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Steroid-Induced Metabolic Dysfunction After Kidney Transplantation: Mechanisms, Risk Factors, and Preventive Strategies

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ABSTRACT

***Background*:** Steroids remain essential components of immunosuppressive therapy in kidney transplantation, yet their metabolic adverse effects continue to challenge long-term graft and patient outcomes. Steroid-induced metabolic dysfunction encompasses a spectrum of disturbances, including impaired glucose tolerance, new-onset diabetes after transplantation (NODAT), dyslipidemia, central adiposity, hypertension, and nonalcoholic fatty liver disease. These abnormalities contribute significantly to cardiovascular risk, graft dysfunction, and reduced patient survival. Although steroid minimization strategies have evolved over recent decades, many transplant recipients continue to require maintenance steroids or intermittent high-dose therapy for rejection treatment, making an understanding of steroid-related metabolic mechanisms essential for modern transplant care.

The metabolic effects of steroids arise from their diverse genomic and non-genomic actions across liver, skeletal muscle, adipose tissue, and pancreatic β-cells. Hepatic gluconeogenesis increases markedly under steroid exposure, while insulin-mediated glucose uptake in muscle becomes impaired due to disruption of insulin receptor signaling and GLUT4 translocation. Adipose tissue becomes a major contributor to systemic insulin resistance through enhanced lipolysis, free fatty acid release, and visceral fat expansion. In parallel, chronic steroid exposure compromises β-cell function through oxidative stress, mitochondrial impairment, and dysregulation of incretin pathways, collectively reducing insulin secretory capacity.

Importantly, steroid-induced metabolic dysfunction rarely occurs in isolation. Modern immunosuppressive regimens, particularly those containing tacrolimus or mTOR inhibitors, impose additional metabolic stressors that synergize with steroid effects. Recipient-specific factors such as age, obesity, ethnicity, viral infections, pre-transplant metabolic syndrome, and early post-operative hyperglycemia further shape individual vulnerability. Early detection of dysglycemia requires sensitive monitoring strategies beyond fasting glucose, including oral glucose tolerance testing and continuous glucose monitoring.

Preventive strategies center on steroid minimization or avoidance in selected patients, optimization of immunosuppressive combinations, and targeted metabolic therapy. Lifestyle interventions, early insulin administration during high-dose steroid exposure, and the cautious use of agents such as metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors offer promising benefits. Future directions include precision approaches that incorporate molecular markers of steroid sensitivity, predictive metabolic profiling, and individualized immunosuppressive plans.

This review synthesizes current evidence on mechanisms, risk factors, and prevention of steroid-induced metabolic dysfunction after kidney transplantation, highlighting opportunities to improve long-term metabolic and graft outcomes.

Keywords: Steroid-Induced Metabolic Dysfunction, Kidney Transplantation

INTRODUCTION

Steroids constitute a core component of most kidney transplant immunosuppression protocols and remain widely used despite their well-established metabolic toxicity. Their ability to reduce cytokine transcription, inhibit antigen presentation, and suppress T-cell activation has made them indispensable in both induction and maintenance regimens. However, major guidelines, including KDIGO, acknowledge that chronic steroid exposure contributes significantly to long-term complications such as impaired glucose tolerance, new-onset diabetes after transplantation (NODAT), dyslipidemia, and cardiovascular disease, all of which adversely affect graft and patient survival [1],[2].

The metabolic consequences of steroid therapy arise from its pleiotropic effects on multiple organ systems involved in glucose and lipid metabolism. Steroids enhance hepatic gluconeogenesis, impair skeletal muscle insulin signaling, promote adipocyte hypertrophy and lipolysis, and reduce pancreatic β-cell secretory capacity. Clinical studies have consistently shown that even moderate steroid doses substantially increase the risk of hyperglycemia and NODAT after kidney transplantation, particularly in combination with other diabetogenic immunosuppressants such as tacrolimus [3],[4]. These effects not only compromise glycemic control but also contribute to obesity, hypertension, dyslipidemia, and nonalcoholic fatty liver disease, amplifying long-term cardiovascular risk.

