DIABETOGENIC EFECT OF IMMUNOSUPPRESSIVE DRUGS IN TRANSPLANT RECIPIENTS

Mihalachi-Anghel Maria[1], Bacinschi-Gheorghita Stela[2], Bacinschi Nicolae[1]
[1]Department of Pharmacology and Clinical Pharmacology, *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova
[2]Department of Endocrinology, *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Introduction. In organ transplant patients, new onset diabetes mellitus after transplantation (NODAT) has been found to be a frequent and serious complication. The use of immunosuppressive drugs after transplantation has been shown to be one of the most significant risk factors for the development of NODAT. It has been estimated that the pathogenetic links of NODAT are reduced to impaired insulin secretion, insulin resistance and damage of the pancreatic beta-cells.
Materials and methods. A selection and analysis of english-language articles in the PubMed database from the last 10 years was performed in order to elucidate the pathogenic mechanisms of glucose metabolism disorders in the use of immunosuppressive drugs for allograft preservation.
Results. Calcineurin inhibitors (cyclosporine, tacrolimus) produce hyperglycemia by decreasing insulin secretion, increasing insulin resistance and direct toxic damage to beta-cells. Insulin resistance increases due to dysregulation of genes responsible for insulin sensitivity in myocytes and adipocytes, as well as by decreasing the number of GLUT-4 transporters in muscle and adipose cell membranes. The diabetogenic effect becomes more pronounced when combined with glucocorticoids. Tacrolimus has proven to be more effective than cyclosporine as an immunosuppressant, but also with a more pronounced diabetogenic effect. mTOR (mammalian target of rapamycin) inhibitors, such as sirolimus and everolimus, may induce hyperglycemia through multiple mechanisms, including increased insulin resistance due to impaired insulin signaling, direct β-cell dysfunction with reduced insulin secretion, and enhanced hepatic gluconeogenesis. Glucocorticoids can contribute to the development of NODAT by: increasing insulin resistance; decreasing insulin secretion; stimulating gluconeogenesis in the liver; inducing beta-cell apoptosis. Studies have shown that short-term post-transplant glucocorticoid pulse therapy continued with low-dose maintenance therapy reduces the risk of NODAT. Antimetabolites (azathioprine, mycophenolate mofetil) are not considered to have diabetogenic effect. At the same time, these drugs may reduce the diabetogenic effects of calcineurin inhibitors and glucocorticoids by allowing the use of lower doses of these immunosuppressants. Belatacept showed a lower incidence of NODAT, but also reduced the hyperglycemic effects of calcineurin inhibitors.
Conclusions. Immunosuppressants used in the post-transplant period, calcineurin inhibitors, mTOR inhibitors and glucocorticoids, may be responsible for disturbances in glucose metabolism and the development of NODAT. The incidence may increase with the combined use of these immunosuppressants. Belatacept demonstrated a low incidence of hyperglycemia, and antimetabolites did not show a diabetogenic effect. The combination of immunosuppressive agents at lower doses may potentiate the therapeutic effect and reduce the incidence of hyperglycemia.
Keywords: organ transplantation, immunosuppressive drugs, new onset diabetes mellitus after transplantation, calcineurin inhibitors, mTOR inhibitors, antimetabolites.