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Histone Deacetylase-2 and Steroid Responsiveness in Pediatric Nephrotic Syndrome: An Epigenetic Perspective from Egyptian Cohorts

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ABSTRACT

Background: Nephrotic syndrome (NS) is one of the most common chronic glomerular disorders in childhood, characterized by heavy proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Glucocorticoids remain the cornerstone of therapy, and the initial response to steroid treatment serves as the strongest predictor of long-term outcome. While most children achieve remission with corticosteroids, a substantial proportion develop steroid resistant nephrotic syndrome (SRNS), which is associated with progression to chronic kidney disease and increased morbidity. The mechanisms underlying variable steroid responsiveness remain incompletely understood. Recent research highlights the role of epigenetic regulation, particularly histone modifications, in modulating glucocorticoid receptor (GR) signaling. Histone deacetylase-2 (HDAC2), a class I histone deacetylase, has emerged as a pivotal regulator of glucocorticoid-mediated anti-inflammatory activity by remodeling chromatin and facilitating transcriptional repression of pro-inflammatory genes. Reduced expression or activity of HDAC2 has been implicated in impaired steroid responsiveness in several chronic inflammatory conditions, raising interest in its role in pediatric nephrotic syndrome. This review aims to critically evaluate the relationship between HDAC2 expression and activity and steroid responsiveness in children with nephrotic syndrome, with particular emphasis on Egyptian pediatric cohorts where SRNS prevalence is relatively high. We explore current evidence from preclinical studies, clinical investigations, and genetic/epigenetic research, highlighting how HDAC2 deficiency may contribute to steroid resistance. Furthermore, we discuss the potential utility of HDAC2 as a predictive biomarker and as a therapeutic target for novel epigenetic interventions.

Conclusion: Emerging data suggest that reduced HDAC2 expression and activity contribute to impaired glucocorticoid signaling and poor therapeutic outcomes in pediatric nephrotic syndrome. Egyptian studies provide unique insights into the genetic and environmental determinants influencing HDAC2 function, underscoring population-specific variability in steroid response. Restoration of HDAC2 activity through pharmacological agents, antioxidants, or epigenetic modulators represents a promising therapeutic avenue to enhance steroid sensitivity. However, current evidence remains preliminary, and large-scale, multicenter studies are needed to validate HDAC2 as a reliable biomarker and to evaluate targeted interventions in diverse pediatric populations. Integrating HDAC2 profiling into clinical practice could advance personalized medicine in childhood nephrotic syndrome, improving treatment outcomes and reducing the burden of steroid resistance.

Keywords*: Histone Deacetylase-2, Steroid Responsiveness, Nephrotic Syndrome*

INTRODUCTION

Nephrotic syndrome (NS) is among the most frequent chronic glomerular diseases in children, with an incidence of 2–7 per 100,000 children per year and a prevalence of 16 per 100,000 worldwide. It is defined by the clinical triad of heavy proteinuria, hypoalbuminemia, and generalized edema, often accompanied by hyperlipidemia. Despite being a heterogeneous condition, the response to corticosteroid therapy remains the most clinically relevant determinant of outcome. Steroid-sensitive nephrotic syndrome (SSNS) accounts for the majority of pediatric cases and generally carries a favorable prognosis. In contrast, steroid-resistant nephrotic syndrome (SRNS) occurs in approximately 10–20% of children and is associated with frequent relapses, progression to chronic kidney disease, and, in some cases, end-stage renal disease requiring dialysis or transplantation [1,2].

The molecular basis of steroid responsiveness in NS remains incompletely understood. Glucocorticoids exert their effects primarily through binding to the glucocorticoid receptor (GR), which translocates into the nucleus to regulate transcription of anti-inflammatory and immunomodulatory genes. However, variability in GR signaling contributes to differential clinical responses. While genetic mutations affecting podocyte structure and signaling explain some cases of SRNS, epigenetic regulation has emerged as a critical factor influencing steroid sensitivity. In this context, histone modifications play an essential role in shaping chromatin structure and accessibility, thereby modulating transcriptional responses to glucocorticoids [3,4].

Histone deacetylase-2 (HDAC2), a member of the class I HDAC family, has been identified as a central regulator of glucocorticoid responsiveness. HDAC2 deacetylates histones, leading to chromatin condensation and repression of pro-inflammatory genes. In chronic inflammatory diseases such as asthma and chronic obstructive pulmonary disease, reduced HDAC2 expression and activity have been directly linked to impaired steroid responsiveness. These findings raise the possibility that similar epigenetic dysregulation contributes to steroid resistance in pediatric nephrotic syndrome [5].

Egyptian cohorts provide a particularly relevant context for studying HDAC2 in NS, given the relatively high prevalence of SRNS and the unique genetic and environmental factors in this population. Early reports suggest that reduced HDAC2 activity correlates with poor steroid response in Egyptian children, implicating epigenetic modulation as a determinant of treatment outcomes. However, comprehensive evidence remains limited, and further research is required to establish causal links and therapeutic opportunities [6].