While steroid minimization and avoidance strategies have gained traction, their implementation remains variable due to concerns regarding acute rejection in higher-risk patients. Consequently, many recipients continue to receive maintenance steroids, and nearly all patients receive high-dose pulses for rejection treatment at some point during follow-up. The degree of metabolic dysfunction varies substantially among individuals, reflecting differences in baseline metabolic health, age, ethnicity, viral infections, and the cumulative burden of other immunosuppressive agents. Understanding these interactions is critical for optimizing post-transplant metabolic outcomes [5],[6].

The aim of this review is to synthesize current evidence on the mechanisms, risk factors, and prevention of steroid-induced metabolic dysfunction after kidney transplantation. By integrating insights from endocrinology, nephrology, and transplant immunology, this review highlights opportunities for improved risk stratification, earlier detection of metabolic injury, and individualized strategies to reduce steroid-associated morbidity while maintaining adequate immunosuppression.

Role of Steroids in Kidney Transplant Immunosuppression

Steroids have long been central to kidney transplant immunosuppression due to their rapid and broad suppression of immune activation. Their ability to inhibit pro-inflammatory cytokine production and blunt T-cell–mediated responses has historically contributed to major reductions in early acute rejection. However, these same immunologic mechanisms intersect with metabolic pathways in ways that predispose recipients to dysglycemia. High-dose perioperative steroids, rapid tapering schedules, and ongoing low-dose maintenance therapy create repeated periods of metabolic stress, making NODAT a common downstream consequence of steroid-based immunosuppression [7].

Tapering strategies and maintenance dosing vary substantially across centers, reflecting differing philosophies regarding the balance between metabolic toxicity and rejection prevention. Early steroid withdrawal protocols have been shown to reduce the incidence of NODAT, obesity, and dyslipidemia, but may increase acute rejection risk in susceptible patients. Thus, patients at low immunologic risk may benefit from steroid minimization, whereas others remain on chronic therapy despite the well-established diabetogenic effects. This interplay between risk of rejection and metabolic harm is particularly relevant because early post-transplant periods—characterized by the highest steroid exposure—coincide with the time of greatest vulnerability to NODAT [8].

Even in modern regimens that rely heavily on calcineurin inhibitors and antiproliferative agents, steroids remain necessary throughout the transplant course. Their broad immunologic coverage provides stability during immune fluctuations, infections, and episodes of subclinical alloimmunity. Importantly, nearly all patients receive high-dose steroid pulses for treatment of acute rejection, and these bursts frequently precipitate transient hyperglycemia that can evolve into persistent NODAT in individuals with limited β-cell reserve. Thus, intermittent steroid exposure throughout the post-transplant lifespan cumulatively contributes to metabolic deterioration and diabetes risk [9].

Maintenance steroid therapy plays a unique role in shaping long-term NODAT risk. While small doses may seem metabolically benign, even low-dose prednisone sustains hepatic gluconeogenesis, insulin resistance, and appetite stimulation. These chronic

metabolic pressures accumulate over months to years, interacting with other diabetogenic agents such as tacrolimus to produce a synergistic risk profile. Understanding why steroids remain necessary—and how they promote NODAT even at low doses—is essential for designing individualized immunosuppressive strategies aimed at minimizing diabetes without compromising graft protection [10].

Steroid Pharmacology Relevant to Metabolic Effects

The diabetogenic potential of glucocorticoids stems from their combined genomic and non-genomic actions, which directly influence the metabolic tissues essential for maintaining normal glucose homeostasis. Through genomic mechanisms, steroids bind the glucocorticoid receptor (GR), translocate to the nucleus, and regulate transcription of genes involved in hepatic gluconeogenesis, insulin signaling, and adipocyte metabolism. These genomic effects are central to the hyperglycemia and insulin resistance that precede NODAT. Non-genomic actions, which occur rapidly through cytosolic or membrane-associated pathways, further amplify postprandial glucose excursions—an early metabolic abnormality strongly linked to future NODAT in kidney transplant recipients [11],[12].

