FABAD J. Pharm. Sci., 51, 1, 419-434, 2026
Doi: 10.55262/fabadeczacilik.1825544
REVIEW ARTICLE

The Role of Glucocorticoids in Hepatic Gluconeogenesis, Associated Pathologies, and Novel Therapeutic Approaches

Yusuf Anil AY[*], Elif CADIRCI[**°]

The Role of Glucocorticoids in Hepatic Gluconeogenesis, Associated Pathologies, and Novel Therapeutic Approaches

SUMMARY

Glucocorticoids are essential steroid hormones that play a pivotal role in regulating hepatic gluconeogenesis, thereby contributing to the maintenance of systemic glucose homeostasis. This review provides a comprehensive overview of the molecular mechanisms by which glucocorticoids modulate hepatic glucose production and explores their clinical implications in metabolic health and disease. Glucocorticoids exert their primary effects through genomic pathways, involving the translocation of activated glucocorticoid receptors (GRs) into the nucleus, where they bind to glucocorticoid response elements (GREs) on DNA. This interaction promotes the transcription of key gluconeogenic enzymes, notably phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). Additionally, glucocorticoids enhance the expression of these enzymes by synergizing with critical transcriptional regulators such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), forkhead box protein O1 (FOXO1), and hepatocyte nuclear factor 4-alpha (HNF-4α). Beyond their hepatic effects, glucocorticoids influence systemic metabolism by stimulating proteolysis and lipolysis in peripheral tissues, thereby increasing the availability of substrates for gluconeogenesis. Furthermore, they antagonize insulin signaling, contributing to insulin resistance. The local activation of glucocorticoids via the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) adds another layer of regulation. Non-genomic effects through the cAMP/PKA/CREB signaling pathway allows for rapid metabolic responses. Chronic glucocorticoid excess, as observed in conditions like Cushing's syndrome, is linked to the development of type 2 diabetes. Emerging therapeutic strategies, including 11β-HSD1 inhibitors, selective GR modulators, and targeted inhibitors of gluconeogenic enzymes, present promising avenues for managing glucocorticoid-induced metabolic disorders.

Keywords: *Glucocorticoid, gluconeogenesis, glucose metabolism, hyperglycemia, diabetes.*

Glukokortikoidlerin Hepatik Glukoneogenezdeki Rolü, İlişkili Patolojiler ve Yeni Tedavi Yaklaşımları

ÖZ

Glukokortikoidler, hepatik glukoneogenezi düzenlemede önemli bir rol oynayan ve böylece sistemik glikoz homeostazının korunmasına katkıda bulunan temel steroid hormonlardır. Bu derleme, glukokortikoidlerin hepatik glikoz üretimini modüle ettiği moleküler mekanizmalara kapsamlı bir genel bakış sunmakta ve metabolik sağlık ve hastalıklar üzerindeki klinik etkilerini incelemektedir. Glukokortikoidler, aktive edilmiş glukokortikoid reseptörlerinin (GR) çekirdeğe taşınması ve burada DNA üzerindeki glukokortikoid yanıt elemanlarına (GRE) bağlanmasıyla genomik yolaklar aracılığıyla birincil etkilerini gösterir. Bu etkileşim, fosfoenolpiruvat karboksikinaz (PEPCK) ve glikoz-6-fosfataz (G6Pase) gibi önemli glukoneojenik enzimlerin transkripsiyonunu teşvik eder. Ek olarak, glukokortikoidler, peroksizom proliferatör ile aktive olan reseptör gama koaktivatörü 1-alfa (PGC-1α), forkhead box proteini O1 (FOXO1) ve hepatosit nükleer faktör 4-alfa (HNF-4α) gibi kritik transkripsiyon düzenleyicileri ile sinerji oluşturarak bu enzimlerin ekspresyonunu artırır. Karaciğer üzerindeki etkilerinin ötesinde, glukokortikoidler periferik dokularda proteoliz ve lipolizi uyararak sistemik metabolizmayı etkiler ve böylece glukoneogenez için substratların kullanılabilirliğini artırır. Ayrıca, insülin sinyalini antagonize ederek insülin direncine katkıda bulunurlar. 11β-hidroksisteroid dehidrojenaz tip 1 (11β-HSD1) enzimi aracılığıyla glukokortikoidlerin lokal aktivasyonu, düzenlemeye başka bir katman ekler. cAMP/PKA/CREB sinyal yoluyla genomik olmayan etkiler, hızlı metabolik yanıtlara olanak tanır. Cushing sendromu gibi durumlarda gözlenen kronik glukokortikoid fazlalığı, tip 2 diyabetin gelişimi ile bağlantılıdır. 11β-HSD1 inhibitörleri, seçici GR modülatörleri ve glukoneojenik enzimlerin hedefli inhibitörleri dahil olmak üzere ortaya çıkan terapötik stratejiler, glukokortikoid kaynaklı metabolik bozuklukların yönetimi için umut verici yollar sunmaktadır.