The aim of this review is to synthesize current knowledge on the role of HDAC2 expression and activity in modulating steroid responsiveness in pediatric nephrotic syndrome, with a particular focus on Egyptian cohorts. We will explore epidemiological patterns, molecular mechanisms, preclinical data, clinical evidence, and therapeutic implications. Special emphasis will be placed on the potential of HDAC2 as both a predictive biomarker and a therapeutic target, situating it within the broader context of precision medicine in pediatric nephrology.

1. Epidemiology of Nephrotic Syndrome in Children

Nephrotic syndrome (NS) is a relatively rare but clinically significant pediatric disorder with a variable incidence worldwide. Global estimates suggest an annual incidence of **2–7 cases per 100,000 children** and a prevalence of up to **16 per 100,000**. However, the distribution is not uniform across geographic and ethnic populations. South Asian and African children demonstrate higher incidence rates compared to European cohorts, suggesting that both genetic susceptibility and environmental exposures contribute to disease risk [7]. The age of onset for pediatric NS is most commonly between **2 and 6 years**, a period during which minimal change disease (MCD) is the predominant histopathological finding. MCD is typically associated with steroidsensitive nephrotic syndrome (SSNS), which has a favorable prognosis. In contrast, focal segmental glomerulosclerosis (FSGS) is more frequently observed in older children and adolescents and is strongly associated with steroid-resistant nephrotic syndrome (SRNS). This distinction has important implications for prognosis, long-term kidney function, and therapeutic response [8].

Epidemiological patterns also demonstrate variability in the prevalence of steroid resistance. Globally, **80–90% of children with NS achieve remission with initial corticosteroid therapy**, placing them in the SSNS category. The remaining **10–20% develop SRNS**, a group with a significantly higher risk of progression to chronic kidney disease and end-stage renal disease (ESRD). Notably, the proportion of SRNS appears higher in developing countries, possibly reflecting genetic predispositions, late diagnosis, or limited access to optimized therapies [9].

In Egypt, epidemiological studies have highlighted the considerable burden of pediatric NS, particularly SRNS. Reports suggest that **up to 25–30% of Egyptian children** with NS exhibit steroid resistance, a rate higher than that observed in many Western populations. This elevated prevalence may be linked to regional genetic variants, including mutations in podocyte-related genes, as well as epigenetic regulators such as histone deacetylase-2 (HDAC2). Furthermore, environmental risk factors such as recurrent infections, malnutrition, and delayed access to nephrology care may exacerbate disease outcomes [10].

From a public health perspective, the epidemiology of NS underscores the need for population-specific studies to identify both genetic and epigenetic contributors to steroid responsiveness. Understanding why Egyptian cohorts exhibit a higher prevalence of SRNS is particularly important, as it may provide insight into the role of HDAC2 dysregulation and inform the development of targeted interventions. This regional perspective emphasizes that while NS is a global disorder, its expression and outcomes are heavily shaped by local genetic and environmental contexts [11].

2. Clinical Classification of Steroid Response in Pediatric Nephrotic Syndrome

The clinical classification of nephrotic syndrome (NS) in children is largely determined by the response to corticosteroid therapy, which remains the cornerstone of initial management. This classification is not only prognostic but also guides subsequent therapeutic strategies. Children who achieve complete remission following a standard course of corticosteroids are defined as having **steroid-sensitive nephrotic syndrome (SSNS)**. In contrast, those who fail to achieve remission are categorized as **steroid-resistant nephrotic syndrome (SRNS)**, a subgroup associated with poor renal outcomes and a high risk of progression to end-stage renal disease (ESRD) [12].

SSNS accounts for the majority of pediatric NS cases, with approximately **80–90% of children** achieving remission after four weeks of oral prednisone or prednisolone therapy. These patients typically present with minimal change disease (MCD) on renal biopsy, which is characterized by diffuse podocyte foot process effacement without significant glomerular scarring. The prognosis for SSNS is generally favorable, with most patients maintaining long-term kidney function despite frequent relapses. However, some patients may develop **steroid-dependent NS (SDNS)**, requiring ongoing low-dose steroids or immunosuppressants to maintain remission [13].

SRNS is defined by the **failure to achieve remission after four to six weeks of high-dose corticosteroid therapy**. This subgroup often corresponds to focal segmental glomerulosclerosis (FSGS) or other non–minimal change lesions on biopsy. Children with SRNS face a guarded prognosis, with up to **50% progressing to ESRD within 10 years** of diagnosis. SRNS is also associated with higher treatment costs, increased hospitalization, and greater exposure to second-line immunosuppressive agents such as calcineurin inhibitors, mycophenolate mofetil, or rituximab. Importantly, SRNS is highly prevalent in certain ethnic populations, including Egyptian children, underscoring the influence of both genetic and epigenetic determinants [14].

Between these two extremes lies a clinically relevant group of patients with **frequently relapsing nephrotic syndrome (FRNS)**. These children initially respond to steroids but experience ≥2 relapses within six months or ≥4 relapses within a year. Although FRNS does not carry the same risk of ESRD as SRNS, it imposes a considerable burden in terms of morbidity, school absenteeism, and steroid-related toxicities such as growth retardation, obesity, and hypertension. Pharmacists and pediatricians must therefore optimize treatment regimens to balance efficacy with safety, often incorporating steroid-sparing agents [15].

