Glucocorticoid Sensitivity, Receptor Regulation, and the Development of New-Onset Diabetes After Transplant (NODAT): A Comprehensive Review

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Abstract

Background: Glucocorticoids remain a cornerstone of immunosuppressive therapy after kidney transplantation, yet their metabolic adverse effects significantly contribute to post-transplant morbidity. Among these, new-onset diabetes after transplant (NODAT) has emerged as a major determinant of long-term graft and patient outcomes. NODAT increases cardiovascular risk, accelerates graft loss, heightens susceptibility to infection, and raises overall mortality. While multiple immunosuppressive agents contribute to disturbances in glucose metabolism, glucocorticoids exert unique effects due to their pleiotropic actions on hepatic glucose production, pancreatic β-cell function, adipocyte biology, and peripheral insulin sensitivity. Importantly, interindividual variability in glucocorticoid sensitivity—driven by differences in glucocorticoid receptor regulation, expression, and downstream signaling—may explain why some patients develop dysglycemia at relatively low steroid doses while others tolerate higher exposure. Understanding these mechanisms is essential for optimizing post-transplant care.

This review synthesizes current evidence regarding glucocorticoid receptor biology, mechanisms of glucocorticoid sensitivity, and their integration into the pathophysiology of NODAT. We detail how receptor isoforms, tissue-specific co-regulators, chaperone proteins, and post-translational modifications influence glucocorticoid responsiveness. We further examine how glucocorticoid-induced hepatic gluconeogenesis, impaired insulin signaling, adipose tissue dysfunction, and β-cell exhaustion contribute to hyperglycemia. The interaction of glucocorticoids with other diabetogenic immunosuppressants—particularly calcineurin inhibitors and mTOR inhibitors—is also explored, given their synergistic potential in promoting β-cell injury and insulin resistance.

Recognizing predictors of dysglycemia is critical for risk stratification. Pre-existing metabolic syndrome, age, ethnicity, hepatitis C infection, family history of diabetes, and early post-transplant hyperglycemia have all been associated with increased NODAT risk. Advances in glucose monitoring, including continuous glucose monitoring and oral glucose tolerance testing, provide improved tools for early detection of glucocorticoid-related metabolic effects. Lastly, we review emerging strategies for mitigating steroid-associated diabetes, including steroid minimization protocols, individualized immunosuppression, targeted metabolic therapies, and lifestyle interventions.

A comprehensive understanding of glucocorticoid sensitivity and receptor regulation offers an opportunity to refine transplant management through precision medicine. Ultimately, integrating endocrine and immunologic perspectives will enhance early identification of high-risk individuals, improve therapeutic decision-making, and reduce the burden of NODAT in kidney transplant recipients.

Keywords: *Glucocorticoid, New-Onset Diabetes After Transplant*

Introduction

New-onset diabetes after transplant (NODAT) is a frequent and clinically significant metabolic complication following kidney transplantation. Its incidence ranges from 10% to 40%, depending on population characteristics, diagnostic criteria, and immunosuppressive protocols. NODAT substantially increases cardiovascular morbidity, infection risk, graft dysfunction, and patient mortality, making its prevention and management essential components of post-transplant care. Large cohort studies and guidelines from KDIGO and the International Consensus Panel emphasize its impact on long-term outcomes in renal transplant recipients [1–3].

Glucocorticoids play a central role in transplant immunosuppression but remain among the strongest contributors to dysglycemia. Their metabolic effects arise from increased hepatic gluconeogenesis, impaired insulin signaling in muscle and adipose tissue, and direct β-cell dysfunction. However, not all patients experience the same degree of glucocorticoid-induced hyperglycemia, suggesting variability in glucocorticoid sensitivity and receptor regulation. Differences in receptor expression, isoforms, co-regulator interactions, and downstream signaling pathways contribute to this heterogeneity, shaping both therapeutic efficacy and toxicity in individual patients [4–6].

Although research has explored multiple determinants of NODAT, including calcineurin inhibitor toxicity, mTOR inhibitor effects, and traditional diabetes risk factors, the role of glucocorticoid receptor biology has been relatively underexamined in clinical transplant literature. This represents a key research gap, as receptor-level regulation may explain interindividual susceptibility to steroid-related metabolic effects. Understanding how glucocorticoid sensitivity influences NODAT risk has the potential to refine immunosuppressive decision-making and support more personalized approaches to post-transplant care [7–9].

The aim of this review is to provide a comprehensive, nephrology-focused synthesis of glucocorticoid receptor regulation, mechanisms of glucocorticoid sensitivity, and their integration into the pathogenesis of NODAT. By bridging molecular endocrinology and transplant medicine, this article highlights emerging opportunities for risk stratification, early detection, and targeted prevention of glucocorticoid-associated dysglycemia in kidney transplant recipients [10–12].