Anahtar Kelimeler: *Glukokortikoid, glukoneogenez, glikoz, hiperglisemi, diyabet.*

Recieved: 18.11.2025
Revised: 19.02.2026
Accepted: 5.03.2026

[*] ORCID: 0009-0002-6007-694X, Department of Biochemistry, Faculty of Pharmacy, Ataturk University, 25240, Erzurum, Türkiye
[**] ORCID: 0000-0003-0836-7205, Department of Pharmacology, Faculty of Medicine, Ataturk University, 25240, Erzurum, Türkiye

[°] Corresponding Author; Elif CADIRCI
E-mail: ecadirci@atauni.edu.tr

INTRODUCTION

Glucocorticoids (GCs), including endogenous cortisol and synthetic analogues (e.g., dexamethasone, prednisone), are one of the cornerstones of modern medicine due to their anti-inflammatory, immunosuppressive, and metabolic effects. These molecules, widely used in the treatment of rheumatoid arthritis, autoimmune diseases, allergic reactions, chronic obstructive pulmonary disease, and certain malignancies, exhibit complex and multifaceted effects on energy metabolism (De Guia, Rose, & Herzig, 2014). GCs play critical roles in the stress response and maintenance of homeostasis; they bind to glucocorticoid receptors (GR) with high affinity, regulating gene transcription and modulating key components of energy metabolism such as gluconeogenesis, fatty acid oxidation, and mitochondrial function (Vandewalle, Luypaert, De Bosscher, & Libert, 2018). These effects support energy mobilization in acute stress conditions but chronic exposure can lead to metabolic complications such as; insulin resistance, hyperglycemia, dyslipidemia, and mitochondrial dysfunction (Sharma & Singh, 2019). This review aims to comprehensively examine the biochemical effects of glucocorticoids on gluconeogenesis.

Gluconeogenesis is a fundamental metabolic pathway that synthesizes glucose from non-carbohydrate sources (lactate, glycerol, and glucogenic amino acids). It primarily supplies energy to glucose-dependent tissues such as the brain, erythrocytes, and renal medulla during conditions of increased glucose demand such as; fasting, stress, and intense exercise (Kuo, McQueen, Chen, & Wang, 2015). GCs stimulate this process by increasing the transcription of key enzymes of gluconeogenesis, such as phosphoenolpyruvate carboxylase (PEPCK) and glucose-6-phosphatase (G6Pase), in the liver and renal cortex (Shah & Wondisford, 2023). The transactivation of enzymes such as PEPCK and G6Pase occurs through the binding of the activated glucocorticoid receptor (GR) to glucocorticoid response elements (GREs) in DNA (Ratman et al., 2013). Chronic GC exposure increases the risk of insulin resistance and type 2 diabetes due to excessive stimulation of gluconeogenesis. This process is not only related to gluconeogenesis but also to the suppression of glucose transporter 4 (GLUT4) translocation (Sakoda et al., 2000). Additionally the use of amino acids for gluconeogenesis triggers protein catabolism and may leads to muscle mass loss (sarcopenia) (Oray, Abu Samra, Ebrahimiadib, Meese, & Foster, 2016). Considering these effects, GCs are beneficial for energy mobilization in acute conditions but cause metabolic disorders in chronic conditions and may exacerbate existing metabolic disorders.