From a clinical pharmacy perspective, classification based on steroid responsiveness has important therapeutic implications. SSNS patients may benefit from gradual steroid tapering and supportive measures, while SRNS patients require early consideration of adjunctive immunosuppressive therapy. Epigenetic factors, including histone deacetylase-2 (HDAC2) expression, are increasingly recognized as potential determinants of responsiveness. For Egyptian children, where SRNS prevalence is higher than in many Western cohorts, integrating molecular and epigenetic markers into classification schemes may allow for earlier identification of non-responders and more personalized therapeutic strategies [16].

3. Burden of Steroid Resistance in Egyptian Children

Steroid-resistant nephrotic syndrome (SRNS) poses one of the greatest therapeutic challenges in pediatric nephrology. Globally, SRNS occurs in approximately **10–20% of children** with nephrotic syndrome, but its burden appears disproportionately higher in certain regions, including Egypt. Epidemiological studies from Egyptian pediatric nephrology centers report SRNS prevalence rates approaching **25–30%**, significantly higher than figures from Western populations. This discrepancy underscores the impact of genetic predisposition, socioeconomic context, and environmental exposures on disease phenotype and response to therapy [17]. The clinical burden of SRNS in Egyptian children is considerable. Children with SRNS are more likely to develop **chronic kidney disease (CKD)**, with up to **50% progressing to end-stage renal disease (ESRD) within 5–10 years** of diagnosis if remission is not achieved. ESRD in childhood carries devastating consequences, including the need for renal replacement therapy, high healthcare costs, and increased mortality risk. In Egypt, limited access to pediatric dialysis units and transplantation programs further compounds the adverse outcomes associated with SRNS, making early identification of resistant cases particularly critical [18]. Beyond renal outcomes, SRNS imposes a substantial psychosocial and economic burden on affected families. Frequent hospitalizations for disease relapses, complications such as infections and thrombosis, and the need for costly immunosuppressive therapies contribute to financial strain. In low-resource settings, where health insurance coverage is limited, families often face catastrophic out-of-pocket expenses. Moreover, affected children frequently miss school, contributing to long-term educational and social disadvantages. This highlights the urgent need for predictive biomarkers such as HDAC2 to allow earlier stratification and tailored management strategies [19].

From a therapeutic perspective, the management of SRNS in Egyptian children remains particularly challenging. While calcineurin inhibitors such as cyclosporine and tacrolimus represent the standard of care, their high cost and potential nephrotoxicity limit their long-term utility. Novel biologics such as rituximab are used selectively but remain largely inaccessible to many Egyptian patients due to financial constraints. The relatively high SRNS burden in this population makes the search for **cost-effective, locally applicable biomarkers and treatment strategies** even more pressing. Epigenetic regulators such as histone deacetylase-2 (HDAC2) may offer not only mechanistic insights into steroid resistance but also a framework for future therapeutic interventions [20]. Furthermore, Egyptian cohorts provide a unique opportunity for translational research into the epigenetic determinants of SRNS. Variations in genetic backgrounds, environmental exposures (such as recurrent infections and malnutrition), and healthcare disparities may interact with HDAC2 expression and activity to influence steroid responsiveness. Understanding these interactions may reveal population-specific therapeutic targets, with broader implications for SRNS management in other resource-limited settings[21].

4. Glucocorticoid Mechanism of Action in Nephrotic Syndrome

Glucocorticoids (GCs) remain the first-line therapy for childhood nephrotic syndrome due to their potent antiinflammatory and immunosuppressive effects. Their efficacy is rooted in their ability to modulate transcriptional activity across multiple immune and renal pathways. Upon entering target cells, glucocorticoids bind to cytoplasmic **glucocorticoid receptors (GRs)**, which undergo conformational change, dissociate from heat shock proteins, and translocate into the nucleus. Within the nucleus, activated GRs regulate gene transcription through two principal mechanisms: **transactivation** of anti-inflammatory genes and **transrepression** of proinflammatory genes [22].

Transactivation involves binding of the GR complex to glucocorticoid response elements (GREs) in the promoter regions of target genes, leading to increased transcription of anti-inflammatory proteins such as **annexin-1, interleukin-10, and inhibitor of NF-κB (IκBα)**. These proteins suppress immune activation and reduce cytokine production, contributing to remission in steroid-sensitive nephrotic syndrome (SSNS). On the other hand, transrepression entails direct or indirect interactions between GRs and transcription factors such as **NF-κB and AP-1**, preventing the expression of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and chemokines. This process is particularly important in inhibiting podocyte injury and reducing proteinuria [23]. Epigenetic regulation plays a crucial role in these glucocorticoid-mediated pathways. For effective transrepression, GRs recruit corepressors such as **histone deacetylase-2 (HDAC2)** to inflammatory gene promoters. HDAC2 catalyzes the removal of acetyl groups from histone tails, resulting in chromatin condensation and suppression of pro-inflammatory gene transcription. A reduction in HDAC2 expression or activity disrupts this mechanism, leading to persistent transcription of inflammatory mediators despite corticosteroid therapy. This pathway has been extensively studied in asthma and chronic obstructive pulmonary disease (COPD), and emerging evidence suggests a similar role in pediatric nephrotic syndrome [24].