Glucocorticoid Use in Kidney Transplantation

Glucocorticoids have been integral to kidney transplant immunosuppression since the 1960s, used for both induction and maintenance regimens due to their potent anti-inflammatory and immunomodulatory effects. Historically, high-dose prednisone was a standard long-term therapy, aiming to suppress alloimmune activation through inhibition of cytokine transcription and T-cell proliferation. Over time, however, the significant metabolic, cardiovascular, and skeletal toxicities of chronic glucocorticoid exposure became increasingly evident, driving the evolution toward lower-dose regimens and steroid-minimization protocols. Despite these developments, glucocorticoids remain widely used, especially during the early post-transplant period when the risk of acute rejection is highest [13–15].

Current transplant protocols typically include perioperative methylprednisolone followed by a tapering course of oral prednisone over weeks to months. The cumulative steroid burden is strongly influenced by center-specific practices, rejection risk profiles, and concomitant immunosuppressive agents such as tacrolimus or mycophenolate mofetil. Evidence from randomized trials and large registries suggests that early steroid withdrawal can reduce metabolic complications, including NODAT, but may also increase the risk of acute cellular rejection in certain high-risk groups. Consequently, complete avoidance is not universally adopted, and careful balancing of benefits and risks remains central to individualized transplant management [16–18].

The diabetogenic potential of glucocorticoids is particularly pronounced during the first post-transplant

months when doses are highest. Studies consistently demonstrate a steep rise in fasting glucose, postprandial glucose excursions, and insulin resistance during steroid pulses used for rejection treatment or early tapering phases. These effects are compounded by concurrent diabetogenic agents such as calcineurin inhibitors, producing synergistic metabolic stress. Given the close relationship between steroid exposure and hyperglycemia, optimization of dosing strategies and monitoring intervals remains a major clinical priority in reducing NODAT incidence [19–21].

Another challenge is the variability in individual responses to glucocorticoid therapy. Patients with enhanced glucocorticoid sensitivity may experience severe metabolic disturbances even with modest prednisone doses, whereas others tolerate prolonged exposure with minimal dysglycemia. This variability underscores the need for mechanistic insights into glucocorticoid receptor regulation and downstream signaling pathways. Understanding such differences may eventually guide more personalized steroid dosing and identify individuals who would benefit most from minimization strategies or early adjunctive therapies to mitigate metabolic risk [22–24].

Glucocorticoid Receptor (NR3C1) Structure and Function

The glucocorticoid receptor (GR), encoded by the **NR3C1** gene, is a ligand-dependent transcription factor belonging to the nuclear receptor superfamily. It consists of three major functional domains: an N-terminal transactivation domain (NTD), a central DNA-binding domain (DBD), and a C-terminal ligand-binding domain (LBD). The NTD contains activation function-1, a region that recruits coactivators to modulate transcriptional activity. The DBD enables binding to glucocorticoid response elements (GREs) on target genes, while the LBD binds cortisol or synthetic glucocorticoids, initiating conformational changes that regulate transcriptional activation or repression. These structural features underpin the broad physiological actions of glucocorticoids across metabolic, immune, and endocrine pathways [25–27].

In its inactive state, the GR resides in the cytoplasm bound to a multiprotein chaperone complex including heat shock proteins **HSP90**, **HSP70**, and immunophilins such as FKBP52. Ligand binding triggers dissociation of these chaperones, conformational rearrangement, and translocation of the receptor into the nucleus. Once inside the nucleus, the receptor binds directly to GREs or interacts with other transcription factors such as NF-κB and AP-1, thereby modulating gene expression through both genomic and nongenomic pathways. This ability to influence diverse transcriptional networks explains glucocorticoids' powerful anti-inflammatory effects but also their wide range of metabolic consequences, including those contributing to NODAT [28–30].

Importantly, glucocorticoid signaling is not uniform across tissues; instead, it is shaped by local expression of co-regulators, tissue-specific chromatin accessibility, and the presence of GR isoforms. GRα is the classical active isoform mediating glucocorticoid responses, whereas GRβ acts as a dominant-negative regulator, limiting GRα-mediated transcription. The relative abundance of these isoforms can shift under inflammatory conditions or chronic steroid exposure, altering glucocorticoid responsiveness at the cellular level. Kidney transplant recipients undergoing prolonged glucocorticoid therapy may develop alterations in GR isoform expression, which could influence both immunosuppressive efficacy and metabolic side-effect profiles [31–33].

Beyond genomic effects, glucocorticoids exert rapid nongenomic actions that do not require transcriptional regulation. These include modulation of membrane-bound GR, interactions with cytosolic signaling molecules, and rapid influences on glucose transport and insulin signaling. Nongenomic pathways are particularly relevant in the acute post-transplant period when high-dose steroid pulses are administered, rapidly inducing insulin resistance and elevating hepatic glucose output within hours. These fast-acting pathways complement genomic mechanisms and collectively contribute to the complex metabolic phenotype observed in glucocorticoid-treated transplant patients [34–36].