Steroid pharmacokinetics also critically shape NODAT risk. Prednisone, the primary steroid used in transplantation, is converted to prednisolone, which exerts high metabolic potency in liver, muscle, and adipose tissue. Even low daily doses sustain a level of receptor occupancy that disrupts insulin sensitivity throughout the day. Because steroid administration overrides physiologic cortisol circadian rhythms, morning dosing produces metabolic overlap with the largest postprandial glucose load, creating a prolonged window of impaired glucose tolerance. This chronobiologic disruption is a key contributor to the development of NODAT, especially during periods of high-dose exposure or rejection therapy [13].

Tissue-specific amplification of glucocorticoid action through 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) further increases metabolic vulnerability. High 11β-HSD1 activity in liver and visceral adipose tissue regenerates active cortisol locally, intensifying glucocorticoid signaling beyond what is reflected by systemic prednisolone levels. Elevated 11β-HSD1 expression has been associated with impaired insulin sensitivity and central adiposity, two strong predictors of NODAT in transplant recipients. Thus, local steroid activation acts synergistically with systemic steroid exposure to accelerate metabolic dysfunction, even when prednisone doses appear clinically modest [14],[15].

Variability in GR expression and sensitivity adds another key layer of risk. GR density, trafficking, and transcriptional activity differ widely across individuals due to genetic background, inflammation, age, and interaction with co-chaperone proteins such as FKBP51. Increased FKBP51 expression, in particular, has been shown to dampen GR immunologic signaling while allowing substantial metabolic activation, helping explain why some patients progress rapidly to NODAT at doses tolerated by others. This divergence between immunologic and metabolic steroid responsiveness means that two recipients on identical immunosuppression can have significantly different diabetes risk profiles, highlighting the importance of individualized metabolic surveillance [16],[17].

Mechanisms of Steroid-Induced Insulin Resistance

Hepatic insulin resistance is one of the earliest and strongest contributors to NODAT in kidney transplant recipients, and glucocorticoids play a central role in driving this dysfunction. Steroids markedly increase hepatic gluconeogenesis by upregulating key enzymes involved in glucose production, including phosphoenolpyruvate carboxykinase and glucose-6-phosphatase. This enhanced hepatic glucose output continues even in the presence of elevated insulin levels, creating fasting and postprandial hyperglycemia that places sustained pressure on β-cells. Because transplant patients often experience high-dose steroid exposure perioperatively, this hepatic metabolic shift frequently appears within days of transplantation, serving as the metabolic basis for early NODAT development [18].

Skeletal muscle, the primary site of postprandial glucose disposal, is equally affected by glucocorticoids and becomes a major contributor to steroid-induced insulin resistance. Steroids impair the insulin receptor substrate (IRS-1) signaling cascade, reduce Akt activation, and inhibit GLUT4 translocation, resulting in markedly reduced glucose uptake. In the immediate post-transplant period, reduced mobility, muscle deconditioning, and inflammation further amplify this steroid-driven dysfunction. This combination of steroid pharmacology and postoperative physiology creates an environment in which muscle insulin resistance becomes a potent driver of both transient hyperglycemia and long-term progression to NODAT [19].

Adipose tissue significantly amplifies steroid-associated insulin resistance through dysregulated lipolysis and visceral fat accumulation. Glucocorticoids stimulate hormone-sensitive lipase, promoting the release of free fatty acids (FFAs) that directly inhibit insulin action in skeletal muscle and enhance hepatic gluconeogenesis. Steroids also preferentially promote visceral rather than subcutaneous fat deposition, and visceral adiposity is strongly associated with impaired insulin sensitivity and increased risk for NODAT. The inflammatory cytokines secreted by visceral adipose tissue further disrupt insulin signaling pathways, accelerating the metabolic transition from steroid-induced insulin resistance to overt diabetes in susceptible transplant recipients [20].

Steroids also generate insulin resistance through oxidative and mitochondrial stress. Elevated glucocorticoid levels increase reactive oxygen species within metabolic tissues, impairing insulin receptor function and disrupting mitochondrial ATP production—both essential for normal glucose uptake and utilization. Over time, these stress-related pathways weaken the cellular response to insulin and reinforce a state of chronic insulin resistance. For transplant patients, who often face multiple concurrent diabetogenic stressors, steroid-induced oxidative and mitochondrial injury creates a metabolic environment where β-cells must compensate aggressively, hastening the progression to NODAT when compensatory mechanisms fail [21].