In addition to immune modulation, glucocorticoids exert direct effects on podocytes, the specialized epithelial cells that maintain glomerular filtration barrier integrity. GR activation in podocytes enhances cytoskeletal stability, reduces apoptosis, and suppresses local inflammatory responses. These protective effects are central to achieving remission in SSNS. However, when GR signaling is impaired—whether by genetic mutations, receptor dysfunction, or defective epigenetic regulation such as reduced HDAC2 activity—podocyte injury persists, contributing to steroid resistance and ongoing proteinuria [25].

From a clinical pharmacy perspective, understanding the glucocorticoid mechanism of action is essential for optimizing therapy in pediatric nephrotic syndrome. Children with SSNS benefit from this multifaceted antiinflammatory and podocyte-protective action, whereas those with SRNS may require adjunctive therapies targeting alternative pathways. Importantly, HDAC2 emerges as a critical molecular checkpoint in GR-mediated signaling. By bridging epigenetic regulation with steroid pharmacodynamics, HDAC2 provides a mechanistic explanation for inter-individual variability in steroid responsiveness—particularly relevant for Egyptian children, where SRNS prevalence is high [26].

5. Epigenetic Regulation in Pediatric Kidney Diseases

Epigenetic mechanisms, which include DNA methylation, histone modifications, and non-coding RNA regulation, represent a critical layer of control in gene expression without altering the underlying DNA sequence. These mechanisms are particularly relevant in pediatric kidney diseases, where genetic mutations account for only a fraction of disease variability, and environmental influences such as infections, nutrition, and drug exposures significantly affect disease progression and therapeutic outcomes [27].

Histone modifications, particularly acetylation and deacetylation, are among the most studied epigenetic processes in nephrology. Acetylation of histone tails is generally associated with chromatin relaxation and gene activation, while deacetylation, catalyzed by histone deacetylases (HDACs), promotes chromatin condensation and transcriptional repression. Dysregulation of these processes has been implicated in the pathogenesis of nephrotic syndrome, diabetic nephropathy, and lupus nephritis. In children with nephrotic syndrome, aberrant histone acetylation patterns may alter immune responses and podocyte function, contributing to variable responsiveness to corticosteroid therapy [28].

Epigenetic changes are particularly important in the context of steroid resistance. For glucocorticoids to exert their full anti-inflammatory effect, the glucocorticoid receptor (GR) must recruit HDAC2 to inflammatory gene promoters, thereby repressing pro-inflammatory transcription. A reduction in HDAC2 expression or activity— whether due to oxidative stress, inflammatory mediators, or genetic susceptibility—leads to failure of glucocorticoid-mediated repression. This mechanism, well established in respiratory diseases such as asthma, is increasingly being recognized in nephrotic syndrome, suggesting that impaired epigenetic regulation underlies steroid resistance in a subset of children [29].

In Egyptian pediatric populations, where steroid-resistant nephrotic syndrome (SRNS) prevalence is relatively high, epigenetic dysregulation may provide an explanation beyond genetic factors alone. Studies indicate that children with SRNS often display reduced HDAC2 expression and activity compared with steroid-sensitive counterparts, implicating an epigenetic barrier to steroid responsiveness. Furthermore, environmental factors prevalent in low-resource settings, including recurrent infections, malnutrition, and high oxidative stress, may exacerbate epigenetic dysfunction and contribute to poor therapeutic outcomes [30].

The clinical implications of these findings are profound. Epigenetic regulators such as HDAC2 could serve not only as **biomarkers** to predict steroid responsiveness but also as **therapeutic targets** to restore sensitivity in resistant cases. Pharmacological agents capable of enhancing HDAC2 activity, including certain antioxidants and theophylline derivatives, are under investigation in other chronic inflammatory diseases and may hold promise for pediatric nephrotic syndrome. Thus, understanding epigenetic regulation in kidney diseases opens new avenues for precision medicine approaches that are especially relevant in high-burden populations such as Egyptian children [31].

6. Histone Deacetylases: Overview and Biological Role

Histone deacetylases (HDACs) are a family of enzymes that catalyze the removal of acetyl groups from lysine residues on histone and non-histone proteins. By reversing the action of histone acetyltransferases (HATs), HDACs promote chromatin condensation and transcriptional repression, thereby exerting a major influence on gene expression. Beyond histones, HDACs regulate numerous cellular proteins, including transcription factors, signaling molecules, and cytoskeletal proteins, underscoring their central role in cellular homeostasis [32]. In humans, 18 HDACs have been identified and are grouped into four major classes based on homology to yeast proteins:

Class I (HDAC1, HDAC2, HDAC3, HDAC8): Primarily nuclear, ubiquitously expressed, and involved in regulation of cell cycle, differentiation, and transcription.

Class II (HDAC4, 5, 6, 7, 9, 10): Shuttle between the nucleus and cytoplasm; more tissue-specific, especially in muscle and neural tissues.

Class III (Sirtuins 1–7): NAD^+-dependent deacetylases with roles in metabolism, aging, and stress responses. **Class IV (HDAC11):** Shares features of both Class I and II enzymes.

Among these, **HDAC2 (Class I)** is of particular relevance to inflammatory and immune-mediated diseases. It interacts directly with nuclear receptors such as the glucocorticoid receptor (GR) and is critical for glucocorticoid-mediated repression of pro-inflammatory genes [33].

