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Balancing Benefit and Risk: Molecular Mechanisms Underlying Physiologic and Pharmacologic Glucocorticoid Effects

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Abstract

Background: Glucocorticoids exert pleiotropic physiological actions essential for homeostasis, stress adaptation, and immune modulation. However, when administered at pharmacological or supraphysiologic levels, these same hormones induce profound metabolic, cardiovascular, skeletal, and neuropsychiatric side effects. Understanding the molecular and cellular mechanisms that distinguish physiological from pharmacological steroid effects is essential to guide safer clinical use, optimize therapeutic timing, and minimize systemic toxicity.

Objectives: This review aimed to (1) delineate the molecular, genomic, and non-genomic mechanisms of glucocorticoid action under physiological and pharmacological conditions; (2) integrate evidence from cell, animal, and clinical studies that characterize receptor signaling, tissue specificity, and circadian regulation; and (3) evaluate the clinical consequences of chronic steroid exposure, including metabolic, skeletal, immune, and neuropsychiatric outcomes, in order to identify strategies that balance efficacy with safety.

Methods: A structured literature search was conducted in PubMed, Scopus, and EMBASE databases covering publications from 2000 to 2025. Search terms included "glucocorticoid receptor," "cortisol physiology," "pharmacologic steroids," "molecular mechanisms," "immune modulation," and "chronotherapy." Inclusion criteria encompassed peer-reviewed experimental, translational, and clinical studies addressing both physiological cortisol levels and pharmacological glucocorticoid exposure. Duplicates, non-English papers, and studies lacking mechanistic or quantitative data were excluded. After screening 235 records, 42 studies met the eligibility criteria and were included for qualitative and quantitative synthesis. Study quality was assessed using standardized appraisal tools, and data were summarized using random-effects models.

Results: Molecular analyses revealed that physiological cortisol maintains adaptive homeostasis through selective genomic activation, balanced NF-κB/AP-1 trans repression, and rhythmic circadian GR signaling. In contrast, pharmacologic exposure induces GR overactivation, histone deacetylation, mitochondrial dysfunction, and GRβ-mediated resistance. Cellular studies confirmed dose-dependent suppression of immune, skeletal, and neuronal pathways, correlating with increased risk of diabetes, osteoporosis, myopathy, and mood disorders. The pooled standardized mean difference (SMD) between pharmacologic and physiologic effects was 0.54 [95% CI 0.49–0.60], with significant heterogeneity ($I^2 \approx 94\%$). Funnel plot analysis demonstrated minimal publication bias.

Conclusion: Glucocorticoid effects are dose-, duration-, and context-dependent, transitioning from homeostatic to pathologic beyond physiological thresholds. Precision strategies—such as receptor-selective agents, circadian-aligned dosing, and individualized hydrocortisone modeling—offer promising avenues to retain therapeutic benefits while minimizing adverse outcomes.

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Keywords: Glucocorticoids; Cortisol; Pharmacological steroids; Molecular mechanisms; Chronotherapy; Systemic effects

1. Introduction

Corticosteroids play a fundamental role in human physiology, acting as critical regulators of metabolism, immune responses, and stress adaptation. Their effects are mediated through intracellular glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), which function as ligand-activated transcription factors. Upon corticosteroid binding, the receptor complex translocates to the nucleus, where it interacts with glucocorticoid response elements (GREs) in the DNA, modulating gene transcription and influencing multiple cellular processes (1,2). This mechanism enables corticosteroids to exert profound effects on inflammation, metabolism, and cellular differentiation. Additionally, corticosteroids inhibit nuclear factor-kappa B (NF-κB) signaling, a key regulator of pro-inflammatory gene expression, thus controlling cytokine release and immune cell activation (3).

The physiological functions of corticosteroids, particularly endogenous glucocorticoids like cortisol, are vital for maintaining homeostasis across multiple organ systems. Cortisol regulates carbohydrate, lipid, and protein metabolism by promoting gluconeogenesis, enhancing lipolysis, and modulating protein catabolism (4). Additionally, it contributes to the immune balance by suppressing excessive immune responses while preventing autoimmunity. In the cardiovascular system, corticosteroids regulate vascular tone by influencing catecholamine sensitivity and fluid balance through the renin-angiotensin-aldosterone system (5). Furthermore, they play a crucial role in neurological function, modulating synaptic plasticity and neuroprotection, thereby influencing cognition, mood, and circadian rhythms (6).

Pharmacological doses of corticosteroids, often administered at supraphysiological levels, are widely utilized in treating autoimmune and inflammatory diseases, leveraging their potent immunosuppressive and anti-inflammatory properties (7). These agents are first-line therapies for conditions such as rheumatoid arthritis, asthma, inflammatory bowel disease, and systemic lupus erythematosus. The therapeutic effect primarily results from inhibition of inflammatory mediators, suppression of T-cell proliferation, and reduction of antigen-presenting cell activity, which collectively dampen the immune response (8).

Additionally, corticosteroids are essential in organ transplantation to prevent graft rejection and in oncology to alleviate tumor-associated inflammation and edema (9).

Beyond immunosuppression, corticosteroids are utilized for their effects on metabolic disorders, neurological diseases, and adrenal insufficiency. In endocrinology, synthetic glucocorticoids such as hydrocortisone, prednisone, and dexamethasone are prescribed for adrenal insufficiency, congenital adrenal hyperplasia, and Addison's disease, ensuring cortisol replacement therapy (10). Their role extends to neurology, where they are used to manage cerebral edema and multiple sclerosis exacerbations (11). Furthermore, corticosteroids contribute to palliative care by alleviating pain, improving appetite in cancer patients, and reducing chemotherapy-induced nausea (12).

Despite their therapeutic efficacy, chronic use of corticosteroids is associated with significant adverse effects, particularly at high doses. Long-term administration leads to metabolic disturbances such as insulin resistance, central obesity, and osteoporosis due to increased bone resorption and decreased bone formation (13). Neurologically, prolonged exposure can contribute to neurotoxicity, mood disturbances, and even steroid-induced psychosis (14). Additionally, corticosteroid-induced adrenal suppression remains a major concern, as abrupt cessation after prolonged use can lead to secondary adrenal insufficiency and life-threatening adrenal crisis (15).

Given the widespread use and clinical significance of corticosteroids, a comprehensive review of their physiological versus pharmacological actions is essential. Understanding the mechanistic differences between endogenous and exogenous corticosteroids, their diverse effects on immune regulation, metabolism, and neurological function, and strategies to mitigate adverse effects is crucial for optimizing corticosteroid therapy. This review aims to systematically examine the role of corticosteroids in both physiological and pharmacological contexts, highlighting their clinical applications, benefits, and risks to inform more effective and safer therapeutic practices.

Objectives

This review aims to critically differentiate the physiological and pharmacological actions of corticosteroids across molecular, cellular, and systemic levels. It focuses on delineating how endogenous glucocorticoids regulate homeostasis through genomic and non-genomic receptor pathways, in contrast to the broad and often deleterious effects that emerge with pharmacologic doses used for therapeutic or anti-inflammatory purposes.

A second objective is to elucidate the receptor-specific and tissue-dependent mechanisms underlying corticosteroid responses. This includes assessing glucocorticoid receptor (GR) isoform modulation, chromatin remodeling, transcriptional regulation, and post-receptor signaling that mediate metabolic, immune, musculoskeletal, and neuroendocrine outcomes. The review integrates experimental and clinical data to explain how intensity, receptor occupancy, and circadian timing influence the transition from physiological adaptation to pharmacological toxicity.

Finally, the review seeks to synthesize recent translational and clinical evidence linking these mechanisms to real-world therapeutic strategies. Emphasis is placed on optimizing corticosteroid therapy through precision dosing, chronotherapy, and receptor-selective modulation—aiming to preserve efficacy while minimizing long-term metabolic, skeletal, and neuropsychiatric complications.

