonstrated a prevalence of 2% to 53% and an increased risk especially in the first three months after the transplantation. Its clinical presentation may be characterized by an asymptomatic hyperglycemia or diabetic ketoacidosis (DKA). However, despite this potential, DKA occurrence in patients receiving immunosuppressants, including, tacrolimus, in kidney post-transplant is a rare event and only a few cases have been reported in the literature (PALEPU; PRASAD, 2015).

CASE REPORT

Female patient, 49, a native of Maringá - Paraná, black, ex-smoker, diagnosed with chronic kidney disease on hemodialysis, underwent renal transplantation in which graft received from her husband. He began therapy with immunosuppressant mycophenolate sodium (1440 mg / day), prednisone (20mg / day) tacrolimus (12mg / day). Two months after surgery, the patient has begun vomiting episode and failure of her general state. She complained of drowsiness, confusion, loss of appetite, dysgeusia, polydipsia, polyuria, lower weakness and sweating members. In her background story was reported hypertension, hypercholesterolemia, hyperuricemia and angioplasty. There was no diabetes mellitus history prior to transplant. In her family history: mother and older brother with diabetes mellitus. When looking for emergency service, showed poor general condition and mental confusion. We chose to transfer her to the Intensive Care Unit (ICU) with clinical suspicion of diabetic ketoacidosis. Exams further evidenced in venous blood gases - ph: 7.09; pCO₂ 23 mmHg; pO₂: 45 mmHg; O₂ saturation: 60%; B.E: -21.2; HCO₃: 7 mEq / L; lactate: 25.22 mg / dl; Sodium 127 mg / dl; Potassium: 6.2mg / dl; glucose 500 mg / dl. Confirmed the diagnosis, she remained in the ICU for four days in use of insulin therapy and control of fluid and electrolyte disorders, being transferred to the ward after her recovery. She was hospital discharged in use of insulin therapy.

DISCUSSION

PTDM IMPACT

Diabetes post-transplant diabetes mellitus (PTDM) is a common complication that can occur after performing a kidney transplant with potential to adversely affect the outcome of patient's transplants and their grafts (COPSTEIN et al., 2008).

The impact of this disorder consists of a notable risk of death and loss of the transplanted organ. Moreover, it is likely that hyperglycemia after transplantation promotes a long-term risk of micro vascular complications (retinopathy, neuropathy and nephropathy) and macro vascular (myocardial infarction, coronary heart disease and peripheral vascular disease), and the involvement of multiple systems bodies (MASKEY, 2015).

However, the hyperglycemia is not always permanent and can occasionally be normalized without any treatment within weeks or months after initial diagnosis (PIMENTEL et al., 2014).

EPIDEMIOLOGY

The prevalence of DMPT after transplantation has increased, and ranges between 2% and 53% based on various estimates. One reason for the wide variation in prevalence may be due to challenges such as non-standardization of diagnostic criteria. Other variants that impact the estimates incidence consist of following-up patients after transplantation, the intensity of routine screening and the use of standardized definitions of PTDM that are distinctly adopted in many transplant centers (BASTOS et al., 2005).

Moreover, the improvement of glycemic control in some patients with increased post-transplant time, reducing the dose of immunosuppressive drugs and other interventions has also affected the prevalence estimates and interpretation of the incidence rates (PALEPU; PRASAD, 2015).

However, it is well established in the literature that PTDM generally occurs early after renal transplantation. A long-term study carried out between 1976 and 2004 in 1,580 Egyptians after receiving kidney transplantation showed that 18.2% of patients developed global DMPT, in which 52.4% were diagnosed at 6 months and 11.5% between 6 and 12 months. Another French study including 527 patients receiving renal transplantation showed an average time to onset of PTDM 1.6 months, with an incidence of 7% in 2 years. The estimated incidence in the United States corresponds to 9.1% in 3 months, 16% at 12 months and 24% at 36 months (PALEPU; PRASAD, 2015).

RISK FACTORS

The main risk factors for PTDM can be classified into three categories: 1) non-modifiable factors: age over 45, black race, male, deceased donor, family history of diabetes mellitus and HLA mismatch. 2) potentially modifiable factors: impaired fasting glucose and impaired glucose tolerance prior to transplant, virus infection of hepatitis and cytomegalovirus infection and. 3) modifiable factors: immunosuppressive agents (cyclosporin, tacrolimus and corticosteroids), obesity and other components of the metabolic syndrome (PIMENTEL et al., 2014).