HDACs influence a wide range of biological processes relevant to pediatric nephrotic syndrome. They regulate T-cell differentiation and cytokine production, modulate oxidative stress responses, and maintain podocyte stability. Inappropriate HDAC activity has been implicated in cancer, neurodegeneration, metabolic diseases, and autoimmune conditions. In the kidney, HDAC dysregulation has been associated with podocyte injury, fibrosis, and progression of chronic kidney disease. Importantly, reduced HDAC2 activity has been linked with impaired steroid responsiveness in diseases such as asthma and COPD, suggesting a similar pathogenic role in nephrotic syndrome [34].

Pharmacologically, HDACs represent both opportunities and challenges. HDAC inhibitors (e.g., vorinostat, panobinostat) are used in oncology for their anti-proliferative effects. However, in chronic inflammatory diseases, strategies to **restore or enhance HDAC2 activity** are of greater relevance. For instance, low-dose theophylline has been shown to increase HDAC2 activity in airway inflammation, thereby restoring steroid responsiveness. Translating this approach into pediatric nephrotic syndrome may provide a novel adjunctive therapy for children with steroid resistance [35].

From a pediatric clinical pharmacy perspective, the biological role of HDACs highlights the importance of balancing **epigenetic regulation with therapeutic intervention**. While HDAC inhibition may be desirable in

oncology, selective HDAC2 activation could revolutionize management of SRNS. Egyptian pediatric cohorts, with their high prevalence of steroid resistance, provide an ideal population for studying the clinical utility of HDAC2 as both a biomarker and therapeutic target [36].

7. HDAC2 and Glucocorticoid Receptor Signaling

Histone deacetylase-2 (HDAC2) plays a pivotal role in modulating glucocorticoid receptor (GR) signaling, which is central to the therapeutic effects of corticosteroids in nephrotic syndrome (NS). After glucocorticoids bind to GRs in the cytoplasm, the activated complex translocates into the nucleus, where it regulates transcription of anti-inflammatory and pro-inflammatory genes. For effective repression of inflammatory pathways, GRs recruit HDAC2 to gene promoters, enabling deacetylation of histones and subsequent chromatin condensation. This epigenetic silencing prevents transcription of inflammatory mediators such as **tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)**, which are implicated in podocyte injury and proteinuria [37].

In conditions where HDAC2 expression or activity is reduced, this critical partnership between GRs and HDAC2 becomes dysfunctional. As a result, despite adequate glucocorticoid exposure, pro-inflammatory genes remain transcriptionally active. This phenomenon, termed **glucocorticoid resistance**, has been extensively documented in chronic inflammatory airway diseases and is now emerging as a central mechanism in pediatric steroid-resistant nephrotic syndrome (SRNS). Egyptian pediatric studies have demonstrated significantly lower HDAC2 activity in peripheral blood mononuclear cells of SRNS patients compared to those with steroidsensitive nephrotic syndrome (SSNS), supporting this mechanistic link [38].

Beyond histone modifications, HDAC2 also interacts directly with transcription factors. For example, GRmediated repression of **nuclear factor-kappa B (NF-κB)** requires HDAC2 recruitment. NF-κB is a master regulator of immune and inflammatory responses, and its unchecked activation contributes to glomerular injury and steroid resistance. Reduced HDAC2 activity impairs this suppressive pathway, perpetuating NF-κB–driven inflammation in renal tissues. This creates a self-sustaining loop of inflammation and glucocorticoid resistance, particularly detrimental in children with SRNS [39].

Furthermore, oxidative stress, a common feature in nephrotic syndrome due to chronic inflammation and recurrent infections, has been shown to impair HDAC2 activity through post-translational modifications such as nitration and carbonylation. This modification decreases HDAC2 stability and enzymatic function, further disrupting GR signaling. Children in low- and middle-income settings, including Egypt, may be especially vulnerable due to higher environmental oxidative stressors, compounding the epigenetic impairment of steroid responsiveness [40].

From a therapeutic standpoint, targeting the HDAC2-GR axis offers novel opportunities for restoring steroid sensitivity in resistant patients. Strategies that enhance HDAC2 expression or protect it from oxidative inactivation—such as low-dose theophylline, antioxidants, or selective HDAC2 activators—could potentiate the efficacy of glucocorticoids. For pediatric nephrologists and clinical pharmacists, this pathway provides both a **predictive biomarker** (HDAC2 expression/activity levels) and a **therapeutic target**, paving the way for more personalized management of nephrotic syndrome [41].

8. Mechanisms Linking HDAC2 to Steroid Responsiveness

The ability of glucocorticoids to induce remission in nephrotic syndrome depends heavily on the integrity of **histone deacetylase-2 (HDAC2)** activity. Several interconnected molecular mechanisms link reduced HDAC2 expression or function to impaired steroid responsiveness, particularly in children with steroid-resistant nephrotic syndrome (SRNS). Understanding these mechanisms provides valuable insights into disease pathogenesis and potential therapeutic targets.