Mechanisms of Glucocorticoid Sensitivity and Resistance

Glucocorticoid sensitivity varies widely among individuals, driven by complex interactions between receptor isoforms, transcriptional co-regulators, and intracellular signaling proteins. Variability in

glucocorticoid receptor (GR) expression, nuclear translocation efficiency, and DNA-binding capacity all contribute to diverse metabolic and immunologic responses. Studies in endocrine and rheumatologic populations have shown that increased GRα expression enhances glucocorticoid signaling, while higher GRβ levels promote resistance by competitively inhibiting GRα-mediated transcription. This isoform-dependent balance influences cellular behavior in key metabolic tissues, determining whether hepatocytes increase gluconeogenesis sharply or whether adipocytes and muscle cells exhibit heightened insulin resistance in response to glucocorticoids [37–39].

Post-translational modifications also play a critical role in modulating glucocorticoid responsiveness. GR phosphorylation at specific serine residues alters receptor stability, coactivator recruitment, and transcriptional output. Additionally, ubiquitination and acetylation influence GR turnover and chromatin interactions. Enhanced phosphorylation of GR at serine-226, for example, has been associated with decreased nuclear retention and reduced therapeutic glucocorticoid activity. These modifications are impacted by inflammatory cytokines, oxidative stress, and pharmacologic exposures—conditions commonly present in kidney transplant recipients. Such molecular changes may explain why some individuals develop profound glucocorticoid-induced dysglycemia even when receiving standard doses of prednisone [40–42].

Chaperone and co-regulator proteins provide another layer of control, shaping the receptor's ability to respond to ligand binding. Proteins such as HSP90, HSP70, FKBP51, and FKBP52 stabilize the receptor complex and regulate its readiness to translocate to the nucleus. FKBP51, in particular, is a potent inhibitor of GR signaling, and higher expression levels have been linked to diminished glucocorticoid sensitivity. Increased FKBP51 expression has been described during chronic glucocorticoid therapy and inflammatory states, suggesting that transplant-related immune activation or prolonged steroid exposure might shift the intracellular chaperone milieu, altering glucocorticoid responsiveness and metabolic outcomes [43–45].

Genomic interactions also influence glucocorticoid sensitivity at the tissue level. Chromatin accessibility determines which regulatory regions the GR can bind, and this landscape varies across hepatocytes, adipocytes, pancreatic β-cells, and immune cells. In metabolic tissues, glucocorticoids preferentially activate genes promoting gluconeogenesis, lipolysis, and insulin resistance, whereas in immune cells they strongly repress pro-inflammatory transcriptional networks. These tissue-specific transcriptional signatures can shift with aging, obesity, inflammation, and metabolic stress—conditions common in kidney transplant candidates. As a result, transplant patients may exhibit altered glucocorticoid transcriptional responses that increase susceptibility to NODAT [46–48].

Glucocorticoid-Mediated Metabolic Effects

Glucocorticoids exert powerful effects on hepatic glucose metabolism, primarily by stimulating gluconeogenesis and enhancing the expression of key gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase. These actions occur through GR-mediated transcriptional activation, promoting increased hepatic glucose output even in the presence of hyperinsulinemia. Studies in humans and animal models consistently demonstrate that glucocorticoid administration increases fasting glucose levels and exacerbates postprandial hyperglycemia by altering hepatic insulin sensitivity. Because transplant recipients often receive high glucocorticoid doses early postoperatively, these hepatic effects contribute significantly to the early metabolic disturbances that set the stage for NODAT [49–51].

In skeletal muscle, glucocorticoids impair insulin-stimulated glucose uptake by reducing GLUT4 translocation and altering insulin receptor substrate (IRS)-1–mediated signaling. Elevated glucocorticoid levels lead to increased proteolysis, reduced muscle mass, and impaired oxidative metabolism, amplifying insulin resistance. Muscle accounts for up to 80% of postprandial glucose disposal, so disruptions in insulin action in this tissue substantially elevate systemic glycemia. Transplant patients may be particularly vulnerable due to preexisting sarcopenia, inactivity during the perioperative period, and the additive effects of calcineurin inhibitors on muscle insulin signaling

pathways [52–54].

Adipose tissue is another major target of glucocorticoids, where they promote lipolysis, increase circulating free fatty acids (FFAs), and modulate adipokine secretion. Elevated FFAs impair insulin signaling in the liver and muscle, thereby creating a cycle of worsening insulin resistance. Glucocorticoids also induce adipocyte differentiation and central fat deposition, contributing to metabolic syndrome phenotypes frequently observed after kidney transplantation. Increased visceral adiposity has been strongly associated with NODAT risk, suggesting that glucocorticoid-driven changes in adipose biology have clinically meaningful consequences for transplant recipients [55–57].

