New-onset Diabetes after Renal Transplantation – A Clinical Insight

Transplant patients may have preexisting diabetes mellitus or develop transient postoperative hyperglycemia or permanent new-onset diabetes after transplantation (NODAT). NODAT increases mortality rate due to allograft rejection and also leads to increased cardiovascular disease.[1] NODAT excludes transient posttransplant hyperglycemia and pretransplant undiagnosed diabetes, which are often unrecognized due to lack of effective pretransplant screening.[2] Posttransplant diabetes mellitus, that is, presence of diabetes in posttransplant setting irrespective of timing of diabetes, may be preferred nomenclature.[3] NODAT risk is highest in the first 6 months post transplant and increases progressively over time.[1] Perioperative stress, infection, high calcineurin inhibitors' (CNI) exposure, and glucocorticoid induction can cause transient post-transplantation hyperglycemia (TPH) in 90% of kidney allograft recipients, so diagnosis of NODAT should be delayed until the patient is on stable maintenance doses of immunosuppressants, with stable kidney graft function and in the absence of acute infections.[4,5] TPH is also a risk factor for NODAT.[1]

The prevalence of NODAT is variable and is reported to be between 2% and 50%, probably owing to inconsistent definitions used for diagnosing NODAT.[1] Though fasting glucose has a low sensitivity for diagnosing NODAT and oral glucose tolerance test (OGTT) is considered the gold standard test for diagnosis of NODAT screening patients using fasting glucose or afternoon glucose monitoring (induced by morning steroid) can identify high-risk patients requiring OGTTs.[6] HbA1c greater than 6.5% is unlikely to be false-positive but may not exclude NODAT in the initial 3 months post transplantation due to anemia and rapid diabetes onset, so a lower HbA1c cut-off may be more sensitive. No glycemic indicator post transplantation is co-related with long-term outcomes.

There are many nonmodifiable and modifiable risk factors for NODAT, both conventional and novel. Pretransplant risk assessment can help individualize therapy and reduce NODAT risk. Nonmodifiable risk factors such as age, sex, and HLA type help in identifying patients at risk, and interventions on modifiable risk factors such as obesity, metabolic syndrome (MS), and HCV/CMV infection may prevent complications and improve outcomes. General risk factors include family history of diabetes mellitus, ethnicity, genetic polymorphisms, increasing age, obesity, MS, and prediabetes.[1] Transplant-specific risk factors include donor sex, type of underlying renal disease, graft dysfunction, biopsy-proven rejection, specific antirejection agents, cumulative steroid use, tacrolimus level, human leukocyte antigen and ABO mismatch, TPH, and hypomagnesemia.[1] Pretransplantation insulin resistance contributing to MS is a risk factor for NODAT, but increasingly pancreatic beta cell dysfunction, supported by several genetic (KNNJ11, TCF7L2) polymorphism studies, has gained prominence.[1] The recent Indian study by Choudhury *et al.* found 17% prevalence of NODAT with beta-cell secretory defect, high waist circumference, and trough tacrolimus level as important factors for predicting NODAT.[7]

Antirejection therapies such as glucocorticoids and sirolimus lead to increase in insulin resistance, while steroids increase hepatic glucose output and decrease insulin secretion in high doses. Low-dose corticosteroid is preferred but not steroid withdrawal as it increases acute rejection requiring pulse steroid which counterbalance metabolic beneficial effect.[1] Split corticosteroid dosing may also reduce glycemic variability and peak hyperglycemia. CNI causes dose-dependent reduction in insulin secretion due to vacuolization and degranulation of islet cells and insulin gene transcription defect. Tacrolimus has five times higher risk of diabetes than cyclosporine. Immunosuppressive regimen therapies providing best patient and graft survival should be used irrespective of their NODAT risks as transplant rejection outweighs risks of NODAT.[5]

Admission evaluation includes medical history, family and past history of dysglycemia, MS. Patients discharged without hyperglycemia should have fasting plasma glucose testing at least weekly during the first month, then every 3 months for 1 year, and annually thereafter.[2] Lifestyle modification (LSM) may reduce risk of NODAT.[2] Stepwise approach with LSM followed by oral antihyperglycemic agents (AHA) and then insulin is appropriate for management of late (>6 months) NODAT, but in TPH and early NODAT the reverse regimen is preferred.[2] Dose adjustments or cessation of oral AHA agents in the context of renal allograft dysfunction should be individualized. Insulin is the only safe and effective agent during high glucocorticoid doses and acute illness early post transplant. Basal insulin therapy in early posttransplant hyperglycemia (<3 weeks) reduced risk of NODAT within the first year post transplantation by 73%.[8] Insulin therapy in early postoperative phase may prevent NODAT through β-cell protection.[8]

In summary, NODAT has a sudden onset and rapid development of complications such as graft failure, infection, and cardiovascular disease compared with a garden variety of type 2 diabetes mellitus. NODAT have unique causal factors, some of which may be modifiable. But there are diagnostic difficulties and treatment targets and agents are not well-defined. Early and aggresive management of

hyperglycemia post transplant may prevent β-cell apoptosis and possibly prevent NODAT and its complications. NODAT confers an adverse prognostic outcome for transplant survival and mortality, so pretransplant risk stratification and posttransplant NODAT screening is imperative.

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