First, HDAC2 plays a direct role in facilitating **glucocorticoid receptor (GR)-mediated transrepression** of inflammatory genes. Activated GR recruits HDAC2 to promoter regions of pro-inflammatory transcription factors such as NF-κB and AP-1. HDAC2 then deacetylates histone proteins, condensing chromatin

and preventing transcription of cytokines and chemokines. When HDAC2 levels are reduced, this repression fails, resulting in continued transcription of pro-inflammatory mediators. In the context of nephrotic syndrome, persistent cytokine production contributes to podocyte injury, glomerular hyperpermeability, and sustained proteinuria [42].

Second, **oxidative stress and inflammation** negatively regulate HDAC2 expression and activity. Reactive oxygen species (ROS) and peroxynitrite can nitrate tyrosine residues on HDAC2, leading to reduced enzyme stability and accelerated degradation via the proteasome pathway. In Egyptian children, where recurrent infections and environmental oxidative stress are common, this mechanism may explain the higher prevalence of SRNS. The cumulative oxidative burden effectively silences HDAC2 activity, making glucocorticoid therapy less effective despite adequate dosing [43].

Third, epigenetic **cross-talk between HDAC2 and other chromatin modifiers** further influences steroid responsiveness. For instance, imbalance between histone acetyltransferases (HATs) and HDACs can create a permissive transcriptional environment for pro-inflammatory genes. In SRNS patients, heightened HAT activity combined with reduced HDAC2 function favors open chromatin and sustained transcription of inflammatory mediators. This imbalance shifts the immune response toward resistance, highlighting HDAC2's central role as a regulatory "brake" on inflammation [44].

Additionally, **non-histone protein deacetylation** by HDAC2 influences glucocorticoid signaling. HDAC2 regulates acetylation status of the GR itself, as well as transcriptional corepressors. Hyperacetylated GR exhibits impaired DNA binding and reduced recruitment of co-repressor complexes, weakening glucocorticoid efficacy.

Thus, loss of HDAC2 not only disrupts histone regulation but also directly impairs the steroid receptor complex. This dual disruption contributes to the persistent steroid resistance seen in pediatric SRNS [45].

Finally, HDAC2 deficiency appears to be a convergent point for multiple pathogenic insults in nephrotic syndrome. Genetic predisposition, oxidative stress, chronic inflammation, and environmental factors all converge on reducing HDAC2 expression or activity. This explains why HDAC2 has emerged as a **biomarker of steroid responsiveness** in Egyptian pediatric cohorts. Children with low HDAC2 activity show poor initial response to steroids and worse long-term outcomes, making HDAC2 measurement a potentially valuable clinical tool for guiding therapy [46].

9. Preclinical Evidence of HDAC2 Modulation in Inflammation

Preclinical studies provide strong evidence that **HDAC2 plays a critical role in regulating inflammatory responses** and in determining glucocorticoid sensitivity. Much of this knowledge comes from research in respiratory and immune-mediated diseases, but the findings are highly translatable to nephrotic syndrome (NS), where inflammation and steroid responsiveness are central to disease progression and management.

Animal models have demonstrated that reduced HDAC2 expression or activity leads to exaggerated inflammatory responses and glucocorticoid resistance. In murine models exposed to oxidative stress or cigarette smoke, HDAC2 activity was significantly diminished due to nitration and post-translational modifications. These changes were associated with impaired recruitment of HDAC2 to inflammatory gene promoters and failure of glucocorticoids to suppress NF-κB–driven cytokine expression. Restoration of HDAC2 activity through antioxidants or low-dose theophylline successfully reversed glucocorticoid resistance, highlighting the therapeutic importance of maintaining HDAC2 function [47].

Cellular studies also confirm HDAC2's role in glucocorticoid signaling. Experiments in macrophages and T lymphocytes have shown that HDAC2 knockdown abolishes the anti-inflammatory effects of dexamethasone, leading to sustained expression of cytokines such as TNF-α and IL-6. Conversely, overexpression of HDAC2 enhances glucocorticoid-mediated repression, supporting its role as a molecular checkpoint in steroid

responsiveness. These findings underscore that HDAC2 is not merely a passive cofactor but a central determinant of glucocorticoid efficacy [48].

Although direct preclinical studies in nephrotic syndrome are limited, parallels can be drawn from podocyte and glomerular cell models. Inflammatory stimuli such as IL-1β and TNF-α activate NF-κB and AP-1 pathways in podocytes, leading to cytoskeletal injury and proteinuria. HDAC2 deficiency exacerbates these inflammatory responses, while HDAC2 restoration dampens them, indirectly protecting podocyte integrity. This suggests that the observed clinical association between low HDAC2 activity and steroid resistance in children may be rooted in podocyte-level inflammatory dysregulation [49].

Importantly, preclinical evidence also highlights the role of **epigenetic cross-talk**. In conditions of chronic inflammation, histone acetyltransferase (HAT) activity is often upregulated, leading to an open chromatin configuration and sustained transcription of inflammatory mediators. Without sufficient HDAC2 to counterbalance this activity, the chromatin environment becomes permissive for inflammation and resistant to glucocorticoid suppression. This imbalance between HAT and HDAC2 activities has been observed in both airway models and renal cell studies, providing a unifying mechanism for steroid resistance across organ systems[50].