The impact of glucocorticoids on pancreatic β-cell function is multifaceted. While short-term glucocorticoid exposure can initially increase insulin secretion to compensate for insulin resistance, chronic exposure diminishes β-cell secretory capacity by inducing oxidative stress, impairing mitochondrial function, and suppressing incretin responsiveness. In vitro studies demonstrate that glucocorticoids inhibit insulin gene transcription and reduce β-cell proliferation. When combined with tacrolimus-induced β-cell toxicity, these effects markedly heighten the risk of inadequate insulin production, making β-cell dysfunction a central contributor to glucocorticoid-related NODAT development [58–60].

Pathophysiology of New-Onset Diabetes After Transplant (NODAT)

NODAT arises from the convergence of traditional diabetes risk factors and transplant-specific metabolic stressors. Age, obesity, family history of diabetes, and ethnicity contribute baseline susceptibility, but the post-transplant environment introduces additional layers of immune, endocrine, and pharmacologic disruption. Early postoperative inflammation, surgical stress, fluctuating renal function, and infection risk further destabilize glucose homeostasis. These overlapping influences create a metabolic state in which β-cells are forced to compensate for heightened insulin resistance while simultaneously exposed to diabetogenic immunosuppressive drugs, leading to rapid exhaustion of β-cell reserves [61–63].

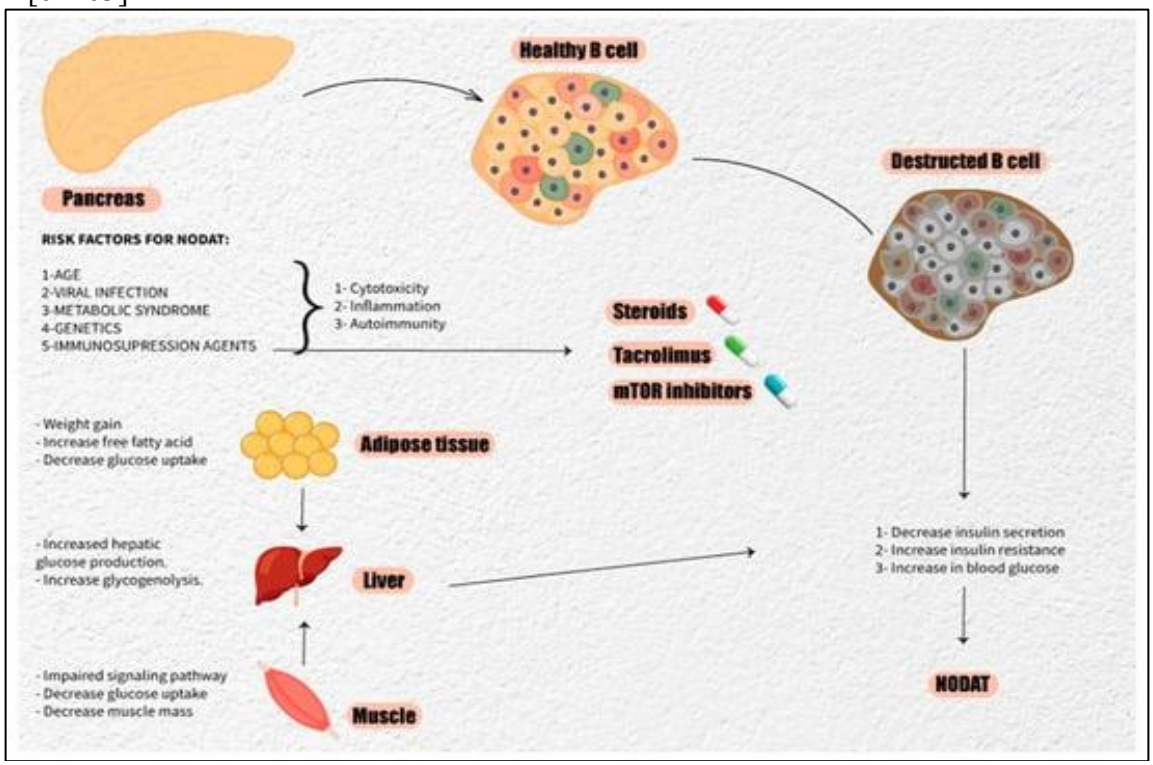

Figure 1. Illustrates risk factors and main pathophysiological mechanisms implicated in pathogenesis of NODAT.[63].

Calcineurin inhibitors (CNIs), particularly tacrolimus, exert potent diabetogenic effects through direct β-cell toxicity. Tacrolimus reduces insulin gene transcription, impairs mitochondrial ATP generation,

and disrupts insulin exocytosis by affecting calcium-dependent signaling. Clinical studies consistently show higher NODAT incidence in tacrolimus-treated patients compared with cyclosporine, even after adjusting for steroid exposure. This β-cell–specific impairment sensitizes patients to even mild additional metabolic stressors, amplifying the hyperglycemic effects of glucocorticoids and other immunosuppressive agents used in combination therapy [64–66].

mTOR inhibitors (sirolimus, everolimus) also contribute to NODAT through mechanisms distinct from CNIs. By inhibiting mTORC1 signaling, these agents reduce β-cell proliferation, impair insulin signaling in peripheral tissues, and worsen hepatic insulin resistance. Studies demonstrate that patients receiving sirolimus have higher fasting glucose levels and greater insulin requirements compared with those receiving tacrolimus alone. When combined with glucocorticoids, mTOR inhibitors significantly increase insulin resistance, highlighting the cumulative metabolic burden imposed by multi-drug immunosuppressive regimens in kidney transplantation [67–69].