Clinically, the effects of glucocorticoids on energy metabolism have both therapeutic and adverse outcomes. Their life-saving effects have been proven in acute inflammatory conditions and/or severe respiratory diseases such as COVID-19 (The RECOVERY Collaborative Group, 2021). However, chronic use is associated with serious side effects such as metabolic syndrome, type 2 diabetes, cardiovascular diseases, and osteoporosis (Noetzlin, Breville, Seebach, & Gastaldi, 2022; Oray et al., 2016; Saag, Furst, & Barnes, 2022). These side effects stem from a combination of excessive stimulation of gluconeogenesis, imbalances in fatty acid metabolism, and the intracellular effects of GR. While the current literature has significantly illuminated the molecular mechanisms of glucocorticoids, there is many unanswered questions regarding tissue-specific effects and long-term outcomes.

This review aims to provide new perspectives for basic science and clinical research by thoroughly examining the biochemical effects of glucocorticoids on gluconeogenesis in the light of current and high-impact studies.

Pharmacological Properties of Glucocorticoids

Glucocorticoids, both endogenous (cortisol, corticosterone) and synthetic (dexamethasone, prednisone, methylprednisolone), play an important role in clinical use due to their pharmacological anti-inflammatory, immunosuppressive, and metabolic effects.

These molecules exert critical functions in physiological processes such as; the regulation of the stress response, suppression of inflammatory processesand maintenance of energy homeostasis (Barnes, 2011; Becker, 2013; Şengül & Çadırcı, 2023). The pharmacological properties of glucocorticoids depend on their GR binding affinity, pharmacokinetic profiles, tissue-specific effects, and interactions with metabolic pathways. These properties enable the therapeutic use of glucocorticoids in conditions such as rheumatoid arthritis, systemic lupus erythematosus, allergic reactions, prevention of organ transplant rejection, and severe COVID-19 cases, while also potentially causing serious side effects such as insulin resistance, hyperglycemia, dyslipidemia, and osteoporosis (Alexaki & Henneicke, 2021; Barnes, 2011; Becker, 2013; Compston, 2018; Lim, Kohli, & Bloom, 2017; Morand, Fernandez-Ruiz, Blazer, & Niewold, 2023; Noetzlin et al., 2022; Oray et al., 2016; Youssef, Novosad, & Winthrop, 2016). In this section, we will summarize the pharmacological properties of GCs to shed light on their relationship with gluconeogenesis.