These preclinical findings collectively strengthen the hypothesis that HDAC2 is a critical determinant of steroid responsiveness in nephrotic syndrome. They also offer a rational foundation for therapeutic strategies that enhance HDAC2 activity to restore glucocorticoid efficacy. Translating these findings into pediatric nephrology, particularly in Egyptian cohorts with high SRNS prevalence, provides a unique opportunity for targeted intervention and precision medicine [51].

10. Clinical Studies of HDAC2 in Pediatric Nephrotic Syndrome

Clinical studies investigating the role of histone deacetylase-2 (HDAC2) in pediatric nephrotic syndrome (NS) are limited but rapidly expanding. The most compelling data come from Egyptian cohorts, where the prevalence of steroid-resistant nephrotic syndrome (SRNS) is relatively high compared to Western populations. These studies provide early clinical evidence that reduced HDAC2 expression and activity correlate with poor steroid responsiveness, supporting the hypothesis derived from preclinical research.

A landmark study conducted in Egyptian children demonstrated that **HDAC2 activity in peripheral blood mononuclear cells was significantly lower in SRNS patients compared to steroid-sensitive nephrotic syndrome (SSNS) patients**. The reduction in HDAC2 activity was associated with impaired glucocorticoid receptor (GR) function and sustained expression of pro-inflammatory cytokines, reinforcing the mechanistic link between HDAC2 deficiency and glucocorticoid resistance. Importantly, the degree of HDAC2 reduction correlated with the severity of proteinuria and disease progression, suggesting its potential utility as both a biomarker and a prognostic indicator [52].

Another study in Egyptian pediatric cohorts examined HDAC2 gene expression and activity before and after corticosteroid therapy. Results revealed that children with SSNS exhibited an upregulation of HDAC2 expression during remission, whereas SRNS patients showed persistently low levels. This differential pattern not only confirms HDAC2's role in mediating steroid responsiveness but also raises the possibility of using **HDAC2 profiling at diagnosis** to predict therapeutic outcomes. Such an approach could enable earlier identification of children unlikely to respond to steroids, allowing for timely initiation of second-line therapies and avoidance of unnecessary steroid exposure [53].

Beyond Egypt, international studies in pediatric populations remain scarce, but parallels can be drawn from adult nephrotic syndrome and other chronic inflammatory conditions. In systemic lupus erythematosus and asthma, for instance, reduced HDAC2 expression has been consistently linked with steroid resistance. These findings, combined with Egyptian pediatric data, suggest that HDAC2 dysfunction may represent a common epigenetic pathway underlying poor glucocorticoid responsiveness across multiple immune-mediated diseases[54].

From a clinical pharmacy perspective, the implications of these studies are profound. HDAC2 could serve as a **predictive biomarker** integrated into diagnostic workups, guiding steroid therapy decisions and reducing trialand-error approaches. Furthermore, therapeutic strategies that aim to restore HDAC2 activity—such as antioxidants or low-dose theophylline—may represent novel adjunctive treatments in SRNS. For Egyptian children, where SRNS prevalence is high and therapeutic options are limited by economic constraints, incorporating HDAC2 monitoring into clinical practice could significantly improve treatment stratification and long-term outcomes [55].

11. Egyptian Cohort Data: Unique Genetic and Epigenetic Insights

Egyptian pediatric cohorts provide a unique lens through which to examine the interplay of genetic and epigenetic determinants of steroid responsiveness in nephrotic syndrome (NS). The prevalence of steroidresistant nephrotic syndrome (SRNS) in Egypt, reported to be as high as **25–30%**, exceeds that of many Western populations. This suggests the presence of distinct regional modifiers, including genetic predisposition, environmental stressors, and epigenetic dysregulation such as impaired HDAC2 activity [56].

Genetically, several podocyte-associated mutations have been identified in Egyptian children with SRNS. Mutations in genes such as **NPHS2 (podocin), WT1, and TRPC6** have been documented in this population, contributing to structural and functional defects in the glomerular filtration barrier. However, while these genetic mutations explain some cases, a significant proportion of Egyptian children with SRNS lack identifiable genetic variants, suggesting additional regulatory mechanisms—particularly epigenetic ones—play a crucial role [57].

Epigenetic studies in Egyptian cohorts have provided compelling evidence that **HDAC2 expression and activity are significantly reduced in SRNS compared to SSNS**. Importantly, this reduction appears independent of underlying genetic mutations, highlighting HDAC2 as a key non-genetic modifier of steroid responsiveness. For instance, in a cohort study of Egyptian children, HDAC2 activity was found to be consistently lower in SRNS patients, regardless of whether they harbored podocyte gene mutations. This finding underscores the additive role of epigenetic dysregulation in shaping treatment outcomes [58].

Environmental and socioeconomic factors prevalent in Egypt further compound this problem. Recurrent infections, poor nutritional status, and increased exposure to oxidative stressors such as environmental pollution may exacerbate HDAC2 impairment. These factors can lead to post-translational modifications of HDAC2, reducing its stability and enzymatic function. Thus, Egyptian children face a **multi-hit model**: genetic predisposition, combined with epigenetic dysfunction and adverse environmental influences, converges to increase SRNS prevalence and worsen outcomes [59].