Steroid-Induced β-Cell Dysfunction

Steroids impair pancreatic β-cell function through multiple direct and indirect mechanisms, making β-cell failure a key determinant of NODAT development in kidney transplant recipients. One of the earliest effects of glucocorticoids on β-cells is the downregulation of insulin gene transcription and inhibition of essential transcription factors such as PDX-1, which is central to β-cell identity and glucose responsiveness. These genomic disruptions reduce insulin synthesis and blunt first-phase insulin secretion, limiting the β-cell's ability to counteract steroid-induced insulin resistance. In clinical practice, this manifests as inadequate compensatory insulin release during periods of high steroid exposure, setting the stage for progression from transient hyperglycemia to persistent NODAT [22].

Oxidative stress represents another major pathway through which steroids impair β-cell survival and function. Because β-cells possess inherently low antioxidant defenses, glucocorticoid-induced reactive oxygen species readily damage mitochondrial membranes, disrupt ATP generation, and interfere with the insulin exocytotic machinery. Mitochondrial dysfunction not only diminishes insulin secretory capacity but also makes β-cells more vulnerable to lipotoxicity—a relevant issue in transplant recipients who commonly exhibit elevated circulating free fatty acids due to steroid-induced adipose lipolysis. Over time, this cumulative metabolic stress erodes β-cell functional reserve and accelerates the transition to NODAT in susceptible individuals [23].

Glucocorticoids also disrupt incretin-mediated insulin secretion, an increasingly recognized contributor to post-transplant dysglycemia. Experimental studies demonstrate that steroids reduce glucagon-like peptide-1 (GLP-1) receptor expression on β-cells and diminish incretin-enhanced insulin release. In clinical settings, impaired incretin signaling leads to exaggerated postprandial hyperglycemia—an early metabolic abnormality strongly associated with NODAT risk. These changes occur even in recipients with preserved fasting glucose levels, indicating that steroid-mediated impairment of incretin pathways contributes to the subtle and progressive β-cell dysfunction preceding overt diabetes [24].

In addition to functional impairment, steroids influence β-cell mass by altering the balance between proliferation and apoptosis. Glucocorticoids reduce β-cell proliferation through inhibition of growth pathways and increase apoptosis via activation of Bim-mediated and caspase-dependent mechanisms. Because adult β-cells have limited regenerative capacity, even modest increases in apoptotic signaling can produce lasting deficits in β-cell mass. When combined with the increased insulin secretory demand imposed by steroid-induced insulin resistance, these structural changes greatly diminish the β-cell's ability to maintain euglycemia and significantly increase the likelihood of NODAT after kidney transplantation [25].

Synergistic Diabetogenicity With Other Immunosuppressants

Steroid-induced metabolic dysfunction is significantly magnified when combined with other diabetogenic immunosuppressants, making NODAT a multifactorial consequence of contemporary transplant pharmacology. Tacrolimus is the strongest contributor among calcineurin inhibitors (CNIs), exerting direct toxic effects on pancreatic β-cells by reducing insulin gene transcription, impairing insulin granule exocytosis, and promoting β-cell apoptosis. When administered alongside steroids, which simultaneously increase insulin resistance, the combined metabolic burden frequently exceeds the compensatory capacity of β-cells. Clinical studies consistently demonstrate that tacrolimus-based regimens have higher NODAT incidence than cyclosporine,

and the addition of steroids further accelerates the transition from transient post-transplant hyperglycemia to persistent NODAT [26].