Inflammatory and infectious complications in the post-transplant period further worsen glycemic control. Inflammation promotes cytokine-mediated β-cell dysfunction and increases hepatic gluconeogenesis through IL-6 and TNF-α pathways. Viral infections such as cytomegalovirus (CMV) have been associated with higher NODAT incidence, potentially through direct β-cell injury and immune activation. These factors often coincide with temporary increases in steroid dosing for rejection treatment or infection management, creating periods of intensified metabolic vulnerability. Thus, NODAT reflects not a single mechanism but the cumulative interaction between immunosuppressive therapy, inflammation, and patient-specific metabolic reserve [70–72].

Glucocorticoid Receptor Regulation in Transplant Recipients

Chronic exposure to glucocorticoids, as occurs in kidney transplant recipients, induces adaptive changes in glucocorticoid receptor (GR) regulation at multiple levels. Prolonged glucocorticoid therapy downregulates GRα expression in several tissues, reducing receptor availability and altering the balance between active (GRα) and inhibitory (GRβ) isoforms. This receptor downregulation is a well-described compensatory mechanism aimed at limiting excessive glucocorticoid signaling, but it may also create tissue-specific glucocorticoid resistance. In metabolic tissues such as liver and adipose tissue, reduced GRα expression can paradoxically heighten metabolic dysregulation by shifting glucocorticoid signaling toward pathways that promote insulin resistance and lipolysis, contributing to NODAT risk in transplant recipients [73–75].

Glucocorticoid therapy also alters the nuclear trafficking and transcriptional activity of the GR. Sustained glucocorticoid exposure decreases GR nuclear retention time and reduces GRE-binding capacity by modifying receptor phosphorylation patterns. This attenuates anti-inflammatory transcriptional responses while preserving or even enhancing certain metabolic gene programs, such as those regulating gluconeogenesis and adipocyte differentiation. Experimental studies demonstrate that chronic glucocorticoid use modifies chromatin accessibility at GRE sites, selectively amplifying genes associated with metabolic dysfunction. These changes may help explain why transplant recipients often exhibit persistent steroid-induced hyperglycemia even after prednisone tapering [76–78].

The cellular chaperone environment—crucial for GR maturation and activation—also undergoes notable changes after transplantation. FKBP51, a negative regulator of GR signaling, is frequently upregulated with chronic steroid use and in conditions of immune activation. Elevated FKBP51 expression reduces ligand affinity and impairs GR nuclear translocation, contributing to glucocorticoid resistance in immune cells while maintaining metabolic glucocorticoid effects that promote hyperglycemia. This differential tissue sensitivity creates a scenario in which higher steroid doses may be required for immunosuppression while metabolic toxicity continues to worsen, compounding the risk of NODAT in vulnerable patients [79–80].

Interactions between GR regulation and other immunosuppressive agents further complicate the metabolic profile of transplant recipients. Calcineurin inhibitors such as tacrolimus impair GR signaling by interfering with transcriptional coactivator complexes, while mTOR inhibitors alter GR-mediated

metabolic pathways by modulating downstream insulin signaling. These interactions can either synergize or oppose glucocorticoid actions depending on the tissue type. In pancreatic β-cells, CNIs exacerbate glucocorticoid-induced suppressive effects on insulin synthesis, while in hepatocytes mTOR inhibition enhances glucocorticoid-driven gluconeogenic activity. These combined molecular effects help explain why even low or moderate glucocorticoid doses can precipitate NODAT in the setting of multi-drug immunosuppressive regimens [80].

Interactions Between Glucocorticoids and Other Immunosuppressive Agents

The combined use of glucocorticoids with calcineurin inhibitors (CNIs) represents the most clinically significant pharmacologic interaction contributing to NODAT. Tacrolimus, more than cyclosporine, impairs pancreatic β-cell insulin secretion by inhibiting calcineurin/NFAT signaling, reducing insulin gene transcription and impairing calcium-mediated insulin exocytosis. When glucocorticoids are co-administered, their hepatic and peripheral insulin resistance–promoting effects increase insulin demand at a time when tacrolimus reduces β-cell output. Multiple clinical studies have demonstrated that patients receiving tacrolimus plus prednisone have substantially higher rates of NODAT compared with those receiving cyclosporine-based regimens, reflecting the synergistic diabetogenic effects of these agents [80].