GCs bind to the inactive GR in the cell cytoplasm. GR is a member of the nuclear receptor superfamily. This receptor forms a multiprotein complex consisting of molecules such as heat shock proteins (HSP90, HSP70, HSP40, HSP56), immunophilins (FKBP51, FKBP52), p23, and Src, which maintain the inactive conformation of GR when no ligand is bound (Heitzer, Wolf, Sanchez, Witchel, & DeFranco, 2007; Oakley & Cidlowski, 2013; Pratt & Toft, 1997). Binding of the GC molecule to GR induces a conformational change in the receptor, which triggers the dissociation of the HSP complex and exposes GR's nuclear localization signals (NLS) (Vandevyver, Dejager, & Libert, 2012). Additionally, FKBP51 in the GR complex converts in FKBP52, facilitating GR interaction with the dynein molecular motor complex (Echeverria & Picard Didier, 2010; Storer, Dickey, Galigniana, Rein, & Cox, 2011; Vandevyver et al., 2012). Once activated, GR is transported along microtubules via dynein to the nuclear pore complex and translocated into the nucleus with the help of nuclear carrier proteins. This process is regulated by post-translational modifications such as sumoylation, ubiquitination, and phosphorylation (Duma, Jewell, & Cidlowski, 2006; Vandevyver et al., 2012). Within the nucleus, GR binds to GRE and activates the transcription of anti-inflammatory proteins (Clark & Belvisi, 2012; Surjit et al., 2011). Additionally, GR binds to negative GREs, directly suppressing the transcription of pro-inflammatory genes and playing a role in inhibiting cytokine and chemokine production (Surjit et al., 2011). Furthermore, GCs can suppress pro-inflammatory transcription factors, including nuclear factor kappa B (NF-κB), activator protein-1 (AP-1), cAMP response element-binding protein (CREB), nuclear factor of activated T cells (NFAT), signal transducer and activator of transcription proteins (STAT3 and STAT6), and interferon regulatory factor 3 (IRF3). This occurs through direct protein–protein interactions without binding directly to DNA, a mechanism known as transrepression (Ratman et al., 2013; Reichardt et al., 2001). In addition to these genomic anti-inflammatory effects, membrane-bound GR variants alter cellular signaling pathways through a non-genomic mechanism and exhibit acute anti-inflammatory and immunosuppressive effects that can occur within minutes (Boldizsar et al., 2010; Panettieri et al., 2019).

The pharmacological effects of glucocorticoids are not limited to the suppression of inflammation and regulation of the immune response, but also play a decisive role at various levels of energy metabolism (Vegiopoulos & Herzig, 2007). The genomic effects that arise following GR activation regulate the transcriptional levels of various metabolic genes. This results in the stimulation of pathways that increase energy production, such as gluconeogenesis, and the suppression of insulin signaling in peripheral tissues (Sacta, Chinenov, & Rogatsky, 2016). On the other hand, the non-genomic effects of GR also contribute to the rapid activation of processes such as hepatic glucose production and lipolysis by modulating intracellular signaling pathways (Kuo et al., 2015; Peckett, Wright,

& Riddell, 2011; Xu et al., 2009). These dual-action mechanisms explain why glucocorticoids play such a central role in physiological adaptations that redistribute energy substrates during the stress response. From this point of view, in addition to the regulatory effects of glucocorticoids on gluconeogenesis, a detailed examination of their metabolic implications on fatty acid oxidation is of great importance for better understanding the contribution of these hormones to energy homeostasis.

Glucocorticoids and Hepatic Gluconeogenesis

GCs are among the key regulators of gluconeogenesis in the liver. They play a critical role in maintaining blood glucose homeostasis, especially during fasting, stress, and inflammatory response. The regulatory effect of these steroid hormones on gluconeogenesis is mediated by several mechanisms.

GCs act by directly activating the expression of genes encoding key enzymes of gluconeogenesis (Rose & Herzig, 2013). This effect, mediated through the genomic pathway, is initiated by activated GR translocating into the nucleus and binding to GRE in the promoter regions of target genes (Ratman et al., 2013). The major gluconeogenic enzymes whose transcription is increased by GR include PEPCK and G6Pase (Imai, Miner, Mitchell, Yamamoto, & Granner, 1993; Pedersen et al., 2007; Vander Kooi et al., 2005). Increased expression of these enzymes, which catalyze rate-limiting steps of gluconeogenesis, results in accelerated glucose synthesis from gluconeogenic substrates such as pyruvate and lactate (Hers & Hue, 1983). The PEPCK gene (PCK1) is among the best characterized targets of GC regulation. GREs present in human and rodent PCK1 promoters markedly increase gene transcription in response to GCs (Friedman, 1994; Wang et al., 2004). The effect of GCs on gluconeogenesis is not limited to direct GRE binding but also involves interactions with other transcription factors and coactivators that regulate gluconeogenesis (Kuo et al., 2015). One of the most important interactions occurs between GR and Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α). PGC-1α is a transcription coactivator that plays a central role in the control of gluconeogenesis in the liver and is induced by GCs (Lin, Puigserver, Donovan, Tarr, & Spiegelman, 2002). Activated PGC-1α acts as a coactivator of transcription factors such as hepatic nuclear factor-4α (HNF-4α) and forkhead box O1 (FOXO1), further increasing the transcription of PEPCK and G6Pase genes (Puigserver et al., 2003). GkCs synergistically stimulate PGC-1α expression and indirectly regulate transcription factors such as HNF-4α and FOXO1 (Yoon et al., 2001). FOXO1, which is negatively regulated by insulin signaling, can be upregulated by GC administration and is a transcription factor that plays a key role in the regulation of gluconeogenesis (Kamagate et al., 2008; Lecker et al., 2004; Shi, Qiao, Mu, Zuo, & Yuan, 2017; Waddell et al., 2008). Furthermore, increased FOXO1 protein levels in chronic GC exposure contribute to insulin resistance (Beaupere, Liboz, Fève, Blondeau, & Guillemain, 2021).