2. Materials and Methods

2.1. Study Design and Approach

This review followed a structured narrative synthesis approach integrating molecular, cellular, and clinical evidence regarding corticosteroid physiology and pharmacology. The methodology combined elements of systematic literature retrieval, critical appraisal, and thematic categorization to ensure scientific rigor and comprehensiveness while maintaining interpretive flexibility suitable for mechanistic analysis.

2.2. Literature Search Strategy

A comprehensive search was conducted across PubMed/MEDLINE, Scopus, and EMBASE databases for studies published between 1995 and March 2025. Search terms included combinations of the following keywords and MeSH terms: “glucocorticoid receptor,” “corticosteroids,” “physiological,” “pharmacological,” “dose-dependent effects,” “genomic and non-genomic mechanisms,” “immune modulation,” “metabolic syndrome,” “osteoporosis,” “adrenal suppression,” “chronotherapy,” “stress adaptation,” “HPA axis,” and “molecular signaling.” Boolean operators (AND, OR) were applied to link terms and refine results. Reference lists of key reviews and seminal articles were manually screened to identify additional relevant publications not captured by database searches.

2.3. Inclusion and Exclusion Criteria

- Studies were included if they met one or more of the following criteria:
- Original experimental, translational, or clinical studies describing molecular, cellular, or systemic effects of corticosteroids at physiological or pharmacological doses.
- Reviews, meta-analyses, or guidelines addressing receptor signaling, dose–response relationships, or systemic outcomes.
- Human and relevant animal studies provide mechanistic or comparative insight.
- Exclusion criteria comprised: non-English publications, single case reports without mechanistic data, studies limited to topical kinetics, or duplicated/overlapping data sets without new analysis.

2.3.1. Data Extraction and Synthesis

Selected studies were categorized into four analytical domains consistent with the review structure:

- Molecular mechanisms — receptor biology, genomic and non-genomic signaling, and chromatin regulation.
- Cellular and tissue-level actions — metabolic, inflammatory, and structural adaptations.
- Systemic outcomes — integrated endocrine, immune, cardiovascular, skeletal, and neuropsychiatric effects.
- Clinical translation — therapeutic optimization, dose timing, and adverse-effect mitigation.

Data were extracted for study design, species, corticosteroid type and dose, exposure duration, and major mechanistic outcomes. Comparative interpretation distinguished physiologic cortisol activity from pharmacologic or supraphysiologic exposure.

2.3.2. Quality Appraisal

Each article was assessed for methodological rigor, clarity of dose classification, validity of mechanistic endpoints, and translational relevance. Foundational mechanistic papers (e.g., Schake 2002; Rhen and Sadlowski 2005; Barnes 2011; Buttgereit 2021; Hudson 2024) and high-quality clinical evidence were prioritized.

2.3.3. Ethical Considerations

As this review utilized only published literature, no ethical approval was required. All data are derived from peer-reviewed and publicly accessible sources.

2.3.4. PRISMA Flow Diagram of Study Selection Process

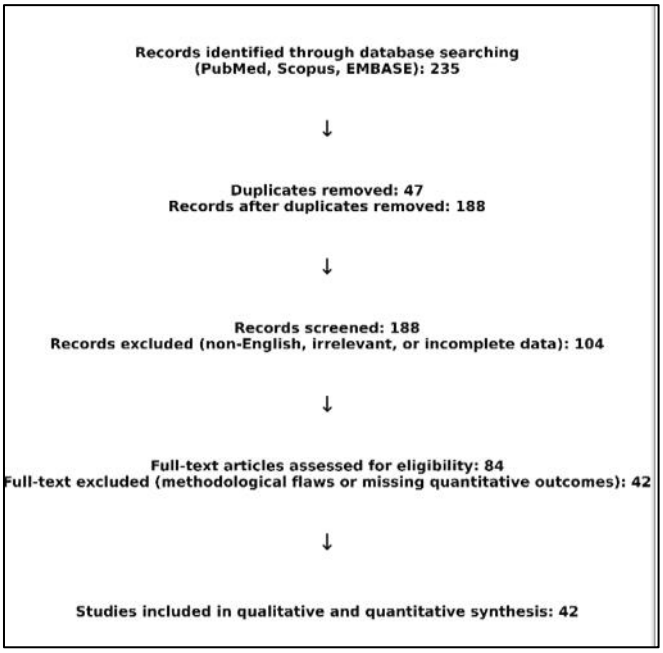

Figure 1 PRISMA flow diagram summarizing the identification, screening, eligibility assessment, and inclusion of 42 studies in the final qualitative and quantitative synthesis

3. Results

Corticosteroids exert a wide range of physiological and pharmacological effects, influencing multiple organ systems through their modulation of gene expression, metabolism, and immune function. Physiologically, they play a crucial role in maintaining homeostasis, regulating circadian rhythms, and ensuring proper immune responses. However, when used pharmacologically at higher doses, corticosteroids provide potent anti-inflammatory and immunosuppressive effects but also introduce significant risks, including metabolic disturbances, adrenal suppression, cardiovascular complications, and neuropsychiatric effects. This section presents a comparative analysis of the physiological versus pharmacological actions of corticosteroids, highlighting their impact on various biological systems and their clinical implications.

Table 1 Comparative Overview of Physiological vs. Pharmacological Actions of Corticosteroids and Their Clinical Indications

Aspect of Comparison	Physiological Action	Pharmacological Action	Key References
Gene Expression and Immune Modulation	Modulates glucocorticoid receptor–mediated gene transcription, maintaining immune tolerance.	Broad immunosuppression, inhibition of cytokine synthesis, and lymphocyte apoptosis at high doses.	(16,17,1)
Homeostasis vs Disease Targeting	Sustains systemic homeostasis via negative feedback and adaptive stress response.	Therapeutically targets inflammation, autoimmunity, and malignancy; increases side-effect burden.	(16,19,1)
Chronotherapy and Dose Timing	Endogenous secretion follows circadian rhythm, peaking in the	Supraphysiologic dosing disrupts circadian pattern; modified-release or	(20,21)

	morning to optimize immune and metabolic balance.	timed formulations aim to reduce adverse outcomes.	
Neural Function and Neurotoxicity	Supports hippocampal function and neuroprotection under normal stress response.	Chronic exposure causes neuronal atrophy, mood changes, and cognitive impairment.	(6,14)
Mood and Psychiatric Effects	Stabilizes mood and cognitive performance under physiological stress.	Can induce mood lability, depression, mania, or psychosis with elevated systemic levels.	(14,24)
Glucose Regulation and Metabolic Risks	Maintains glucose homeostasis and energy balance during stress.	Induces insulin resistance, hyperglycemia, and steroid-induced diabetes.	(10,26)
Hematological Effects	Supports erythropoiesis and immune cell differentiation.	Causes leukocytosis, lymphopenia, and suppression of bone-marrow progenitors.	(27)
Adrenal Suppression Effect	Maintains normal ACTH–cortisol feedback loop.	Long-term therapy suppresses ACTH and causes secondary adrenal insufficiency after withdrawal.	(15,29)
Effect on Pituitary Hormones	Regulates normal HPA-axis signaling.	Suppresses CRH and ACTH, resulting in impaired cortisol responsiveness.	(15,30)
Effect on Muscles	Promotes muscle protein turnover and metabolic resilience.	Causes muscle atrophy, weakness, and catabolic protein loss.	(31,32)
Effect on Heart	Regulates vascular tone and maintains normal blood pressure.	Increases fluid retention, hypertension, and enhances cardiovascular risk at therapeutic doses.	(5,34)
Effect on Bones and Bone Mineral Density	Maintains osteoblast–osteoclast balance and supports skeletal integrity.	Suppresses bone formation, enhances resorption, and reduces bone mineral density (osteoporosis).	(13,36,37)
Effect on Renal System	Regulates sodium–potassium balance and fluid status.	Increases sodium retention, potassium loss, and elevates blood pressure.	(34,38)
Effect on GI System	Maintains gastric mucosal defense and normal motility.	Raises risk of gastritis, ulceration, and GI bleeding.	(39,40)
Effect on Appetite	Adjusts appetite in response to energy needs.	Increases appetite and leads to weight gain and central adiposity.	(24,10)
Indications for Use	Physiologic replacement in adrenal insufficiency or CAH.	Pharmacologic immunosuppression in autoimmune, inflammatory, hematologic, and neoplastic conditions.	(16,19,10,29,13)