The metabolic interaction between glucocorticoids and mTOR inhibitors is similarly impactful. Sirolimus and everolimus disrupt mTORC1 signaling, reducing β-cell proliferation and impairing adaptive insulin secretory responses during periods of heightened insulin resistance. When administered together with glucocorticoids, mTOR inhibitors amplify hyperglycemia by worsening hepatic insulin resistance and diminishing β-cell reserve. Randomized and observational studies have shown that patients on sirolimus–prednisone regimens exhibit higher fasting glucose levels and increased need for insulin therapy early post-transplant, underscoring the clinical importance of drug–drug metabolic interactions in NODAT pathogenesis [79].

Mycophenolate mofetil (MMF), though generally considered metabolically neutral, can influence glucocorticoid effects indirectly. By enabling lower doses of CNIs and steroids in combination regimens, MMF may reduce overall diabetogenic burden. However, when immunologic risk necessitates higher doses of glucocorticoids and tacrolimus despite MMF use, the protective metabolic effect becomes minimal. Clinical experience suggests that MMF-based regimens reduce but do not eliminate the risk of NODAT, particularly when rejection episodes require pulse steroid therapy, which transiently heightens insulin resistance and worsens glycemic variability in susceptible patients [79].

Biologic agents used in induction therapy can modulate glucocorticoid metabolic effects as well. Agents such as antithymocyte globulin (ATG) and basiliximab allow for early steroid minimization in some transplant protocols, thereby reducing the cumulative glucocorticoid exposure. ATG-based induction has been associated with lower early post-transplant hyperglycemia in certain cohorts, likely due to the ability to taper steroids more aggressively without increasing rejection risk. However, the benefits depend heavily on center-specific protocols and patient factors, and biologics do not prevent metabolic complications if high-dose steroids are required later for rejection treatment. These interactions highlight the importance of tailoring immunosuppressive regimens to minimize cumulative metabolic burden while maintaining adequate immunologic protection [80].

Clinical Predictors of Glucocorticoid-Induced Dysglycemia

Several baseline patient characteristics significantly increase susceptibility to glucocorticoid-induced dysglycemia and NODAT in kidney transplant recipients. Age is one of the strongest predictors, with older recipients demonstrating reduced β-cell reserve and heightened insulin resistance prior to transplantation. Obesity and metabolic syndrome components—including hypertension, dyslipidemia, and central adiposity—further potentiate the hyperglycemic effects of glucocorticoids by amplifying hepatic glucose production and impairing peripheral insulin sensitivity. Multiple cohort studies have consistently shown that recipients with elevated BMI or pre-transplant impaired fasting glucose have a markedly higher risk of developing NODAT during the period of maximal glucocorticoid exposure [65].

Ethnicity also plays a major role in determining glucocorticoid susceptibility. Individuals of African American, Hispanic, and South Asian heritage exhibit disproportionately higher rates of NODAT, a pattern attributed to genetic predisposition to insulin resistance and limited β-cell compensatory capacity. Several large registry analyses have demonstrated that these ethnic groups experience higher rates of glucocorticoid-induced hyperglycemia even at comparable steroid doses. Additionally, family history of type 2 diabetes confers an independent risk, likely reflecting inherited impairments in insulin secretion that are unmasked under glucocorticoid-induced metabolic stress. These demographic risk factors are crucial for early identification of patients requiring intensified metabolic monitoring after transplantation [66].

Pre-transplant comorbidities such as hepatitis C virus (HCV) infection further increase the likelihood of dysglycemia. HCV induces chronic hepatic inflammation, disrupts insulin receptor signaling, and impairs β-cell function—mechanisms that synergize with glucocorticoid-driven gluconeogenesis to accelerate hyperglycemia. Several clinical studies have reported significantly higher NODAT incidence among HCV-infected transplant recipients, particularly during steroid pulses for rejection treatment. Improvements in HCV treatment outcomes with direct-acting antivirals have reduced but not eliminated this metabolic vulnerability, emphasizing the need for targeted glycemic surveillance in this population [67].

Early post-transplant hyperglycemia is another strong predictor of subsequent NODAT and reflects the immediate impact of high-dose glucocorticoids, surgical stress, and perioperative inflammation on glucose metabolism. Persistent fasting or postprandial hyperglycemia during the first postoperative week has been associated with a several-fold increase in long-term NODAT risk. This early period represents a critical window in which β-cell exhaustion can be precipitated by high insulin demand. Timely recognition of early dysglycemia allows clinicians to consider steroid-sparing adjustments and initiate corrective measures such as basal insulin therapy to preserve β-cell function and mitigate progression to permanent diabetes [68].