There are also other risk factors for the development of PTDM, such as age at transplantation and possible association with kidney disease autosomal dominant polycystic. It was also proposed that the serum adiponectin level, a peptide derived from adipocytes with anti-inflammatory properties and insulin sensitizers, can be related to the development of DMPT. In a recent study, low levels of adiponectin were considered independent predictive factor for the development of PTDM in renal transplant patients (COPSTEIN et al., 2008).

A study including 11,659 patients in the United States Renal Data System who have received a kidney transplant 1996-2000 showed a cumulative incidence of 9.1% DMPT, 16% and 24% at 3, 12 and 36 months after transplantation respectively. Several factors were associated with the development of DMPT, such as age, race Afro descendant, obesity, infection by viruses of hepatitis C, as well as the type of immunosuppressant drug used to prevent rejection of organs (PEEV, 2014).

Another study retrospectively evaluated 470 renal transplant patients followed up at the Nephrology Service of the Pedro Ernesto University Hospital / UERJ in the period between dated to October 1975 to November 2003 were identified 34 cases of PTDM, and the prevalence of PTDM 7.43 % (BASTOS et

al., 2005).

The most relevant risk factor was the age when receiving the transplant, which proved to be directly associated with PTDM in all analyzes. It is known that the risk of developing DM increases with age and it is associated with aging and insulin resistance due to the reduction of beta cell (CHO et al., 2002).

Some studies have shown that patients aged over 45 can show a bigger risk of developing DMPT, estimating an approximate 2.9-fold risk. The incidence of DMPT can increase by 50% every 10 years (PALEPU; PRASAD, 2015).

The occurrence of DMPT is mainly related to the use of immunosuppressive drugs such as corticosteroids, calcineurin inhibitors, and among these, more often described tacrolimus treated patients than in those treated with cyclosporin (COPSTEIN et al., 2008).

According to a meta-analysis published in 2002, the type of immunosuppressive agent used in the post-transplant period is associated with 74% of the variability in the cumulative incidence of PTDM during the first year after transplantation (PIMENTEL et al., 2015).

Corticosteroids have direct diabetogenic effect, worsening insulin resistance, as well as indirect, reducing weight and increasing muscle mass. The risk for DMPT with the use of steroids relates to the dose and duration of treatment. Steroid induced glycogenolysis and glycolysis, increase the levels of postprandial and fasting glucose, reduce gluconeogenesis, besides acting detrimentally on the function of pancreatic beta-cells. Insulin resistance, which may be predisposed patients receiving renal transplants, is one important effect of steroid therapy. As the other immunosuppressant cyclosporin or tacrolimus-containing exert their diabetogenic effect probably by direct inhibitory effect on protein secretion from the beta cell, and tacrolimus five times more diabetogenic than cyclosporine (BASTOS et al., 2005).

The relative risk for PTDM has been estimated at 1.68 for blacks and 1.35 for Hispanics compared to Caucasians. It is believed that the increased risk of DMPT in black patients occur due to variation in pharmacokinetics of immunosuppressants. Obesity has also been considered a risk factor for PTDM, with a relative risk of 1.73. However, the risk increases linearly PTDM per 1 kg over 45 kg. While obesity in the context of transplantation is traditionally understood as a body mass index > 30 kg / m². The presence of metabolic syndrome that is associated with other risk factors for the development of DMPT in renal transplant as obesity and dyslipidemia, increasing the risk for DMPT to predispose changes in glucose metabolism (PALEPU; PRASAD, 2015).

A comparative study examined the effect of DMPT is increased in serum positive patients to infection by hepatitis C virus (HCV) relative to HCV-negative. The risk for DMPT with HCV may be exacerbated by the use of tacrolimus. Infection by cytomegalovirus (CMV), has also been considered as a risk factor for DMPT by pathological induction of insulin release. Unlike HCV, however, CMV is much more easily handled in the post-transplant setting (PALEPU; PRASAD, 2015).

Regarding the vital status of the donor is higher prevalence of deceased donor between DMPT, which is explained in clinical practice by necessity, in general, higher doses of immunosuppressants in cadaver donor graft recipients compared to donors alive, which are usually related and have better histocompatibility profile. The diabetogenic effect of immunosuppressants, particularly of corticosteroids is known to be dose dependent (BASTOS et al., 2005).