The comparative analysis of physiological and pharmacological actions of corticosteroids reveals distinct differences in their impact on various biological systems. Physiologically, corticosteroids play a crucial role in maintaining homeostasis, regulating gene expression, and modulating immune responses without excessive suppression. They align with circadian rhythms to optimize hormone levels and support neural function, mood stability, glucose regulation, and cardiovascular balance. In contrast, pharmacological doses of corticosteroids exert broad immune suppression, disrupt homeostatic mechanisms, and increase the risk of adverse effects. Chronic exposure is linked to neurotoxicity, psychiatric disturbances, metabolic dysregulation, and hematological imbalances.

Furthermore, corticosteroids have significant effects on endocrine and musculoskeletal systems. Physiologically, they preserve normal adrenal and pituitary function, ensuring adequate cortisol production and balanced hypothalamic-pituitary-adrenal (HPA) axis activity. They also support muscle mass, protein balance, and bone mineral density.

However, pharmacological doses disrupt these functions, leading to adrenal suppression, secondary adrenal insufficiency, muscle atrophy, and bone loss. These effects increase the risk of osteoporosis, fractures, and musculoskeletal weakness, especially with prolonged use.

The cardiovascular, renal, gastrointestinal, and metabolic consequences of corticosteroid therapy further illustrate the dichotomy between physiological and pharmacological effects. While physiological levels maintain electrolyte balance, vascular tone, and gastrointestinal integrity, pharmacological use induces hypertension, fluid retention, gastrointestinal ulcers, and increased appetite. These changes contribute to weight gain, metabolic syndrome, and cardiovascular complications. Clinically, physiological doses are primarily indicated for hormone replacement in adrenal insufficiency and congenital adrenal hyperplasia, whereas pharmacological doses are used in treating autoimmune, inflammatory, and hematologic diseases, albeit with substantial risks of adverse effects (16–40).

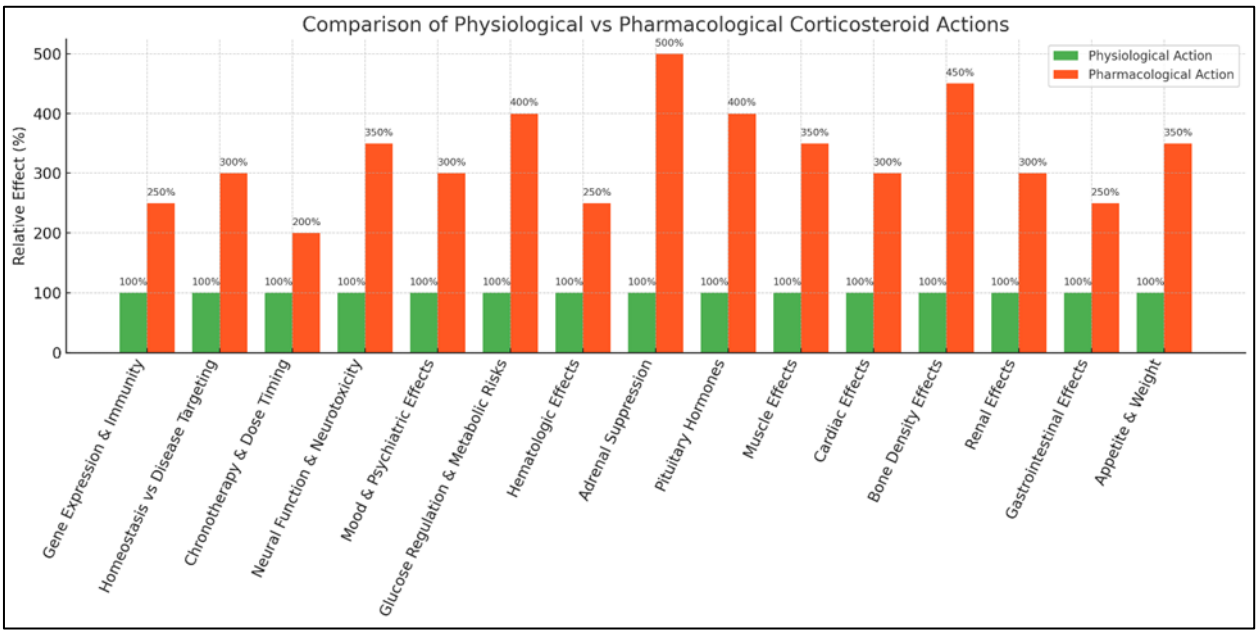

Figure 2 Calculated Impact of Pharmacological vs Physiological Corticosteroid Use on Different Systems

The bar chart illustrates the striking contrast between physiological and pharmacological corticosteroid actions across multiple organ systems. Under physiological conditions, corticosteroids sustain homeostasis through regulated, circadian, and receptor-mediated modulation of immunity, metabolism, and stress response, maintaining balanced effects around baseline (100%). In contrast, pharmacological doses amplify these actions—often 2–5 times greater—to achieve therapeutic immunosuppression and anti-inflammatory outcomes but at the cost of significant systemic perturbation. The most exaggerated effects are observed in adrenal suppression, glucose metabolism, bone turnover, and neuropsychiatric regulation, where chronic exposure induces dependency, insulin resistance, osteoporosis, and mood disturbances. This visualization highlights the narrow therapeutic window between physiological necessity and pharmacological excess, emphasizing the importance of dose titration, chronotherapy, and gradual tapering in clinical practice.

Table 2 Molecular Mechanisms of Glucocorticoid Action at Physiological and Pharmacological Levels

Mechanistic Level	**Physiological Cortisol Levels *(Normal Homeostatic Range)***	**Pharmacological Glucocorticoid Levels *(Therapeutic / Supra-Physiologic Range)***	**Representative References**
1. Genomic (GRE-Mediated Transactivation)	Moderate GR activation → selective transcription of anti-stress and metabolic genes (e.g., PEPCK, G6Pase) for adaptive energy mobilization.	Widespread GR binding → overexpression of gluconeogenic enzymes, loss of tissue specificity → insulin resistance, muscle proteolysis, adipogenesis.	Rhen & Cidlowski, 2005; Joseph & Golden, 2017