GCs not only increase the expression of gluconeogenic enzymes but also enhance the efficiency of the metabolic pathway by increasing substrate availability for gluconeogenesis. This effect is mediated through stimulation of proteolysis and lipolysis in peripheral tissues (Finn & Dice, 2006; Magomedova & Cummins, 2015; Rose & Herzig, 2013). GCs increase protein degradation in skeletal muscle, allowing amino acids such as alanine, important precursors for gluconeogenesis, to reach the liver (Kuo et al., 2015). It also increases glycerol release by stimulating lipolysis in adipose tissue. Glycerol is used as a direct substrate for gluconeogenesis in the liver (Exton et al., 1972; Kuo et al., 2015; Xu et al., 2009). In a study, it was reported that dexamethasone administration increased amino acid transport to the liver but there was no increase in liver amino acid amount due to gluconeogenesis and the urea cycle (Okun et al., 2015).

The suppressive effect of insulin on gluconeogenesis and the stimulatory effect of GCs have an antag-

onistic relationship (Beaupere et al., 2021). Under normal conditions, insulin phosphorylates FOXO1 via phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, translocates it from the nucleus to the cytoplasm, and suppresses gluconeogenic gene expression (Sin, Yung, & Siu, 2015). At the molecular level, GCs reduce the expression of insulin receptor substrate-1 (IRS-1) and IRS-2 and consequently suppress the insulin-activated PI3K/Akt signaling pathway (Hu, Wang, In, Du, & Mitch, 2009; Xie, Perry, Espinoza, Zhang, & Price, 2018).

In addition to genomic effects, GCs also have non-genomic effects that provide rapid metabolic adaptations that can occur within minutes. Some of these rapid effects are mediated by membrane-bound GR or the interaction of GR with other signaling molecules in the cytoplasm (Song & Buttgereit, 2006). For example, GR phosphorylates activated protein kinase A (PKA); increases cAMP levels resulting in cAMP response element binding protein (CREB) phpsphorilation, which can rapidly induce the expression of PEPCK and G6Pase genes (Choi et al., 2017). They also can activate stress kinases such as p38 mitogen-activated protein kinase (MAPK) (Liu et al., 2024).

The activity of GCs at the tissue level is also regulated by the expression and activity of 11β-hydroxysteroid dehydrogenase (11β-HSD) enzymes (Chapman, Holmes, & Seckl, 2013). 11β-HSD1 and 11β-HSD2 are the two main isoforms and regulate cortisol-cortisone conversion in tissues (Krozowski, 1999). 11β-HSD1 is highly expressed in the liver and potentiates hepatic GC signaling by converting inactive GCs to their active forms (Chapman et al., 2013). In transgenic mice overexpressing liver-specific 11β-HSD1, PEPCK expression was increased, and insulin sensitivity was enhanced (Paterson et al., 2004). Another study reported that 11β-HSD1 knockout mice were protected from glucose intolerance, supporting that 11β-HSD1 enhances gluconeogenesis (Morgan et al., 2014). In another study, decreased activity of direct gluconeogenesis enzymes was observed in 11β-HSD1 knockout mice (Yao et al., 2017). The genomic and non-genomic pathways described in this section are shown in Figure 1.