EFFECTS OF CORTICOSTEROIDS

The use of corticosteroids is still often used in immunosuppressive therapy transplant patients and the main risk factor. The DMPT is influenced by the dose and duration of therapy. Its diabetogenic effect is elucidated by induction of gluconeogenesis, glycolysis, increased peripheral insulin resistance and direct damage to the beta cells. Calcineurin inhibitors - such as Tacrolimus and cyclosporine - are also used concurrently with corticosteroids in immunosuppressive therapy patient (LV et al., 2014).

It is known that calcineurin deficiency causes reduced insulin production and reduction in adipocyte GLUT4 transporters and thus indirectly to hyperglycemia (PEREIRA, 2014).

It was also demonstrated damage in the beta cells by cytoplasmic vacuolization and edema. Cyclosporine is more selective and has been used in combination therapy. Despite all the risks, the Tacrolimus is still preferred in renal post-transplant to be effective and present certain superiority in relation to cyclosporine to prevent acute rejection (TIZO; MACEDO, 2015).

DIAGNOSIS PTDM

The diagnosis of PTDM is performed by most of the literature works, the use of insulin or other antidiabetic drugs for a minimum period (usually 30 days), abnormal fasting plasma glucose or random blood glucose levels and / or clinical record of DM as a complication after renal transplantation. That is, two or more fasting plasma glucose levels of > 126 mg / dl or DM symptoms associated with random plasma glucose > 200 mg / dl. Some recent studies also include the oral glucose tolerance test (OGTT) as a diagnostic criterion: plasma glucose 2 hours in the oral glucose tolerance test - with 75g of dextrose > 200 mg / dl (BASTOS et al., 2005).

One study examined 151 non-diabetic patients initially submitted to a kidney transplant and demonstrated that the presence of glucose during pre-transplant random from 108 mg / dL was associated with a 25% higher risk for developing DMPT and increased to 50% when blood glucose random pretransplant was above 129.6 mg / dL. By the beginning of the last decade, there were no guidelines for the diagnosis, management and treatment of PTDM. In 2003, it was published in the International Consensus Guidelines on New-onset diabetes after transplantation. According to this consensus, the diagnosis should be made according to the same criteria recommended by the American Diabetes Association (ADA) and the World Health Organization (WHO) (PIMENTEL et al., 2014).

Recently a meeting update to PTDM discussed and reviewed the current diagnostic and therapeutic challenges. According to this review, hyperglycemia is very common in the early post-transplant period, and ideally the diagnosis of DMPT must not be done until the immunosuppressive levels are stable. Since several studies have shown that OGTT is a more sensitive diagnostic test to diagnose PTDM the consensus recommended for use as first-choice test. The use of glycated hemoglobin is not recommended for use in renal transplant patients before the first three months after transplantation. During this period, hemodialysis, blood transfusion and non-use of erythropoietin after

transplantation can lead to a worsening of anemia resulting in low levels of A1C. Some studies evaluated the use of glycated hemoglobin as a diagnostic tool for PTDM, but the results are controversial. Discrepancies between sensitivity and specificity to glycated hemoglobin ($\geq 6.5\%$) have been reported depending on the post-transplant period in which the test was performed. According to current guidelines, patients with glycated hemoglobin levels between 5.7% and 6.4% or higher in the early period after transplantation, must be accompanied by another diagnostic test, and it is unlikely to glycated hemoglobin results $\geq 6.5\%$ is a false positive result (PIMENTEL et al., 2014).

TREATMENT

The initial treatment of the patient consists of large volume intravenous SF IV insulin and sodium and bicarbonate. After standardization of pH and anion gap should be administered SC insulin (CHO et al., 2002).

The management of hyperglycemia in relation to the initial therapeutic approach depending on the patient, administers exogenous insulin or glucose control with oral hypoglycemic agents associated with diet control (MATOS et al., 1995).

In cohort study found that in 42 patients (97.6%), the PTDM manifested by hyperglycemia and clinical symptoms arising. In one patient, the presentation was hyperosmolar coma. Three patients (6.9%) went onto the hypoglycaemic treatment with glyburide, six (13.9%) were managed with diet and 34 (79%) required the use of insulin. Seven patients (16.2%) showed normalization of blood glucose levels, without the use of hypoglycemic agents or insulin, on average 22 months (range 1.7 to 52 months) after the start of PTDM. The average of the first abnormal fasting glucose was 372 mg / dL (median: 300mg / dl, range 130 a1484mg / dL) (COPSTEIN et al., 2008).