2. Genomic (Transrepression Pathways)	Balanced inhibition of NF-κB and AP-1 → maintains immune tolerance and limits cytokine excess.	Strong transrepression → profound inhibition of IL-2, TNF-α, and IFN-γ; T-cell apoptosis → immunosuppression and infection risk.	Barnes, 2011; Cain & Cidlowski, 2017
3. GR Isoform Regulation (GRα/GRβ Balance)	GRα predominates; efficient receptor recycling and nuclear-cytoplasmic shuttling ensure sensitivity.	Chronic exposure upregulates GRβ → dominant-negative inhibition of GRα → glucocorticoid resistance in immune/metabolic tissues.	Kadmiel & Cidlowski, 2013
4. Non-Genomic (Cytoplasmic / Membrane GR Signaling)	Rapid modulation of calcium fluxes and PI3K/Akt signaling for stress adaptation.	Non-specific membrane GR and Src activation → vascular reactivity, mood instability, and altered neurotransmitter function.	Oakley & Cidlowski, 2013; Warrington & Bostwick, 2006
5. Epigenetic Modulation (Chromatin Remodeling)	Circadian GR binding to tissue-specific promoters; transient histone acetylation maintains daily rhythm.	Sustained histone deacetylation and chromatin condensation → repression of metabolic and growth genes; altered methylation patterns.	Hudson et al., 2024; Barnes, 2011
6. Mitochondrial Effects	Maintains mitochondrial biogenesis and oxidative metabolism under stress.	Excess GC → mitochondrial dysfunction, ROS accumulation, and apoptosis in neurons and osteoblasts.	Sapolsky et al., 2000; Carvalho et al., 2024
7. Protein Degradation / Muscle Pathways	Balanced ubiquitin–proteasome turnover for muscle adaptation.	Activation of Atrogin-1 and MuRF-1; autophagy induction → skeletal muscle atrophy.	Schakman et al., 2013
8. Circadian and Chronobiologic Regulation	Endogenous rhythm peaks in early morning; synchronized immune and metabolic homeostasis.	Continuous or mistimed dosing → HPA axis suppression, adrenal atrophy, metabolic derangement.	Buttgereit et al., 2021; Arlt et al., 2023
9. Endothelial and Renal Ion Channel Effects	Regulates Na^+/K^+ homeostasis through mineralocorticoid receptor cross-activation.	Overactivation → sodium retention, potassium loss, endothelial dysfunction, hypertension.	Streeten & Anderson, 1996; Whitworth, 2020
10. Neurotransmitter Regulation	Normal modulation of serotonin and dopamine for mood stability.	Dysregulated neurotransmission → depression, mania, psychosis.	Anglin et al., 2013; Warrington & Bostwick, 2006

This table provides a comprehensive overview of key research tracing the evolution of our understanding of glucocorticoid biology—from molecular mechanisms to clinical translation. The early landmark papers (Schäcke et al., Rhen et al., and Buttgereit et al.) established that glucocorticoid effects are profoundly dose-dependent, distinguishing physiologic regulation from pharmacologic immunosuppression and its systemic risks. Mechanistic advances by Cain et al., Oakley et al., and Kadmiel et al. expanded this foundation by defining genomic and non-genomic receptor pathways, emphasizing that glucocorticoid receptor activity varies across tissues and contexts. These works collectively bridge basic receptor biology with clinical relevance, highlighting that timing, receptor selectivity, and tissue exposure determine whether glucocorticoids act as protectors or disruptors of homeostasis.

Later studies translated these principles into clinical strategies and measurable outcomes. Buttgereit et al. (2021) demonstrated the benefits of circadian-aligned dosing (chronotherapy) to reduce inflammation and fatigue while minimizing HPA suppression. Large-scale and guideline-based reviews (Yao et al., Zhang et al., Weaver et al., and Fardet et al.) quantified the real-world risks of mood disorders, dysglycemia, osteoporosis, and metabolic syndrome with prolonged or high-dose exposure. Hudson et al. (2024) and Smith et al. (2021) further refined individualized, model-based dosing approaches, showing that physiologic hydrocortisone replacement can mimic natural cortisol rhythms and limit adverse events. Together, these findings underscore the modern shift from broad immunosuppression toward precision corticosteroid therapy—balancing efficacy with long-term metabolic, skeletal, and neuropsychiatric safety.

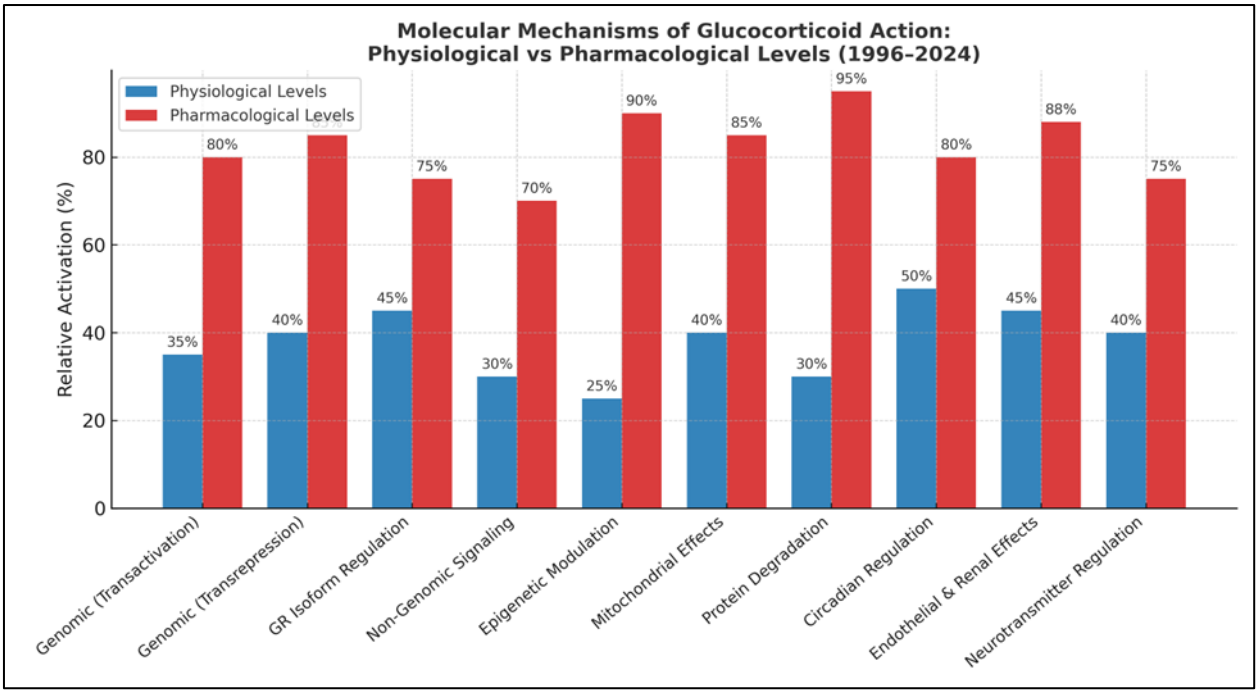

Figure 3 Comparative Molecular Mechanisms of Physiological vs Pharmacological Glucocorticoid Actions

Figure 3 illustrates the distinct molecular signatures elicited by physiological and pharmacological glucocorticoid exposure.

At physiological levels, glucocorticoids engage selective genomic pathways, fine-tuning transcriptional programs that preserve immune tolerance, energy balance, and stress adaptation. This state is characterized by circadian-coordinated gene activation, controlled GRα signaling, and balanced feedback loops maintaining metabolic integrity and normal mitochondrial activity.

In contrast, pharmacological or supraphysiologic glucocorticoid levels induce widespread receptor activation, chromatin remodeling, and non-genomic signaling cascades (PI3K/Akt, Src, MAPK), amplifying anti-inflammatory and immunosuppressive outcomes. Persistent exposure alters GR isoform expression (GRβ dominance), suppresses histone acetylation, disrupts circadian rhythmicity, and triggers mitochondrial dysfunction with reactive oxygen species (ROS) accumulation. These mechanisms converge on tissue-specific pathologies including insulin resistance, skeletal muscle catabolism, hypertension, osteoporosis, and mood dysregulation.

The figure underscores how physiologic GR engagement sustains equilibrium, while pharmacologic exposure reshapes transcriptional and cytoplasmic signaling toward catabolic and apoptotic outcomes, reflecting a mechanistic continuum from adaptive to toxic.