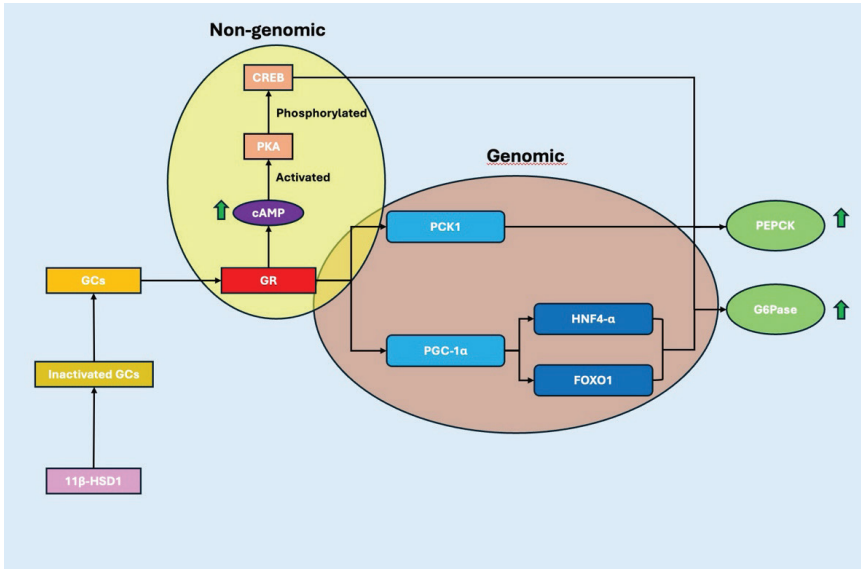

Figure 1. The effect of glucocorticoids on gluconeogenesis enzymes via genomic and non-genomic pathways. (GCs: Glucocorticoids, GR: Glucocorticoid Receptor, cAMP: cyclic Adenosine Monophosphate, CREB: cAMP Response Element-Binding protein, PKA: Protein Kinase A, PCK1: Phosphoenolpyruvate Carboxykinase 1, PGC-1α: Peroxisome Proliferator-activated receptor Gamma Coactivator 1-alpha, HNF4-α: Hepatocye Nuclear Factor 4-alpha, FOXO1: Forkhead box O transcription factor 1, 11β-HSD1: 11β-Hydroxysteroid Dehydrogenase type 1, PEPCK: Phosphoenolpyruvate Carboxykinase, G6Pase: Glucose-6-Phosphatase)

Overactivation of GCs on gluconeogenesis can be seen in a variety of pathological conditions and can exacerbate these pathological conditions, leading to metabolic imbalances. For example, in Cushing's syndrome, GCs excess increases glucose production by increasing the expression of gluconeogenesis enzymes in the liver, while suppressing insulin signaling in the liver and skeletal muscle, leading to insulin resistance (Pivonello et al., 2010). In addition, these metabolic changes can also lead to the development of type 2 diabetes over time (Di Dalmazi, Pagotto, Pasquali, & Vicennati, 2012). Therapeutic approaches targeting GC-mediated overactivation of gluconeogenesis include 11β-HSD1 inhibitors, GR antagonists, or selective inhibitors of gluconeogenic enzymes (Agius, 2007; Clark, 2008; Yuan et al., 2007). Clinical trials have shown that some 11β-HSD1 inhibitors improve insulin sensitivity and reduce hepatic glucose production (Anderson & Walker, 2013). Similarly, liver-specific G6Pase and fructose 1,6-bisphosphatase inhibitors are being investigated as potential targets for the treatment of diabetes (Agius, 2007). Recent technological advances enable more selective modulation of glucocorticoid signaling. Selective glucocorticoid receptor modulators (SGRMs) have the potential to reduce the stimulatory effects of glucocorticoids on gluconeogenesis and other potential side effects while preserving their anti-inflammatory effects (De Bosscher, Haegeman, & Elewaut, 2010). Preclinical studies suggest that these compounds may significantly reduce metabolic side effects (Sundahl, Bridelance, Libert, De Bosscher, & Beck, 2015).