Cyclosporine also contributes to dysglycemia, though to a lesser degree than tacrolimus. It interferes with insulin transcription via calcineurin pathway inhibition and impairs mitochondrial function in β-cells, reducing ATP-dependent insulin release. When combined with steroids, cyclosporine amplifies peripheral insulin resistance and worsens dyslipidemia, thereby increasing metabolic strain on β-cells already weakened by steroid-induced oxidative and inflammatory stress. The early post-transplant period—characterized by high-dose steroids and supratherapeutic CNI levels—is particularly high risk for the development of NODAT, as multiple diabetogenic mechanisms converge simultaneously during this vulnerable phase [27].

mTOR inhibitors, such as sirolimus and everolimus, further compound steroid-induced metabolic dysfunction by impairing insulin signaling pathways and β-cell viability. Sirolimus inhibits mTORC1, a key regulator of β-cell growth and adaptation, limiting the ability of β-cells to proliferate and compensate for rising insulin requirements. mTOR inhibitors also aggravate steroid-associated dyslipidemia and increase hepatic glucose production, promoting both insulin resistance and β-cell stress. Clinical evidence indicates that recipients exposed to both steroids and sirolimus experience significantly higher rates of NODAT, hypertriglyceridemia, and progressive metabolic deterioration compared with those on steroid-sparing regimens [28].

The cumulative diabetogenic effects of steroids, CNIs, and mTOR inhibitors extend beyond glucose metabolism, creating a metabolic profile that heavily predisposes transplant recipients to NODAT. Steroids induce visceral adiposity and systemic insulin resistance, tacrolimus causes profound β-cell injury, and sirolimus disrupts insulin signaling and lipid homeostasis. Together, these overlapping mechanisms drive a powerful synergy that accelerates progression to NODAT in patients with even modest baseline metabolic vulnerability. Understanding how these agents interact is essential for individualizing immunosuppressive regimens and implementing early preventive strategies to mitigate long-term metabolic consequences after kidney transplantation [29].

Clinical Predictors of Steroid-Associated NODAT

Multiple clinical and demographic factors modify susceptibility to steroid-associated NODAT, making early identification of high-risk individuals essential for targeted monitoring. Age is one of the strongest predictors, as older recipients exhibit reduced β-cell reserve and diminished ability to compensate for steroid-induced insulin resistance. Aging impairs mitochondrial function and decreases β-cell proliferation capacity, amplifying the metabolic effects of glucocorticoids. Clinical studies consistently show that recipients over age 45 have significantly higher rates of NODAT following steroid exposure, underscoring the need for heightened surveillance in this group [30].

Obesity and pre-existing metabolic syndrome markedly increase the diabetogenic consequences of steroids. Visceral adiposity promotes chronic low-grade inflammation, elevated free fatty acids, and impaired insulin signaling—all of which are magnified by steroid therapy. Steroids further enhance central fat deposition, creating a metabolic environment that accelerates progression from insulin resistance to overt NODAT. Recipients with elevated BMI, impaired fasting glucose, or a history of gestational diabetes are especially vulnerable, as they enter the post-transplant period with diminished metabolic flexibility and limited β-cell compensatory capacity [31].

Ethnicity is another important determinant of steroid-related NODAT risk. African American, Hispanic, and South Asian recipients consistently demonstrate higher incidence of post-transplant diabetes, even after adjusting for immunosuppressive exposure and BMI. These ethnic disparities are attributed to increased baseline insulin resistance, limited β-cell reserve, and genetic traits affecting glucose metabolism. Steroids amplify these pre-existing vulnerabilities by further increasing hepatic glucose output and adipose-mediated lipolysis, pushing predisposed recipients more rapidly toward NODAT. For these groups, early preventive strategies are especially critical [32].

Viral infections—particularly hepatitis C virus (HCV) and cytomegalovirus (CMV)—further heighten NODAT risk in the context of steroid exposure. HCV induces hepatic insulin resistance and β-cell dysfunction through inflammatory and viral-mediated pathways, while CMV infection has been linked to impaired insulin release and heightened systemic inflammation. When steroids are administered in recipients with active or prior viral infections, the combinatorial effects on insulin signaling and β-cell function significantly increase the likelihood of NODAT. Screening for viral risk factors is therefore essential when evaluating the metabolic consequences of steroid-based immunosuppression [33].

