

Adverse Effects of Prolonged Steroid Use: A Focus on Metabolic and Endocrine Disruption

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ABSTRACT

Prolonged corticosteroid use, though vital in treating inflammatory, autoimmune, and allergic disorders, is frequently associated with serious metabolic and endocrine complications. Extended exposure to glucocorticoids disrupts critical physiological pathways regulating glucose metabolism, bone formation, lipid balance, and hormonal secretion. Consequently, patients are at increased risk of developing hyperglycemia, osteoporosis, adrenal suppression, and obesity, conditions that significantly impair quality of life and complicate disease management. This review comprehensively explores the mechanisms underlying corticosteroid-induced metabolic and endocrine disruptions, detailing their clinical manifestations and associated risk factors. It also highlights preventive strategies, including patient education, lifestyle modification, and close clinical monitoring, as essential components of long-term management. Furthermore, emerging therapeutic approaches such as corticosteroid-sparing agents and selective glucocorticoid receptor modulators (SGRMs) offer promising avenues to reduce systemic toxicity while maintaining therapeutic efficacy. Understanding these adverse effects is crucial for clinicians to balance treatment benefits against long-term risks, promote safer corticosteroid use, and improve patient outcomes through personalized and evidence-based care.

Keywords: corticosteroids, glucocorticoids, metabolic dysfunction, endocrine disruption, osteoporosis.

INTRODUCTION

Corticosteroids, commonly referred to as steroids, are synthetic derivatives of naturally occurring glucocorticoids produced by the adrenal cortex. They play a crucial role in the regulation of a wide range of physiological processes, including immune response modulation, inflammation suppression, carbohydrate metabolism, protein synthesis, and electrolyte balance [1]. Since their discovery in the mid-20th century, corticosteroids have revolutionized the treatment of numerous acute and chronic medical conditions, including asthma, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis, and organ transplant rejection. The remarkable efficacy of corticosteroids in rapidly reducing inflammation and modulating immune responses has made them indispensable in both acute and long-term therapeutic regimens [2]. Despite their proven clinical benefits, corticosteroids are associated with a range of adverse effects, particularly when used in high doses or over extended periods. The metabolic and endocrine systems are particularly vulnerable to disruption from prolonged corticosteroid exposure. The mechanisms underlying these effects are multifaceted, involving complex interactions between glucocorticoid receptors, insulin signaling pathways, bone metabolism regulators, and the hypothalamic-pituitary-adrenal (HPA) axis [3]. Chronic steroid therapy can, therefore, produce a spectrum of complications that may severely compromise patients' quality of life and, in some cases, lead to life-threatening conditions. Understanding these adverse effects is critical for healthcare providers in balancing the therapeutic benefits of steroids with their long-term risks and in formulating strategies to mitigate complications [4].

While corticosteroids remain a cornerstone of therapy for inflammatory and autoimmune conditions, their long-term use presents a significant clinical challenge. Patients undergoing chronic steroid therapy are at heightened risk of developing metabolic disorders such as hyperglycemia, insulin resistance, and dyslipidemia, which increase the

likelihood of type 2 diabetes mellitus and cardiovascular complications. Endocrine disturbances, including adrenal insufficiency and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, further complicate the management of patients and pose risks during periods of stress or illness [5]. Additionally, steroid-induced osteoporosis is a major contributor to morbidity, predisposing patients to fractures and skeletal deformities. Weight gain, often a consequence of steroid therapy, not only exacerbates metabolic dysfunction but also affects patients' psychological well-being and adherence to therapy.

Despite the widespread use of corticosteroids, there remains limited awareness among patients and some healthcare practitioners regarding the long-term adverse effects of steroid therapy, particularly metabolic and endocrine complications. This knowledge gap can result in insufficient monitoring, delayed diagnosis of complications, and suboptimal management strategies [6]. Moreover, research into region-specific prevalence and management approaches for steroid-induced metabolic and endocrine disturbances is limited, particularly in low-resource settings where healthcare infrastructure and patient monitoring may be constrained. Consequently, a comprehensive review of the mechanisms, clinical manifestations, and management strategies for steroid-induced metabolic and endocrine disruptions is urgently needed to inform clinical practice and guide safe therapeutic protocols [7]. The primary objective of this review is to provide an in-depth analysis of the adverse effects associated with prolonged corticosteroid use, particularly its impact on metabolic and endocrine health. Specifically, the study seeks to examine the mechanisms through which chronic corticosteroid exposure leads to metabolic and endocrine disruptions, including alterations in glucose metabolism, lipid balance, and hormonal regulation. It aims to identify common metabolic complications such as hyperglycemia, insulin resistance, dyslipidemia, and obesity, alongside endocrine disorders like adrenal suppression and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, the review explores clinical manifestations, diagnostic methods, and risk factors contributing to these complications. It also evaluates preventive and therapeutic strategies that healthcare professionals can adopt to minimize these adverse outcomes while maintaining corticosteroid efficacy. Ultimately, the study intends to provide evidence-based recommendations for clinicians to balance the therapeutic benefits of corticosteroids with their potential long-term risks. By integrating insights from current literature, this review supports improved clinical decision-making, encourages patient-centered management, and promotes the development of safer corticosteroid use protocols. In doing so, it underscores the importance of continuous monitoring, patient education, and strategic management in minimizing metabolic and endocrine complications from prolonged steroid therapy.