GCs are complex and versatile regulators of the gluconeogenesis process in the liver, increasing glucose production both at the gene level and through cellular mechanisms. This regulation involves both the expression of gluconeogenic enzymes and the provision of substrates required for gluconeogenesis. However, the adverse effects of GCs on insulin signaling can lead to metabolic imbalances and insulin resistance, especially in long-term exposures. While local enzyme activities in the liver modulate the effects of these hormones, pathological conditions caused by excessive activation play an important role in the development of metabolic diseases. Therefore, selective modulation of glucocorticoid signaling and novel therapeutic strategies targeting this pathway are critical in the prevention and treatment of metabolic diseases.

Pathologies Associated with Glucocorticoid-Impaired Gluconeogenesis and Therapeutic Approaches

GCs induce hyperglycemia by increasing hepatic gluconeogenesis (upregulation of PEPCK and G6Pase expression), reducing insulin sensitivity in peripheral tissues and enhancing lipolysis and visceral adiposity in adipose tissue. These effects are dose- and duration-dependent and can emerge rapidly, within hours to days (Barker, Morrison, Llano, Sainsbury, & Jones, 2023). Clinical studies and guidelines report that the risk of hyperglycemia becomes particularly pronounced at doses exceeding the daily equivalent of 20 mg prednisolone, 50 mg hydrocortisone, or 4 mg dexamethasone; however, even low doses carry a risk for new-onset diabetes and metabolic dysregulation (Shah et al., 2022). In our previous study, we also demonstrated that serum glucose and vaspin levels increased in mice receiving prednisolone at doses of 5 mg/kg, 10 mg/kg and 20 mg/kg in a dose-dependent manner (Noyin, Akpinar, Cadirci, Cinar, & Aydin, 2018). Therefore, in patients with substantial steroid exposure (particularly those requiring inpatient care), early initiation of glucose monitoring and implementation of dose-specific glucose management algorithms—such as those described in the JBDS-IP guidelines—is recommended (Roberts et al., 2018). From the perspective of muscle tissue, GCs are known to cause proximal muscle weakness and myopathy when used at high doses (e.g., approximately 40 mg/day prednisolone or high-dose IV regimens) and/or over prolonged periods of weeks to months. Both clinical and preclinical evidence indicate that this effect is mechanistically linked to increased pro-

teolysis, inhibition of protein synthesis and activation of the ubiquitin–proteasome pathway (Wu, Michalski, Cortes, Rozenberg, & Mathur, 2022; Wu, Liu, & Sun, 2024). Consequently, metabolic adverse effects may further manifest as an impaired gluconeogenic response.

Strategies aimed at correcting GC-induced metabolic dysfunction largely focus on two major domains: first, pharmacological innovations (Selective glucocorticoid receptor modulators (SEGRAMs) and dissociative GR ligands, 11β-HSD1 inhibitors, tissue-targeted or nano-formulations) (Lesovaya et al., 2022; Othonos et al., 2023) and second, the implementation of steroid-sparing regimens in clinical practice (biologic agents, JAK inhibitors, etc.) alongside protocolized monitoring and prevention approaches (Hanberg & Miloslavsky, 2023; Kameda, 2023; Kubo, Nakayamada, & Tanaka, 2023).