The control PTDM was made with insulin in 80% of cases. The treatment of dyslipidemia was performed with statins. All patients used the triple regimen of immunosuppression, and tacrolimus and azathioprine scheme and most prescribed prednisone in 52.2% of cases (SECUNDO et al., 2008).

CONCLUSION

Immunosuppressants are necessary to transplant patients, since they avoid the loss of the new graft. However, they increase the risk of developing metabolic disorders in the patient. The post-renal transplant Diabetes Mellitus (PTDM) is a common complication that may adversely affect the development of transplant patients and grafts, as the carrier develops infections resulting from immunosuppression framework and presents metabolic complications such as dyslipidemia (hypercholesterolemia and hypertriglyceridemia), hypertension (SAH) when poorly controlled accelerates glomerular aggression and hyperglycemia increases the synthesis of growth factors and renal fibrosis mediators, promoting the expansion of the matrix and hyperplasia of mesangial cells.

Due to metabolic disorders (hypertension, dyslipidemia, and hyperglycemia) patients with PTDM present micro vascular and macro vascular modifications and consequently greater risk of cardiovascular changes. Hypertension appears in post transplant in normotensive patients and may

correlate with stenosis of the transplanted artery, chronic rejection, the applicant glomerulonephritis, and the use of corticosteroids. Hyperglycemia is a risk factor for the occurrence of cerebrovascular accident (CVA). The systemic inflammation present in PTDM results in endothelial disorder which can result in thrombus formation and increase the risk of bleeding.

Kidney transplantation is proven, the most cost-effective renal replacement therapy. Compared to hemodialysis and peritoneal dialysis, provides the patient with longer survival and better quality and still have lower costs. However, complications after transplantation may compromise the evolution of graft and patient survival.

REFERÊNCIAS

BASTOS, M. et al. Risk factors for developing diabetes mellitus after renal transplantation. **Arquivos Brasileiros de Endocrinologia & Metabologia**, v. 49, n. 2, p. 271-277, 2005.

CHO, Y. M. et al. A Case Showing Complete Insulin Independence After Severe Diabetic Ketoacidosis Associated With Tacrolimus Treatment. **Diabetes care**, set, 2002.

COPSTEIN, L. et al. Diabete Melito Pós-Transplante em Pacientes Transplantados Renais Tratados com Ciclosporina. **J.Bras.Nefrologia**. 2008, p. 59-65.

LV, C. et al. Influencing factors of new-onset diabetes after a renal transplant and their effects on complications and survival rate. 2014.

MASKEY, R. New-Onset Diabetes after Transplant (NODAT). **Kathmandu University Medical Journal**, v. 12, n. 4, p. 301-305, 2015.

MATOS, C. M. et al. Diabetes pós-transplante renal: ocorrência, aspectos clínicos e possíveis fatores de risco. **J.Bras.Nefrologia**. 1995, p. 177-184.

PALEPU, S.; PRASAD, G. New-onset diabetes mellitus after kidney transplantation: Current status and future directions. **World journal of diabetes**, v. 6, n. 3, p. 445, 2015.

PEEV, V.; REISER, J.; ALACHKAR, N. Diabetes mellitus in the transplanted kidney. **Frontiers in endocrinology**, v. 5, 2014.

PEREIRA, M. J. et al. Cyclosporine A and tacrolimus reduce the amount of GLUT4 at the cell surface in human adipocytes: increased endocytosis as a potential mechanism for the diabetogenic effects of immunosuppressive agents. **The Journal of Clinical Endocrinology & Metabolism**, v. 99, n. 10, p. E1885-E1894, 2014.

PÉREZ R, A. et al. Comportamiento de la diabetes mellitus postrasplante en el Instituto de Nefrología" Dr. Abelardo Buch López". **Revista Cubana de Medicina**, v. 50, n. 4, p. 405-414, 2011.

PIMENTEL, A. L. ; BAUER, A. C. ; CAMARGO, J. Renal posttransplantation diabetes mellitus: An overview. **Clinica Chimica Acta**, v. 450, p. 327-332, 2015.

SECUNDO, I. et al. Fatores de Risco e Prevalência no Desenvolvimento de Diabetes Mellitus e Hipercolesterolemia Pós-Transplante Renal no Estado de Alagoas. **Revista Brasileira de Clínica Médica**. 2008, p. 163-168.

TIZO, J. M. ; MACEDO, L. C. Principais complicações e efeitos colaterais pós - transplante renal. **Revista UNINGÁ Review**. Maringá. Vol.24, n.1, p.62-70. Out-Dez 2015.