Monitoring Glucocorticoid Effects and Glucose Metabolism

Monitoring glucose metabolism after kidney transplantation requires a multimodal approach that captures fasting, postprandial, and dynamic glycemic responses to glucocorticoid exposure. Fasting plasma glucose alone is insufficient, as glucocorticoids disproportionately elevate postprandial glucose levels and impair insulin sensitivity throughout the day. The **oral glucose tolerance test (OGTT)** remains the most sensitive diagnostic tool for detecting early glucose dysregulation, particularly in the first months post-transplant when steroid doses are highest. Several studies have shown that OGTT identifies a substantial proportion of patients with impaired glucose tolerance or early diabetes that would be missed using fasting glucose or HbA1c alone, underscoring its importance in high-risk transplant populations [69].

HbA1c has limitations in the early post-transplant period due to rapid shifts in erythropoiesis, use of erythropoietin-stimulating agents, and anemia associated with chronic kidney disease. These factors can artificially lower HbA1c values, obscuring the extent of hyperglycemia. However, after stabilization of hemoglobin levels, HbA1c becomes a useful adjunct for long-term monitoring of glucocorticoid-related glycemic trends and treatment response. Clinical guidelines from KDIGO and the International Consensus Panel emphasize combining HbA1c with fasting glucose and OGTT rather than relying on any single measure—a strategy particularly crucial in patients receiving ongoing glucocorticoid therapy [70].

Continuous glucose monitoring (CGM) has emerged as a valuable tool for detecting glycemic variability, postprandial excursions, and nocturnal hyperglycemia—patterns frequently seen in glucocorticoid-treated transplant recipients. Studies in solid-organ transplant populations demonstrate that CGM identifies a broader spectrum of glucose abnormalities compared with traditional finger-stick monitoring. CGM is especially helpful during steroid pulses for rejection episodes, where rapid increases in glucose levels require timely therapeutic adjustments. Its ability to depict glycemic trends

over days to weeks offers clinicians a dynamic assessment of glucocorticoid metabolic effects that can guide more individualized diabetes management [71].

Beyond glucose measurements, biomarkers of glucocorticoid activity provide additional insight into metabolic risk. Serum cortisol levels are poor indicators of glucocorticoid sensitivity due to wide inter-individual variability. However, markers such as **FKBP51**, **11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1)** activity, and downstream glucocorticoid-responsive transcripts have been proposed as potential tools to quantify tissue glucocorticoid exposure. Although not yet part of routine clinical practice, emerging studies suggest that these biomarkers correlate with insulin resistance and may predict which patients are most susceptible to steroid-induced metabolic complications—a promising avenue for future precision medicine in transplantation [72].

Strategies to Reduce Steroid-Induced Metabolic Complications

Steroid minimization and withdrawal strategies are central approaches for reducing glucocorticoid-induced metabolic toxicity in kidney transplant recipients. Early steroid withdrawal—often within the first week after transplantation—has been shown in multiple randomized trials to decrease NODAT incidence without significantly increasing acute rejection in selected low-risk recipients. Meta-analyses have demonstrated reductions in post-transplant diabetes, weight gain, and dyslipidemia when prednisone is discontinued early, particularly in combination with tacrolimus and mycophenolate-based regimens. However, these benefits must be balanced against slightly higher rejection rates in certain populations, underscoring the need for individualized selection of candidates for early withdrawal [73].

Steroid avoidance protocols, in which glucocorticoids are omitted entirely after induction therapy, represent a more aggressive approach. Induction agents such as antithymocyte globulin (ATG) or basiliximab enable steroid-free regimens in some centers, with studies reporting excellent graft survival, lower rates of metabolic complications, and improved cardiovascular risk profiles. Nevertheless, steroid avoidance is typically restricted to low-immunologic-risk recipients, as patients with high rejection risk—such as sensitized individuals or those with delayed graft function—may benefit from the immunosuppressive support of maintenance steroids. Thus, steroid avoidance is effective in reducing NODAT but requires robust immunologic monitoring and experienced center protocols [74].

Lifestyle interventions, though often underutilized in transplant populations, play a crucial role in mitigating glucocorticoid-induced metabolic effects. Structured protocols emphasizing early mobilization, weight management, and dietary modifications can significantly improve insulin sensitivity and reduce visceral adiposity. Evidence suggests that exercise interventions initiated within the first three months after transplantation improve glucose tolerance and attenuate the diabetogenic effects of ongoing steroid therapy. Nutritional guidance focusing on controlled carbohydrate intake, reduction of high-glycemic foods, and weight optimization is particularly important for obese recipients or those with early hyperglycemia following high-dose glucocorticoid exposure [75].

Pharmacologic strategies aimed at countering glucocorticoid-induced dysglycemia are increasingly important for preventing progression to overt NODAT. Basal insulin therapy during periods of high-dose steroid administration has been shown to preserve β-cell function and reduce long-term diabetes risk by reducing glucotoxicity. Oral agents such as metformin may improve insulin sensitivity in select recipients, though renal function and gastrointestinal tolerability must be assessed carefully. DPP-4 inhibitors and GLP-1 receptor agonists offer promising benefits due to weight-neutral or weight-reducing effects, minimal hypoglycemia risk, and potential β-cell protective properties. Several small-scale trials support their safety and effectiveness in transplant recipients, making them valuable tools for managing glucocorticoid-associated metabolic disturbances [76].