Other Steroid-Related Metabolic Effects Relevant to NODAT

Steroids exert numerous metabolic effects beyond glucose dysregulation, many of which indirectly contribute to the development and progression of NODAT. One of the most clinically relevant is steroid-induced dyslipidemia. Glucocorticoids increase hepatic very-low-density lipoprotein (VLDL) production, elevate triglyceride levels, and reduce high-density lipoprotein (HDL) concentrations. These lipid abnormalities impair insulin signaling and promote ectopic fat accumulation in liver and muscle—two key processes that worsen insulin resistance. In kidney transplant recipients, dyslipidemia frequently emerges early due to high-dose perioperative steroid exposure and often persists throughout maintenance therapy, exerting a compounding effect on NODAT pathogenesis [34].

Weight gain is another major metabolic consequence of steroid therapy. Steroids stimulate appetite, promote positive energy balance, and preferentially increase visceral adiposity rather than subcutaneous fat stores. Visceral fat is metabolically detrimental, producing inflammatory cytokines, free fatty acids, and adipokines that disrupt insulin signaling and accelerate β-cell stress. This pattern of fat redistribution is strongly associated with both insulin resistance and NODAT risk. Kidney transplant recipients who experience rapid post-transplant weight gain often show greater glycemic instability, especially when weight gain coincides with ongoing steroid exposure and reduced physical activity in the early postoperative period [35].

Steroid-induced hypertension also contributes to metabolic dysfunction and NODAT development. Through sodium retention, mineralocorticoid receptor cross-activation, and increased systemic vascular resistance, steroids elevate blood pressure in a dose-dependent manner. Hypertension is closely linked to insulin resistance via endothelial dysfunction and microvascular impairment, which diminish insulin-mediated glucose uptake in muscle tissue. In transplant recipients—who often have pre-existing hypertensive nephropathy—the additive effect of steroid-induced hypertension further destabilizes glucose metabolism and intensifies long-term cardiometabolic risk [36].

Nonalcoholic fatty liver disease (NAFLD) represents a growing concern in kidney transplant patients receiving chronic steroid therapy. Steroids promote hepatic lipogenesis, increase triglyceride storage, and impair hepatic insulin sensitivity, all of which contribute to hepatic steatosis. NAFLD itself is an independent risk factor for both insulin resistance and diabetes. When NAFLD develops in transplant recipients already exposed to diabetogenic agents such as tacrolimus, the combined effects on hepatic metabolism markedly increase susceptibility to NODAT. Recognition of NAFLD as part of the post-transplant metabolic syndrome emphasizes the need for proactive screening and early intervention in patients maintained on steroid therapy [37].

Monitoring Strategies for Steroid-Associated NODAT

Early and accurate detection of steroid-associated NODAT requires monitoring tools capable of capturing the full spectrum of glucose abnormalities that occur in the post-transplant period. Fasting plasma glucose alone is insufficient because steroids disproportionately elevate postprandial glucose levels and induce diurnal glycemic variability. The oral glucose tolerance test (OGTT) remains the most sensitive method for diagnosing early dysglycemia and is especially useful during the first three to six months post-transplant when steroid exposure is highest. Clinical studies have shown that OGTT identifies a substantial proportion of patients with impaired glucose tolerance or early diabetes who would otherwise be missed by fasting glucose alone, making it a preferred diagnostic tool in high-risk recipients [38].

Hemoglobin A1c (HbA1c) has important limitations in the early post-transplant period due to fluctuating erythropoiesis, anemia, and the use of erythropoiesis-stimulating agents, all of which can falsely lower values. Despite these limitations, HbA1c becomes more reliable after hematologic stabilization and provides a useful adjunct to fasting glucose for long-term metabolic monitoring. In steroid-treated transplant recipients, HbA1c should therefore be interpreted cautiously in the early months and used in combination with other measures rather than as a standalone diagnostic test [39].