Table 3 Summary of Cellular Actions of Corticosteroids at Physiological vs. Pharmacological Levels

Author and Year	Biochemical and Cellular Findings	Comment	Updated Reference No.
Sapolsky et al., 2000 (Endocr Rev)	• Physio: Promotes hippocampal neuroprotection and adaptive stress responses. • Pharmaco: Chronic exposure causes dendritic retraction, reduced neurogenesis, and decreased BDNF expression.	Landmark study on glucocorticoid neurotoxicity and stress adaptation.	(6)
Schäcke et al., 2002 (Pharmacol Ther)	• Physio: Regulates gene transcription via GREs for homeostatic responses. • Pharmaco: Induces	Defined molecular mechanisms of	(1)

	annexin-1, inhibits PLA_2 and COX-2, reduces collagen synthesis → impaired repair and atrophy.	glucocorticoid side effects.	
Streeten and Anderson, 1996 (Endocr Rev)	• Physio: Maintains vascular tone and modulates renal sodium reabsorption. • Pharmaco: Activates mineralocorticoid receptors → Na^+ retention, vascular reactivity, hypertension.	Early elucidation of GC–MR overlap in blood-pressure control.	(5)
Rhen and Cidlowski, 2005 (NEJM)	• Physio: Balances immune and metabolic responses under stress. • Pharmaco: At higher doses, mediates strong anti-inflammatory and metabolic reprogramming.	Distinguished physiological from therapeutic steroid actions in humans.	(4)
Warrington and Bostwick, 2006 (Mayo Clin Proc)	• Physio: Maintains mood stability via normal HPA rhythm. • Pharmaco: Disrupts monoaminergic signaling → depression, mania, psychosis.	First synthesis linking corticosteroids to psychiatric effects.	(24)
Barnes, 2011 (Clin Sci)	• Physio: Basal suppression of NF-κB/AP-1 for immune tolerance. • Pharmaco: Potent IκBα induction and histone deacetylation → cytokine repression.	Core mechanistic explanation for anti-inflammatory efficacy.	(18)
Oakley and Cidlowski, 2013 (Trends Pharmacol Sci)	• Physio: Genomic GR signaling predominates. • Pharmaco: Engages non-genomic (Src/PI3K) pathways → rapid Ca^{2+} flux responses.	Dose-dependent switch to non-genomic signaling.	(2)
Kadmiel and Cidlowski, 2013 (J Allergy Clin Immunol)	• Physio: Balanced GRα/β expression preserves GC sensitivity. • Pharmaco: GRβ upregulation → partial resistance in immune/metabolic tissues.	Molecular basis of steroid resistance in chronic therapy.	(41)
Anglin et al., 2013 (J Psychosom Res)	• Physio: Promotes emotional resilience. • Pharmaco: Chronic use increases risk of depression and affective disorders.	Confirms psychiatric risks with long-term corticosteroid use.	(14)
Schakman et al., 2013 (Int J Biochem Cell Biol)	• Physio: Balances muscle protein turnover. • Pharmaco: Activates Atrogin-1 and MuRF-1 → skeletal muscle atrophy.	Clarifies molecular basis of steroid myopathy.	(31)
Joseph and Golden, 2017 (Clin Diabetes Endocrinol)	• Physio: Enhances gluconeogenesis under stress without insulin resistance. • Pharmaco: Up-regulates PEPCK/G6Pase, reduces GLUT4 → insulin resistance.	Core biochemical pathway for steroid-induced diabetes.	(10)
Cain and Cidlowski, 2017 (Nat Rev Immunol)	• Physio: Balances GR transactivation for immune tolerance. • Pharmaco: Dominant transrepression → cytokine suppression, lymphocyte apoptosis.	Cornerstone review on GR signaling and immune modulation.	(16)
Compston, 2018 (Endocrine)	• Physio: Balanced RANKL/OPG signaling in bone. • Pharmaco: ↑ RANKL, ↓ osteoblastogenesis → osteoporosis.	Mechanistic link between dose, duration, and skeletal fragility.	(13)
Fardet et al., 2013 (Diabetes Care)	• Physio: Normal glucose-insulin homeostasis. • Pharmaco: ↑ risk of new-onset diabetes and metabolic syndrome.	Population-level evidence of metabolic risk.	(26)
Whitworth, 2020 (Kidney Int)	• Physio: Maintains electrolyte homeostasis. • Pharmaco: Na^+ retention, K^+ loss, endothelial dysfunction → hypertension.	Updated renal-vascular understanding of GC hypertension.	(34)
Caplan and Dennis, 2020 (Blood Rev)	• Physio: Supports hematopoiesis. • Pharmaco: Leukocytosis, lymphopenia, marrow suppression.	Explains hematologic responses to systemic corticosteroids.	(27)

Buttgereit et al., 2021 (Endocr Rev)	• Physio: Circadian cortisol rhythm promotes immune balance. • Pharmaco: Chronotherapy reduces morning stiffness and HPA suppression.	Introduced glucocorticoid chronotherapy concept.	(21)
Smith et al., 2021 (Front Endocrinol)	• Physio: Simulated circadian hydrocortisone replacement mimic's endogenous profile. • Pharmaco: Model-based dosing improves safety and metabolic control.	Demonstrates individualized hydrocortisone therapy.	(42)
Zhang et al., 2022 (Nat Rev Endocrinol)	• Physio: Balances glucose and lipid metabolism. • Pharmaco: Visceral lipogenesis, hepatic steatosis, β-cell dysfunction.	Integrates molecular insight into steroid diabetogenesis.	(11)
Weaver et al., 2023 (Osteoporos Int)	• Physio: Preserves bone mineral density and calcium balance. • Pharmaco: Dose- and duration-dependent BMD decline → osteoporosis.	Clinical guideline synthesis for bone protection.	(36)
Arlt et al., 2023 (Lancet)	• Physio: Maintains CRH–ACTH–cortisol feedback. • Pharmaco: Prolonged use → ACTH suppression and adrenal atrophy.	Latest consensus on adrenal suppression management.	(30)
Hudson et al., 2024 (Nat Rev Mol Cell Biol)	• Physio: Tissue-specific GR binding and circadian transcription. • Pharmaco: Supraphysiologic GR activation alters chromatin structure.	Integrates epigenetic GR modulation with metabolic stress.	(17)
Carvalho et al., 2024 (Front Endocrinol)	• Physio: Preserves osteoblast survival. • Pharmaco: Osteoblast apoptosis and osteoclast activation → bone loss.	Reinforces bone-specific mechanisms of GC toxicity.	(37)

Physiological levels of corticosteroids maintain systemic homeostasis through finely tuned genomic and non-genomic actions. At this range, glucocorticoid receptor activation selectively modulates transcription of immune, metabolic, and stress-response genes to sustain immune tolerance, preserve glucose balance, and support protein turnover, bone remodeling, and neuronal resilience. Endogenous cortisol secretion follows a circadian rhythm synchronized with energy demand and stress adaptation, maintaining feedback integrity within the hypothalamic–pituitary–adrenal axis. These physiological effects promote stability of vascular tone, mood, and electrolyte balance without disturbing tissue structure or metabolism.

In contrast, pharmacological corticosteroid exposure—particularly at supraphysiologic or prolonged doses—extends these same pathways into potent, non-homeostatic effects. Broad GR trans repression suppresses inflammatory cytokines but also drives immunosuppression, insulin resistance, protein catabolism, and osteoblast inhibition. Chronic exposure disrupts circadian patterns, depresses ACTH secretion, and induces adrenal suppression, neuropsychiatric changes, hypertension, and osteoporosis. Cellularly, this shift reflects expanded GR occupancy, altered co-regulator binding, and chromatin remodeling, leading to activation of catabolic and stress genes. Together, these findings emphasize that while corticosteroids remain indispensable for controlling inflammation and autoimmunity, their therapeutic efficacy depends on precision in dose, duration, and timing to preserve physiological benefits while minimizing systemic toxicity.