Future Directions and Research Needs

Future research on NODAT and glucocorticoid-related metabolic dysfunction increasingly centers on **precision medicine**, aiming to tailor immunosuppressive therapy based on individual metabolic and molecular profiles. Advances in transcriptomics and proteomics have identified glucocorticoid-responsive signatures in hepatocytes, adipocytes, and immune cells that differ considerably between

individuals. These signatures may eventually guide clinicians in predicting which transplant recipients are likely to experience severe glucocorticoid-induced dysglycemia. Studies integrating genomic, epigenetic, and metabolomic data are already providing insights into interindividual variability in glucocorticoid receptor (GR) signaling, paving the way for personalized steroid dosing strategies that maintain immunosuppression while reducing metabolic risk [77].

Another priority area is the development of **biomarkers that accurately reflect tissue-specific glucocorticoid exposure and sensitivity**, beyond circulating cortisol levels. Candidate biomarkers such as FKBP51 expression, 11β-HSD1 activity, and GR phosphorylation profiles show potential for identifying individuals with altered glucocorticoid responses. Future prospective studies are needed to validate these markers in transplant populations and evaluate whether biomarker-guided steroid tapering can decrease NODAT incidence. The integration of biomarker monitoring into clinical practice could represent a major step toward improving the safety of glucocorticoid therapy in kidney transplantation [78].

Novel immunosuppressive strategies may also help mitigate NODAT risk by reducing dependence on glucocorticoids and other diabetogenic agents. Research into costimulation blockade (e.g., belatacept) has demonstrated lower rates of metabolic complications, including improved glucose tolerance and reduced insulin requirements compared with CNI-based regimens. However, broader adoption of belatacept faces challenges such as increased early rejection rates and the need for Epstein–Barr virus seropositivity. Continued development of targeted immunomodulatory therapies may eventually allow for safer long-term regimens that minimize the metabolic burden associated with glucocorticoids while maintaining robust graft protection [79].

Finally, clinical trials focused on **early interventions to preserve β-cell function** in high-risk transplant recipients are needed. Strategies such as prophylactic basal insulin during steroid pulses, early use of GLP-1 receptor agonists, and leveraging CGM data to guide therapeutic adjustments represent promising avenues for preventing progression to persistent diabetes. Longitudinal studies evaluating the effects of these interventions on β-cell preservation, cardiovascular outcomes, and graft survival will be essential for establishing evidence-based protocols. As NODAT continues to impact long-term outcomes in kidney transplantation, the development of integrated endocrine–immunologic management strategies represents a critical goal for future research and clinical innovation [80].

Conclusion

New-onset diabetes after transplant (NODAT) remains a significant and multifactorial metabolic complication in kidney transplantation, driven by the combined effects of patient-specific risk factors, perioperative stress, and the diabetogenic properties of modern immunosuppressive regimens. Among these contributors, glucocorticoid therapy occupies a central role due to its profound influence on hepatic glucose production, peripheral insulin sensitivity, adipose metabolism, and β-cell function. The diversity of glucocorticoid responses across individuals underscores the importance of understanding glucocorticoid receptor regulation, signaling dynamics, and tissue-specific sensitivity. These molecular processes shape not only the efficacy of immunosuppression but also the degree to which metabolic toxicity manifests in the post-transplant period.

The pathophysiology of NODAT reflects a convergence of glucocorticoid-induced insulin resistance, calcineurin inhibitor-mediated β-cell dysfunction, mTOR inhibition, inflammation, and pre-existing metabolic vulnerabilities. As a result, early identification of at-risk individuals is essential, supported by sensitive monitoring strategies such as OGTT and continuous glucose monitoring. Clinical predictors—including age, obesity, ethnicity, hepatitis C infection, and early post-transplant hyperglycemia—offer valuable tools for stratifying metabolic risk and guiding proactive management.

Efforts to reduce glucocorticoid-induced metabolic complications have expanded through steroid minimization and avoidance strategies, lifestyle interventions, and targeted pharmacologic therapies. Emerging data suggest that precision medicine approaches incorporating molecular biomarkers, personalized immunosuppression, and early β-cell–preserving interventions hold promise for reducing

NODAT incidence and improving long-term outcomes.

Ultimately, optimizing the balance between immunologic protection and metabolic safety requires an integrated approach that brings together nephrology, endocrinology, transplant immunology, and metabolic sciences. Continued research into glucocorticoid sensitivity, receptor biology, and immunosuppressive interactions will be essential for developing more refined, individualized treatment strategies. As the field advances, translating molecular insights into clinical decision-making will play a pivotal role in reducing the burden of NODAT and enhancing the longevity and quality of life of kidney transplant recipients.

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