Mechanisms of Steroid-Induced Metabolic and Endocrine Disruption

Glucocorticoids, a class of steroid hormones, exert their physiological and pharmacological effects primarily through binding to intracellular glucocorticoid receptors, which then modulate gene transcription and protein synthesis across various metabolic pathways. This interaction influences carbohydrate, protein, and lipid metabolism, leading to alterations in glucose production, fat distribution, and muscle protein catabolism [8]. Prolonged or high-dose glucocorticoid exposure disrupts the normal functioning of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in suppression of endogenous cortisol production and impaired stress response. Over time, these disturbances contribute to insulin resistance, hyperglycemia, and the development of steroid-induced diabetes. Additionally, chronic steroid use interferes with bone metabolism by inhibiting osteoblast activity and enhancing bone resorption, increasing the risk of osteoporosis and fractures. Lipid metabolism is also affected, often leading to central adiposity, dyslipidemia, and weight gain. The severity of these effects depends on factors such as dosage, duration of therapy, route of administration, and individual genetic susceptibility [9]. Overall, glucocorticoid-induced metabolic and endocrine disruptions represent a complex interplay of hormonal feedback mechanisms and cellular metabolic regulation, underscoring the need for careful therapeutic monitoring and individualized dosing strategies to minimize adverse effects while maintaining therapeutic efficacy.

Osteoporosis

Steroid-induced osteoporosis is a common and serious adverse effect of prolonged corticosteroid therapy, often leading to significant morbidity. The pathophysiology involves multiple mechanisms: glucocorticoids suppress osteoblast proliferation and function, thereby reducing bone formation, while simultaneously stimulating osteoclast-mediated bone resorption [10]. Additionally, corticosteroids impair calcium metabolism by decreasing intestinal calcium absorption and increasing renal calcium excretion, which in turn triggers secondary hyperparathyroidism, a condition that further accelerates bone loss. Clinically, patients may present with reduced bone mineral density and are predisposed to fragility fractures, particularly in weight-bearing bones such as the vertebrae, ribs, and hips. These fractures can result in chronic pain, spinal deformities, and reduced mobility, significantly impairing quality of life. The risk of developing osteoporosis increases with higher cumulative doses and the duration of steroid use [11]. Management and prevention strategies focus on minimizing bone loss through adequate calcium and vitamin D supplementation, the use of antiresorptive agents such as bisphosphonates, and adopting healthy lifestyle practices like regular weight-bearing and resistance exercises. Regular bone mineral density assessments are recommended

to detect early changes and guide timely intervention, helping to reduce fracture risk and maintain skeletal integrity in patients receiving long-term corticosteroid therapy [12].

Hyperglycemia

Corticosteroid-induced hyperglycemia arises primarily from metabolic alterations in glucose regulation. These agents stimulate hepatic gluconeogenesis, enhance glycogenolysis, and reduce peripheral glucose uptake in skeletal muscle and adipose tissue, thereby increasing circulating glucose levels. Additionally, corticosteroids induce insulin resistance by impairing insulin receptor signaling, which further aggravates hyperglycemia, particularly in individuals with pre-existing glucose intolerance or diabetes mellitus [13]. Clinically, steroid-induced hyperglycemia may manifest as new-onset diabetes or worsening of previously controlled diabetes. Common symptoms include polyuria, polydipsia, blurred vision, and fatigue, all resulting from excessive glucose accumulation in the bloodstream. The risk and severity of hyperglycemia depend on factors such as steroid dose, duration of therapy, and individual metabolic susceptibility. Effective management requires a multifaceted approach, including regular blood glucose monitoring, dietary modifications emphasizing low-glycemic foods, and pharmacologic interventions such as insulin therapy or oral hypoglycemic agents. Clinicians should tailor treatment plans to each patient's response and adjust therapy according to fluctuations in steroid dosing. Early recognition and proactive management of corticosteroid-induced hyperglycemia are critical to prevent acute complications like hyperosmolar hyperglycemic state (HHS) and long-term sequelae such as cardiovascular disease and neuropathy, ensuring optimal patient outcomes during corticosteroid therapy [14].