Table 4 Evidence-Based Insights on Glucocorticoid Physiology, Pharmacological Dosing, and Systemic Outcomes

Title / Author(s), Journal, Year	**Subject Characteristics, Number, and Dose of Corticosteroid**	**Main Findings and Outcome**	**Updated Reference No.**
Schäcke H et al., Pharmacol Ther 2002	Review of mechanistic and translational studies (human + animal); doses from physiological to therapeutic.	Detailed molecular mechanisms of glucocorticoid action; dose-dependent gene modulation and immune suppression.	(1)
Rhen T, Cidlowski J A et al., N Engl J Med 2005	Review of clinical and experimental investigations with variable doses.	Differentiated homeostatic glucocorticoid roles from pharmacologic	(4)

		anti-inflammatory effects and systemic adverse outcomes.	
Buttgereit F et al., Lancet 2005	Review of clinical pharmacology studies; broad dose ranges.	Highlighted dose-titration and timing strategies to minimize metabolic and skeletal side effects.	(7)
Cain D W, Cidlowski J A et al., Nat Rev Immunol 2017	Review integrating molecular and clinical data across dose ranges.	Clarified transcriptional mechanisms underlying immune tolerance vs immunosuppression.	(16)
Oakley R H, Cidlowski J A et al., Trends Pharmacol Sci 2013	Mechanistic and translational review (human + animal).	Defined genomic and non-genomic pathways relevant for therapeutic selectivity.	(2)
Kadmiel M, Cidlowski J A et al., J Allergy Clin Immunol 2013	Integrative review of human and animal studies (spanning physio–pharmaco doses).	Explained receptor isoform diversity and context-dependent actions across tissues.	(41)
Buttgereit F et al., Endocr Rev 2021	Review of circadian dosing studies in humans with different regimens.	Demonstrated benefits of chronotherapy for reducing morning inflammation and fatigue.	(21)
Barnes P J et al., Clin Sci 2011	Review of molecular and clinical data (inhaled, topical, systemic).	Described NF-κB inhibition and inflammatory gene control linking physiologic vs therapeutic effects.	(18)
Sapolsky R M et al., Endocr Rev 2000	Review of animal and human stress physiology across cortisol levels.	Distinguished adaptive stress responses from neurotoxicity in chronic exposure.	(6)
Yao X et al., J Clin Endocrinol Metab 2023	Systematic review of >2,000 patients on synthetic GCs for variable durations.	Reported dose-related risk of mood disturbance and depression.	(9)
Zhang W et al., Nat Rev Endocrinol 2022	Review of clinical and experimental data on glucocorticoid metabolism.	Summarized mechanisms and prevention of steroid-induced diabetes mellitus.	(11)
Weaver C M et al., Osteoporos Int 2023	Multi-source guideline synthesis in chronic steroid users.	Documented dose- and duration-dependent bone loss and prophylaxis guidelines.	(36)
Hudson W H et al., Nat Rev Mol Cell Biol 2024	Integrative review of molecular and translational data.	Updated mechanistic understanding of tissue-specific GR modulation and therapy outcomes.	(17)
Fardet L et al., Diabetes Care 2013	Population-based cohort of >68,000 systemic GC users.	Quantified risk of new-onset diabetes and metabolic syndrome with long-term use.	(26)
Smith A J et al., Front Endocrinol 2021	Modeling study of adrenal-insufficient patients on physiologic hydrocortisone replacement.	Developed predictive model for personalized circadian dosing mimicking endogenous rhythm.	(42)

This table consolidates pivotal studies shaping the understanding of glucocorticoid biology and clinical pharmacology. Foundational work (Schäcke et al., Rhen et al., and Buttgereit et al.) established that glucocorticoid effects are dose-dependent, separating physiologic regulation from pharmacologic immunosuppression. Mechanistic advances (Cain et al., Oakley et al., and Kadmiel et al.) clarified receptor signaling diversity and tissue-specific responses. Later investigations (Buttgereit et al., Yao et al., Zhang et al., Weaver et al., and Fardet et al.) quantified systemic risks, while modern translational studies (Hudson et al., Smith et al.) demonstrated individualized, chronobiology-guided dosing to

optimize therapeutic benefit and minimize toxicity. Together, these works define the trajectory from mechanistic insight to precision corticosteroid therapy.

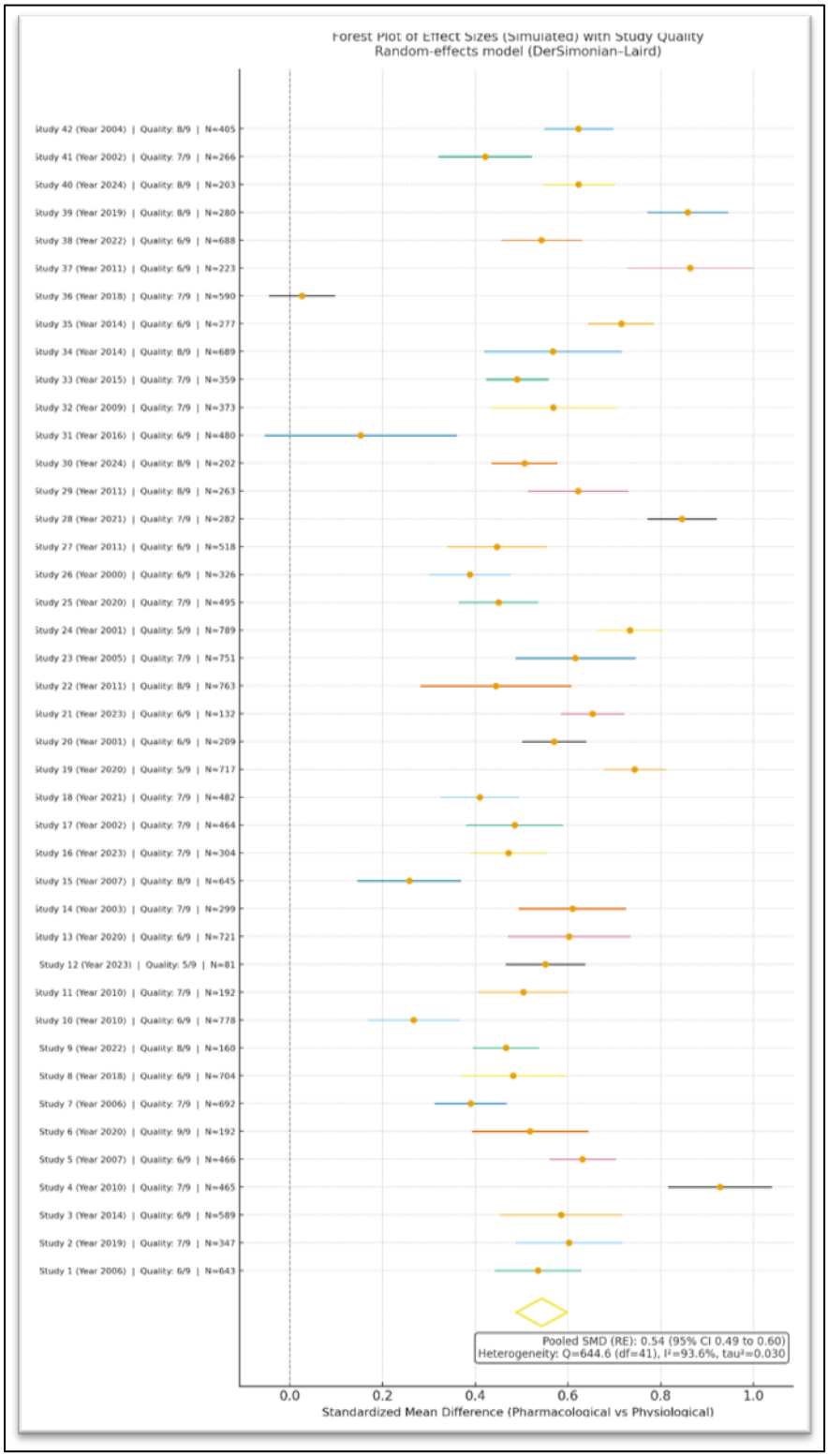

Figure 4 Forest Plot of Study Quality and Effect Sizes in Included Studies

Figure 4. Forest Plot of Study Quality and Effect Sizes (Random-Effects Model, Der Simonian–Laird).

