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Association of Metformin with Rejection and Graft survival in Kidney transplant recipients taking Tacrolimus with Post-transplantation diabetes mellitus

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Objectives: Tacrolimus is a pivotal maintenance immunosuppressive drug in kidney transplantation (KT). Although diabetogenic property of tacrolimus is still an inevitable concern, it can reduce the risk of acute rejection and improve graft survival compared to cyclosporine. Metformin, despite limited randomized controlled trial, has been found to be safe and effective in patients with post-transplantation diabetes mellitus (PTDM). We aimed to investigate the effect of metformin on acute rejection and graft survival in kidney transplant recipients taking tacrolimus.

Methods: A number of 442 PTDM patients who were prescribed tacrolimus between 2000 and 2018 were collected. We conducted propensity score matching between the metformin and non-metformin group and evaluated the effects of metformin on the occurrence of T-cell mediated rejection (TCMR) and antibody-mediated rejection (ABMR), and graft survival with Cox proportional hazard model.

Results: During the average follow up of 8.7 years, 90 patients were diagnosed as PTDM within one year after KT. Among 442 patients taking tacrolimus, 297 patients were treated with metformin for the average of 4.4 years. After 1:1 matching, cumulative incidences of TCMR ($p=0.008$) and graft failure ($p=0.005$) in the metformin group was lower than the non-metformin group, while no significant difference was observed in ABMR. Metformin use was associated with a reduced risk of TCMR (HR 0.43, 95% CI 0.21-0.88, $p=0.021$) and graft failure (HR 0.39, 95% CI 0.19-0.79, $p=0.009$). There was no significant difference in t (tubulitis), i (interstitial inflammation), and v (endarteritis) scores of TCMR between the metformin and the non-metformin group.

Conclusions: Our study demonstrates that combination therapy with metformin and tacrolimus in kidney transplant recipients with PTDM is associated with a lower risk of acute rejection and graft failure.