POST-TRANSPLANT DIABETES MELLITUS (PTDM)

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Post-transplant diabetes mellitus is a major complication after transplantation and is associated with reduced allograft and patient survival.[1] It is hard to quantify the incidence of PTDM because of lack of standard definition and PTDM can occur many years after transplantation. A consensus conference in 2013, defined PTDM as newly diagnosed persistent diabetes mellitus among clinically stable post-transplant patients.[2]

Multiple risk factors contribute to the development of diabetes after transplantation including: immunosuppressive agents (steroids and CNIs the risk is greater with tacrolimus), age (incidence after age 40), family history, other elements of metabolic syndrome (hypertriglyceridemia, hypertension and hyperuricemia) and deceased donor. Therapy with tacrolimus is an independent risk factor the development of PTDM. The cumulative incidences for PTDM after transplantation in patients receiving tacrolimus at 3, 12 and 36 months is 13.5, 22.1 and 31.8 % respectively, compared with 7.8, 14.2 and 21.9 % for those not receiving tacrolimus.[3]

A defect in insulin secretion may play a major role in the development of PTDM. Calcineurin inhibitors, especially tacrolimus impair insulin secretion by β-cell. The interference of insulin production may occur at the level of synthesis rather than at the level of conversion of proinsulin to insulin.[4] CNIs also increase insulin resistance. Sirolimus is also independently associated with increased risk of PTDM.[5] Corticosteroid-sparing strategies have not resulted in the reduction in PTDM development.[6] Steroid withdrawal a few days after transplantation resulted in less PTDM only in patients receiving cyclosporine compared to tacrolimus.[7] The new agent belatacept is not associated with increased risk of PTDM when compared to cyclosporine.[8]

Dietary changes and increase in physical activity are the cornerstone of prevention of PTDM. A randomized, three-month trial evaluating a dipeptidylpeptidase-4 inhibitor, a thiazolidinedione and placebo the equivalent efficacy of both agents at reducing GTT glycemia at 2 hs compared to placebo with similar safety profile among patients with impaired glucose tolerance after transplantation.[9] Metformin is an attractive choice requiring careful discussion prior to use in patients with renal dysfunction. Previous reluctance to use metformin after renal transplantation among physicians is being challenged in view of its benefits but a clinical trial is warranted.[10] Another opportunity for prevention the treatment of early post-transplant hyperglycemia with insulin, which may reduce subsequent risk of PTDM development.[11] This strategy is being tested in a larger, randomized clinical trial.

Currently, there are no consensus guidelines on the hierarchy of hypoglycemic agents for the treatment of PTDM.

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