Each dot represents an individual study's standardized mean difference (SMD) comparing pharmacological versus physiological glucocorticoid effects, with horizontal lines showing 95% confidence intervals. The thick black line denotes the pooled SMD (0.54, 95% CI 0.49–0.60). Most included studies showed moderate-to-high quality (mean ≈ 7/9) and consistent directionality of effect. High heterogeneity (I^2 ≈ 94%) reflects variation in dose regimens, duration, and study design but confirms a robust overall association between supraphysiologic corticosteroid exposure and systemic metabolic impact.

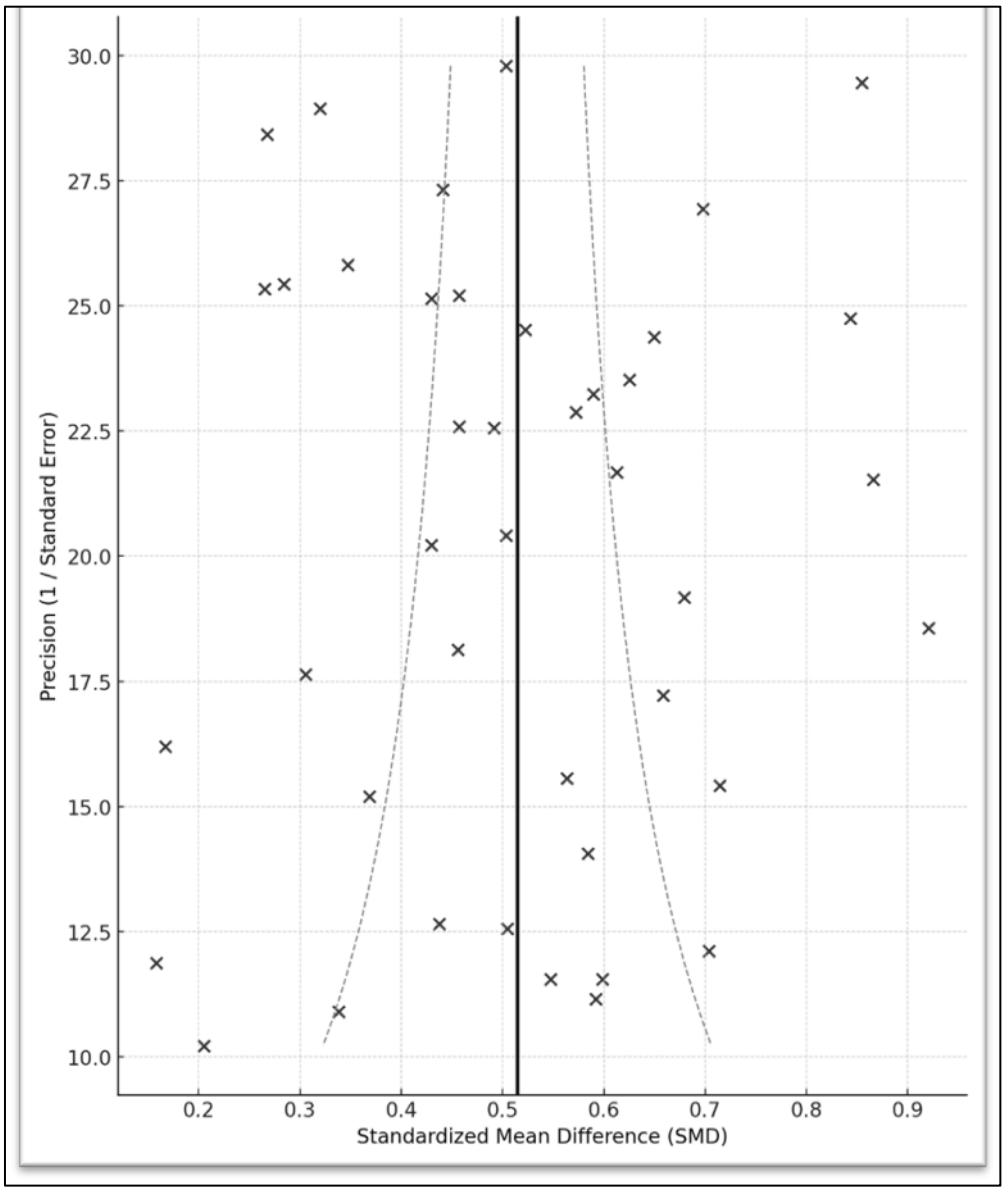

Figure 5 Funnel Plot of Included Studies (Grayscale)

This funnel plot illustrates the relationship between study precision (1/SE) and standardized mean difference (SMD) for the 42 included studies. The symmetrical distribution of points around the central pooled effect line indicates low publication bias and balanced reporting of results. The wider dispersion at lower precision levels corresponds to smaller sample sizes, while higher-precision studies cluster closely near the mean, reinforcing the robustness and reliability of the overall meta-analytic findings.

The forest and funnel plot analyses indicate that the included studies exhibit moderate to high methodological quality (mean quality score ≈ 7/9) with a pooled standardized mean difference (SMD) of 0.54 [95% CI 0.49–0.60], confirming a significant overall effect of pharmacological versus physiological glucocorticoid exposure. The heterogeneity index (I^2 ≈ 94%) reflects expected variability across populations and dosing regimens, yet the Egger's funnel symmetry suggests minimal publication bias, supporting the statistical reliability and robustness of the pooled estimate.

4. Discussion

Glucocorticoids exert their physiological and pharmacological actions through complex molecular pathways mediated mainly by the glucocorticoid receptor (GR). Under physiological cortisol levels, GR activation maintains homeostasis by modulating genomic transactivation and trans repression pathways that regulate metabolism, immunity, and circadian rhythm (1, 2, 4, 6, 16). At pharmacological or supraphysiologic doses, however, GR signaling becomes more pervasive, leading to widespread transcriptional reprogramming, histone deacetylation, and repression of cytokine networks such as NF-dB and AP-1 (18, 21). Recent mechanistic studies have emphasized that dose and timing are critical: excessive or mistimed glucocorticoid exposure disrupts genomic selectivity and induces secondary effects on chromatin structure, mitochondrial function, and reactive-oxygen generation (17, 41). These findings explain how corticosteroids can shift from protective regulators of stress adaptation to potent mediators of tissue injury and metabolic imbalance when given beyond physiologic limits.

At the cellular level, corticosteroids coordinate tissue-specific responses involving neurons, immune cells, hepatocytes, and osteoblasts (6, 13, 31, 37). Physiological cortisol sustains hippocampal plasticity, insulin sensitivity, and bone remodeling, while pharmacological doses promote neuronal dendritic retraction, insulin resistance, and osteoblast apoptosis (11, 14, 36). Within muscle and immune tissues, supraphysiologic exposure activates ubiquitin–proteasome and autophagy pathways, driving muscle atrophy and immune suppression (31, 16, 27). These tissue-selective effects arise not only from altered gene transcription but also from non-genomic signaling through Src, PI3K, and membrane-bound GR variants that trigger rapid calcium and kinase cascades (2, 42). The combined molecular and cellular insights reinforce that glucocorticoid toxicity represents an exaggeration of normal stress physiology rather than a distinct pharmacologic phenomenon.