Continuous glucose monitoring (CGM) has emerged as a valuable modality for capturing the dynamic glycemic patterns characteristic of steroid-associated dysglycemia. CGM identifies postprandial excursions, nocturnal hyperglycemia, and glycemic variability far more effectively than intermittent capillary glucose measurements. Studies in kidney transplant recipients demonstrate that CGM detects abnormalities earlier and with greater precision, allowing clinicians to identify evolving NODAT before fasting or HbA1c abnormalities appear. CGM is particularly useful during periods of steroid pulses for rejection, when rapid metabolic deterioration may occur and timely therapeutic adjustments are essential [40].

In addition to glucose-centered monitoring, biomarkers of steroid exposure and glucocorticoid sensitivity may offer future opportunities for early detection of metabolic risk. Molecules such as FKBP51, 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), and glucocorticoid-responsive transcripts have been proposed as tools to quantify individual tissue sensitivity to steroids. Although not yet integrated into clinical practice, preliminary data suggest that elevated FKBP51 expression correlates with insulin resistance and may predict susceptibility to steroid-associated NODAT. These biomarkers highlight the potential for precision metabolic monitoring in transplant recipients receiving glucocorticoid therapy [41].

Steroid Minimization and Avoidance Protocols

Steroid minimization strategies have emerged as a central component of efforts to reduce NODAT risk in kidney transplant recipients. Early withdrawal protocols, where steroids are tapered and discontinued within the first week post-transplant, significantly reduce exposure during the highest-risk period for dysglycemia. Randomized trials have shown that early steroid withdrawal is associated with lower rates of NODAT, improved metabolic profiles, and reduced weight gain. These benefits result from eliminating sustained gluconeogenic stimulation and mitigating the synergistic diabetogenic effects of concurrent tacrolimus therapy. In appropriately selected recipients, early withdrawal can substantially reduce long-term metabolic complications without compromising graft survival [42].

Steroid avoidance protocols seek to eliminate oral steroids entirely after induction by using potent adjunct immunosuppressive agents such as basiliximab or antithymocyte globulin combined with tacrolimus and mycophenolate. These regimens have demonstrated favorable metabolic outcomes, including markedly lower NODAT incidence and reduced dyslipidemia. However, avoidance strategies require careful patient selection, as recipients at higher immunologic risk—such as those with high panel-reactive antibodies or delayed graft function—may be more vulnerable to acute rejection if steroids are withheld. Thus, the decision to pursue avoidance protocols must balance immunologic safety with metabolic benefit, particularly in patients with pre-existing risk factors for NODAT [43].

For many recipients, complete steroid avoidance is not feasible, making long-term low-dose steroid maintenance a common practice. Even low doses, however, exert cumulative metabolic pressure through persistent insulin resistance and appetite stimulation. Strategies to mitigate this include using the lowest effective maintenance dose, slow taper schedules tailored to immunologic risk, and careful monitoring during rejection treatment. Notably, steroid pulses for biopsy-proven rejection remain a major precipitating factor for acute hyperglycemia and can unmask subclinical dysglycemia, accelerating progression to NODAT. Continuous glucose monitoring during steroid pulses may help detect early metabolic deterioration and allow timely intervention [44].

Emerging personalized approaches to steroid minimization consider genetic and molecular predictors of glucocorticoid sensitivity, allowing immunosuppression to be tailored to the individual's metabolic and immunologic profile. Research into glucocorticoid receptor signaling, FKBP51 expression, and tissue-specific steroid activation suggests that metabolically vulnerable recipients may benefit most from early withdrawal or avoidance strategies. Conversely, patients with greater immunologic risk but lower metabolic susceptibility may safely continue low-dose steroids. Although these precision-based protocols are not yet standard practice, they represent a promising direction for reducing NODAT without increasing rejection rates [45].

Management and Preventive Strategies for Steroid-Associated NODAT

Preventing steroid-associated NODAT begins with early metabolic risk mitigation during periods of high-dose glucocorticoid exposure. Lifestyle interventions, particularly structured nutritional counseling and promotion of early physical activity, play a foundational role. Diets emphasizing low glycemic load, reduced saturated fat intake, and moderate caloric restriction help attenuate postprandial glucose excursions intensified by steroids. Regular physical activity improves muscle insulin sensitivity, counteracting steroid-induced disruptions in glucose transport and insulin signaling. Transplant recipients who adopt lifestyle modifications early—during the period of steroid taper—demonstrate more stable glycemic trajectories and lower NODAT incidence over time [46].