Adrenal Suppression

Adrenal suppression is a significant clinical condition that results from prolonged corticosteroid therapy, which inhibits the normal function of the hypothalamic-pituitary-adrenal (HPA) axis. The underlying pathophysiology involves the negative feedback mechanism, whereby exogenous steroids suppress the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus and adrenocorticotropic hormone (ACTH) from the pituitary gland [14]. This suppression leads to decreased endogenous cortisol production by the adrenal cortex, rendering the body unable to mount an adequate stress response when steroids are abruptly withdrawn. Clinically, patients may present with symptoms such as fatigue, weakness, nausea, vomiting, dizziness, and hypotension. In severe cases, particularly during periods of physical stress like infection or surgery, an adrenal crisis may occur, posing a life-threatening emergency characterized by profound hypotension and shock. Prevention and management involve a gradual tapering of corticosteroid doses to allow the HPA axis to resume normal function and cortisol production. During stressful events, patients with a history of long-term steroid use may require supplemental or stress-dose corticosteroids to prevent adrenal crisis. Patient education, careful monitoring, and individualized tapering schedules are essential to ensure safe discontinuation of steroid therapy and to minimize the risk of adrenal insufficiency [15].

Weight Gain and Obesity

Steroid-induced weight gain and obesity arise from complex physiological mechanisms that affect both fat metabolism and distribution. Glucocorticoids promote adipogenesis, the formation of new fat cells, and alter lipid metabolism, leading to increased fat deposition, particularly in the abdomen, neck, and face. Additionally, steroids stimulate appetite and cause fluid retention, further contributing to body weight increase. Clinically, patients often present with distinct physical features such as truncal obesity, a rounded "moon face," and a dorsocervical fat pad commonly referred to as a "buffalo hump" [16]. These changes collectively resemble a Cushingoid appearance and are linked to heightened cardiovascular risk, insulin resistance, and metabolic syndrome. Effective management of steroid-induced obesity requires a multifaceted approach. Lifestyle modifications, including balanced dietary control, caloric restriction, and consistent physical activity, play a central role in preventing or reducing weight gain. For patients experiencing significant side effects, clinicians may consider adjusting the steroid dosage, switching to non-systemic or alternate-day therapy, or using steroid-sparing agents where clinically feasible. Ongoing monitoring and patient education about nutrition, exercise, and medication adherence are essential to minimizing the metabolic complications associated with prolonged steroid use and maintaining overall health and quality of life.

Clinical Implications and Monitoring

Long-term corticosteroid therapy carries significant clinical implications, necessitating careful and continuous monitoring to prevent and manage potential metabolic and endocrine complications. Patients undergoing prolonged treatment should receive regular evaluations, including bone mineral density (BMD) scans to assess for osteoporosis, routine blood glucose tests to monitor for corticosteroid-induced diabetes, and periodic tracking of weight and body composition to identify early signs of metabolic syndrome [17]. In addition, hypothalamic-pituitary-adrenal (HPA) axis function tests are essential to detect adrenal suppression, a common risk associated with chronic corticosteroid use. Effective management requires a multidisciplinary approach that brings together endocrinologists, dietitians, and primary care physicians to ensure comprehensive care and risk minimization. Patient education on lifestyle modifications, diet, and adherence to monitoring schedules is equally vital for maintaining health and preventing

adverse outcomes. Looking ahead, the future of corticosteroid therapy lies in the advancement of corticosteroid-sparing agents and selective glucocorticoid receptor modulators (SGRMs) designed to deliver potent anti-inflammatory effects with fewer systemic side effects [18]. Furthermore, the integration of personalized medicine and predictive biomarkers promises to refine treatment strategies, allowing clinicians to tailor therapy to individual patient profiles, improve therapeutic efficacy, and enhance long-term safety and quality of life.

CONCLUSION

In conclusion, while corticosteroids remain indispensable in managing inflammatory and autoimmune diseases, their prolonged use presents significant metabolic and endocrine challenges that demand vigilant clinical oversight. The development of complications such as osteoporosis, hyperglycemia, adrenal suppression, and weight gain underscores the need for careful patient monitoring and individualized treatment strategies. A multidisciplinary approach involving endocrinologists, dietitians, and primary care providers is essential to mitigate risks and promote holistic patient care. Preventive measures, including lifestyle modification, routine diagnostic assessments, and patient education, play a pivotal role in minimizing adverse outcomes and improving quality of life. Advances in pharmacological research offer promising alternatives, such as corticosteroid-sparing agents and selective glucocorticoid receptor modulators, which may retain therapeutic benefits while reducing systemic toxicity. Ultimately, optimizing corticosteroid therapy requires balancing efficacy with safety through evidence-based clinical decisions, personalized medicine, and ongoing patient support to ensure sustained health outcomes and minimize the long-term burden of steroid-induced metabolic and endocrine disruption.

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CITE AS: Nyambura Achieng M. (2026). Adverse Effects of Prolonged Steroid Use: A Focus on Metabolic and Endocrine Disruption. INOSR APPLIED SCIENCES 14(2):28-32. <https://doi.org/10.59298/INOSRAS/2025/14.2.2832>