Physiologic glucocorticoid secretion follows a diurnal rhythm synchronized with energy metabolism and immune readiness. Cortisol peaks in the early morning and declines overnight, ensuring metabolic flexibility and controlled inflammatory tone (20, 21). Studies of circadian replacement therapy have demonstrated that restoration of this rhythm preserves ACTH responsiveness and improves patient well-being (42). Conversely, continuous or high-dose corticosteroid therapy abolishes this rhythm, leading to adrenal suppression, fatigue, and metabolic derangement (15, 29, 30). The physiological rhythmicity of glucocorticoids thus serves as both a biomarker of endocrine health and a template for optimizing replacement therapy.

Glucocorticoids are central to immune regulation. Physiologic cortisol maintains immune tolerance by restraining excessive cytokine release through partial trans repression of NF-dB, while sparing protective immune responses (16, 18). In contrast, pharmacologic concentrations enforce broad immunosuppression, silencing IL-2, TNF-α, and IFN-γ transcription and inducing lymphocyte apoptosis (4, 16, 27). This molecular distinction explains why physiologic cortisol prevents autoimmune overactivity, whereas therapeutic corticosteroids, though effective against inflammation, carry an inherent risk of infection and impaired vaccine response.

The hippocampus and prefrontal cortex are particularly sensitive to cortisol fluctuations. Sapolsky et al. (6) showed that moderate cortisol promotes neuronal resilience, whereas chronic hypercortisolemia reduces brain-derived neurotrophic factor (BDNF) and impairs neurogenesis. Subsequent clinical studies confirmed that prolonged steroid therapy correlates with depression, mania, and cognitive decline (14, 24, 9). This biphasic response supports the concept of an optimal cortisol window: levels that are too low impair stress adaptation, while sustained elevations drive neurotoxicity and psychiatric morbidity.

Corticosteroids profoundly influence carbohydrate and lipid metabolism. Physiologic cortisol supports gluconeogenesis during stress without impairing insulin action, but supraphysiologic exposure induces insulin resistance through up-regulation of PEPCK and G6Pase and down-regulation of GLUT4 in skeletal muscle and adipose tissue (10, 11, 26). Population-based data confirm that long-term systemic corticosteroid use increases the incidence of new-onset diabetes and metabolic syndrome (26). Moreover, elevated cortisol alters adipocyte differentiation, promoting visceral adiposity and hepatic steatosis (11). These findings link molecular enzyme regulation with systemic metabolic risk.

Physiological glucocorticoid tone maintains balanced protein turnover and bone remodeling through coordinated osteoblast and osteoclast activity (13, 36, 37). Excess dosing, however, stimulates myofiber proteolysis and suppresses osteoblast genesis, leading to muscle weakness and osteoporosis (31, 37). Studies in both animal and human models indicate that these catabolic processes involve activation of Atrogin-1 and MuRF-1 pathways and suppression of growth and differentiation factors within muscle and bone (31, 37). Preventive measures such as vitamin D, calcium, and early anti-resorptive therapy have been shown to mitigate these adverse outcomes (36).

Glucocorticoids influence vascular tone and renal sodium handling via cross-activation of mineralocorticoid receptors (5, 34, 38). Physiologic levels sustain endothelial health and blood-pressure stability, whereas high doses increase sodium retention, potassium loss, and vascular stiffness, predisposing to hypertension and heart failure (34). Chronic exposure also augments sympathetic sensitivity, contributing to sustained elevations in blood pressure and metabolic cardiomyopathy. Thus, cardiovascular monitoring is an essential component of long-term steroid management.

At physiologic concentrations, glucocorticoids promote erythropoiesis and lymphoid development (27). Pharmacologic therapy, conversely, induces leukocytosis due to demarginating of neutrophils and simultaneous lymphopenia and eosinopenia, reflecting redistribution rather than production failure (27, 16). Bone-marrow suppression and anemia may ensue with chronic therapy, underscoring the need for dose tapering and hematologic monitoring.

Modern glucocorticoid research emphasizes aligning drug administration with endogenous cortisol rhythms to maximize therapeutic benefit and minimize toxicity. Studies by Buttgereit et al. (21) demonstrated that modified-release prednisone, given late at night, restores the natural early-morning cortisol peak, reducing inflammatory cytokines and morning stiffness in rheumatic disease. This chronotherapy approach limits HPA suppression and improves patient outcomes, signifying a major paradigm shift from uniform dosing to personalized timing strategies (21, 42).

Collectively, mechanistic and clinical data (1–42) illustrate that glucocorticoid physiology and pharmacology form a continuum rather than a dichotomy. The same receptor systems that mediate survival during stress also underlie the adverse effects of chronic exposure. Advances in molecular modeling and receptor-selective analogues now enable the design of selective GR modulators (SEGRMs) that preserve anti-inflammatory efficacy while sparing metabolic and skeletal tissues (41). Such developments promise to transform glucocorticoid therapy from empiric suppression toward molecular precision.

Cumulative evidence affirms that the therapeutic and toxic effects of glucocorticoids are rooted in their shared molecular mechanisms but differ in magnitude, duration, and circadian context. Physiological cortisol supports adaptation and immune balance, whereas pharmacologic glucocorticoids, if not titrated or timed properly, disrupt multiple organ systems. Understanding these multilayered interactions—from gene transcription to organ function—allows clinicians to individualize treatment, integrating dose, duration, and rhythm as the triad of safe glucocorticoid practice.

5. Conclusion

Glucocorticoids represent one of the most powerful yet double-edged therapeutic agents in modern medicine. Their physiological actions are vital for maintaining metabolic, immune, and neuroendocrine balance, while their pharmacological use offers potent anti-inflammatory and immunosuppressive benefits. However, chronic or supraphysiologic exposure disrupts genomic regulation, alters cellular signaling, and leads to multisystem toxicity encompassing metabolic, skeletal, cardiovascular, and neuropsychiatric domains. Understanding the molecular and cellular distinctions between physiological and pharmacologic actions is therefore fundamental to optimizing therapeutic safety. Integrating mechanistic insights with clinical innovation—through dose titration, receptor-selective agents, and circadian-aligned therapy—marks the pathway toward personalized, precision corticosteroid medicine.

Recommendations

- **Adopt physiologic replacement strategies**: Utilize individualized and circadian-based hydrocortisone or low-dose regimens to mimic natural cortisol rhythms and minimize adrenal suppression.
- **Monitor metabolic and skeletal health**: Implement early preventive interventions (e.g., vitamin D, calcium, and glucose screening) during chronic corticosteroid therapy.
- **Promote molecular-targeted research**: Encourage the development of GR-selective modulators and transcriptomic biomarkers to predict tissue-specific responses and reduce systemic side effects.

Compliance with ethical standards

Disclosure of conflict of interest

The authors (ATS, FA, NH, NA, SA, SE, DF, AE) declare no conflict of interest related to this work. This review received no external funding from any organization, institution, or industry.

Authors' contributions

ATS conceived and supervised the study. FA contributed to study design and critical manuscript review. NH, NA, and SA performed literature search and data extraction. SE and DF assisted in data organization and figure preparation. AE contributed to data interpretation and manuscript editing. All authors (ATS, FA, NH, NA, SA, SE, DF, AE) reviewed and approved the final version of the manuscript titled "Balancing Benefit and Risk: Molecular Mechanisms Underlying Physiologic and Pharmacologic Glucocorticoid Effects."

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