From a therapeutic standpoint, Egyptian cohort data suggest the urgent need for **personalized treatment approaches** that incorporate both genetic and epigenetic profiling. Identifying children with low HDAC2 activity at the time of diagnosis could enable clinicians to predict steroid resistance and initiate alternative therapies earlier. This would reduce unnecessary steroid exposure, limit adverse effects, and potentially improve long-term renal survival. In this way, Egypt provides a crucial model for integrating epigenetic biomarkers like HDAC2 into clinical decision-making in pediatric nephrology [60].

12. Biomarker Potential of HDAC2 in Predicting Steroid Response

One of the most promising clinical applications of histone deacetylase-2 (HDAC2) research in pediatric nephrotic syndrome (NS) is its role as a **biomarker** to predict steroid responsiveness. Unlike genetic testing, which only identifies a subset of steroid-resistant nephrotic syndrome (SRNS) cases, HDAC2 activity reflects the dynamic interplay between genetic, epigenetic, and environmental factors. This makes it an attractive candidate for early diagnostic stratification in children with newly diagnosed NS [61].

Clinical studies in Egyptian children have demonstrated that **baseline HDAC2 expression and activity levels correlate with steroid treatment outcomes**. Children who later achieved remission with corticosteroid therapy (SSNS) showed significantly higher HDAC2 activity at diagnosis compared to those who developed SRNS. Furthermore, serial measurements during therapy revealed that HDAC2 activity increased in responders

but remained low in non-responders. These findings suggest that HDAC2 measurement could serve not only as a predictive biomarker but also as a **dynamic marker of treatment response** [62].

The ability to predict steroid resistance at diagnosis has profound implications for clinical practice. Currently, children with NS are subjected to a standardized four- to six-week trial of high-dose corticosteroids, regardless of their likelihood of responding. This exposes non-responders to unnecessary steroid toxicity, including growth suppression, hypertension, obesity, and increased risk of infections. Incorporating HDAC2 profiling into routine practice could enable early identification of children unlikely to benefit from prolonged steroid therapy, allowing for earlier initiation of second-line immunosuppressants and reduction of avoidable harm [63].

Beyond prediction, HDAC2 also has potential utility as a **prognostic biomarker**. Low HDAC2 activity at baseline has been associated with higher relapse rates, more severe proteinuria, and faster progression to chronic kidney disease (CKD). This prognostic value could assist clinicians in counseling families, tailoring monitoring intensity, and prioritizing patients for advanced therapies such as calcineurin inhibitors, rituximab, or future epigenetic modulators [64].

From a translational perspective, developing assays for **HDAC2 activity measurement** that are cost-effective and feasible in low-resource settings is a critical next step. Techniques such as enzyme-linked immunosorbent assays (ELISA) and quantitative PCR for HDAC2 mRNA are promising, but further validation in multicenter pediatric cohorts is required. If successfully implemented, HDAC2 profiling could transform the diagnostic paradigm in pediatric NS, shifting from a trial-and-error approach to a **precision medicine framework** [65].

Conclusion

Steroid responsiveness remains the most important determinant of prognosis in pediatric nephrotic syndrome (NS). While the majority of children achieve remission with corticosteroids, a significant subset—particularly in Egypt—develops steroid-resistant nephrotic syndrome (SRNS), a condition associated with high morbidity, progression to chronic kidney disease (CKD), and increased healthcare burden. The variability in steroid response has long suggested that factors beyond genetics influence treatment outcomes. Epigenetic regulation, particularly the role of histone deacetylase-2 (HDAC2), has emerged as a central mechanism linking inflammation, glucocorticoid receptor (GR) function, and clinical outcomes.

Clinical and preclinical studies consistently demonstrate that reduced HDAC2 expression or activity impairs glucocorticoid-mediated repression of inflammatory genes, leading to persistent cytokine production, podocyte injury, and steroid resistance. Egyptian pediatric cohorts provide some of the strongest evidence for this association, showing significantly lower HDAC2 levels in SRNS compared to steroid-sensitive nephrotic syndrome (SSNS). Importantly, HDAC2 activity not only correlates with treatment outcomes but also reflects environmental and oxidative stress influences, underscoring its role as a biomarker that integrates genetic, epigenetic, and environmental determinants of disease.

From a translational perspective, HDAC2 holds dual promise as both a predictive biomarker and a therapeutic target. Measurement of HDAC2 activity at diagnosis could help identify children unlikely to respond to steroids, thereby reducing unnecessary exposure to corticosteroid toxicity and allowing earlier initiation of alternative therapies. In parallel, pharmacological interventions that restore HDAC2 activity such as low-dose theophylline or antioxidants offer novel therapeutic avenues for reversing steroid resistance. These strategies may be particularly impactful in resource-limited settings like Egypt, where SRNS prevalence is high and access to costly biologic agents is restricted.

In conclusion, the study of HDAC2 provides critical insights into the pathogenesis of steroid resistance in childhood NS. Its role at the intersection of epigenetics, inflammation, and glucocorticoid signaling highlights the importance of moving toward precision medicine approaches in pediatric nephrology. Future research should prioritize multicenter studies to validate HDAC2 as a clinical biomarker, investigate safe and effective HDAC2

modulators in children, and integrate epigenetic profiling into treatment algorithms. Such efforts have the potential to transform care for Egyptian children with NS and serve as a model for global pediatric nephrology practice.

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