Pharmacologic prevention often requires early identification of patients at high metabolic risk, especially those receiving tacrolimus in combination with steroids. Early basal insulin initiation during high-dose steroid exposure has been shown to preserve β-cell function by reducing glucotoxicity, stabilizing glycemic variability, and preventing the transition from transient hyperglycemia to persistent NODAT. Short-term insulin therapy is particularly useful during rejection treatments, where pulse

steroids rapidly overwhelm β-cell compensatory capacity. This proactive approach supports the concept that β-cell rest, rather than delayed pharmacologic escalation, is crucial to preventing long-term metabolic deterioration in vulnerable recipients [47].

Oral antidiabetic agents offer additional opportunities to manage or prevent steroid-related dysglycemia once kidney function stabilizes. Metformin, when tolerated, improves hepatic and peripheral insulin sensitivity, counteracting two key mechanisms of steroid-induced glucose intolerance. DPP-4 inhibitors are well tolerated in kidney transplant recipients and enhance endogenous incretin signaling, which is impaired by steroids. GLP-1 receptor agonists offer multiple benefits—including weight loss, improved insulin secretion, and reduced appetite—but require careful monitoring for gastrointestinal side effects. These therapies provide important adjuncts for managing steroid-related metabolic stress, particularly when sustained low-dose steroids remain necessary for immunologic protection [48].

SGLT2 inhibitors are emerging as promising agents for kidney transplant recipients with established NODAT, offering glycemic control, weight reduction, and cardiovascular protection. Early studies suggest they can be safely used in carefully selected transplant patients with stable graft function, although the risks of volume depletion or genitourinary infections must be monitored. Their insulin-independent mechanism of action is particularly advantageous for steroid-associated hyperglycemia, which is driven largely by hepatic glucose output and insulin resistance. As evidence grows, SGLT2 inhibitors may become an integral component of long-term metabolic management in steroid-treated transplant recipients [49].

Conclusion

Steroid-induced metabolic dysfunction remains one of the most consequential non-immunologic challenges in kidney transplantation, and its role in driving new-onset diabetes after transplant (NODAT) is increasingly recognized. Steroids disrupt glucose homeostasis at multiple levels—promoting hepatic insulin resistance, impairing muscle glucose uptake, stimulating adipose lipolysis, and damaging pancreatic β-cell function. These mechanisms interact with other diabetogenic stressors inherent to modern immunosuppression, creating a highly permissive environment for the development of NODAT, particularly during periods of high-dose exposure or rejection therapy.

Despite advances in transplant immunology, complete elimination of steroids remains difficult due to their unmatched ability to rapidly suppress immune activation. As a result, the challenge lies not in abandoning steroids entirely, but in optimizing their use to balance immunologic protection with metabolic safety. Early withdrawal protocols, avoidance strategies, and individualized dosing approaches have demonstrated substantial metabolic benefits when applied to carefully selected recipients. At the same time, improvements in monitoring—particularly through OGTT and continuous glucose monitoring—enable earlier detection of evolving dysglycemia, allowing timely intervention before irreversible β-cell decline occurs.

Preventive and therapeutic strategies aimed at mitigating steroid-induced metabolic injury continue to expand. Lifestyle modification, early insulin therapy, and the introduction of modern glucose-lowering agents provide a multifaceted approach to preserving metabolic stability in transplant recipients. Looking ahead, precision medicine strategies that incorporate molecular markers of glucocorticoid sensitivity, β-cell resilience, and metabolic vulnerability hold promise for enabling clinicians to tailor steroid exposure to each patient's unique risk profile.

Ultimately, minimizing the burden of NODAT in kidney transplant recipients will require an integrated approach that recognizes the central role of steroids in both graft protection and metabolic injury. Through careful immunosuppressive planning, improved metabolic surveillance, and timely intervention, it is possible to reduce the long-term impact of steroid-induced metabolic dysfunction and support better outcomes for kidney transplant recipients.

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