Selective glucocorticoid receptor modulators (SEGRAMs) are designed to preferentially increase the GR-mediated transrepression of inflammatory transcription factors while decreasing the GRE-mediated transactivation of metabolic genes. Thus, they aim to separate anti-inflammatory effects from adverse metabolic consequences (Mao, Wei, & Chen, 2023). Among the earliest clinical examples of the SEGRAM approach, vamorolone has been evaluated at doses between 2–6 mg/kg/day in Duchenne muscular dystrophy and has shown the potential to provide a more favorable profile than conventional steroids regarding growth, bone health and metabolic adverse effects (Dang et al., 2024). Preclinical work with other selective GR modulators, such as the non-steroidal ligands Compound A and AL-438, has shown that selective GR binding profiles can skew signaling toward GR transrepression, supporting the potential for reduced glucocorticoid-induced side effects in inflammatory disease models (Doggrell, 2003; Drebert, Bracke, & Beck, 2015). GRM-01, another SEGRAM candidate, displays partial transactivation and robust anti-inflammatory efficacy with minimal effects on glucose regulation and bone metabolism in animal models, highlighting the feasibility of minimizing metabolic adverse effects via selective receptor modulation (Jakob, Hennen, Gautrois, Khalil, & Lockhart, 2025).

11β-HSD1 inhibitors aim to mitigate metabolic adverse effects by reducing the local peripheral activation of prednisolone and similar corticosteroids. Studies combining prednisolone with AZD4017 and related molecules have yielded data suggesting that these agents may attenuate prednisolone-associated metabolic disturbances (Othonos et al., 2023).

JAK inhibitors suppress JAK/STAT-mediated cytokine signaling by targeting JAK1, JAK2, JAK3, and TYK2 isoforms with distinct selectivity profiles (Kameda, 2023). The principal agents approved for the treatment of rheumatoid arthritis include the pan-JAK inhibitor tofacitinib, the JAK1/2 inhibitor baricitinib, the selective JAK1 inhibitors upadacitinib and filgotinib and the predominantly JAK3-targeting agent peficitinib (Kameda, 2023; Kubo et al., 2023). These agents inhibit the signaling of pro-inflammatory mediators, particularly interleukin-6 (IL-6) and interferons, thereby reducing inflammatory cell activation and cytokine production within the synovium. Moreover, JAK inhibitors are considered to possess steroid-sparing potential and may contribute to reducing long-term glucocorticoid exposure (Kubo et al., 2023).

Although nanotechnology-based GC delivery systems may enhance drug bioavailability in target tissues by overcoming physiological barriers while reducing systemic toxicity, challenges in manufacturing and risks of biological accumulation currently limit their translational applicability (Cui et al., 2025).

The main treatment strategies aimed at mitigating GC-related side effects are systematically summarized in Table 1.

Table 1. Overview of therapeutic strategies targeting glucocorticoid-related metabolic adverse effects.

Strategy Category	Mechanistic Target	Representative Agents	Advantages Compared with Conventional Glucocorticoids	References
Selective GR Modulators (SEGRAMs / Dissociative GR ligands)	Selective enhancement of GR-mediated transrepression of pro-inflammatory transcription factors while minimizing GRE-dependent transactivation of metabolic genes.	Vamorolone Compound A AL-438 GRM-01	Preserve anti-inflammatory efficacy while reducing GRE-driven transcription of gluconeogenic genes; improved growth and bone safety profile; attenuated metabolic adverse effects, including hyperglycemia	(Dang et al., 2024; Doggrell, 2003; Drebert et al., 2015; Jakob et al., 2025; Mao et al., 2023)
11β-HSD1 Inhibitors	Inhibition of peripheral cortisol/prednisolone activation	AZD4017	Reduce local hepatic activation of glucocorticoids, thereby attenuating prednisolone-associated dysglycemia and limiting excessive stimulation of hepatic gluconeogenesis.	(Othonos et al., 2023)
JAK Inhibitors (Steroid-sparing strategy)	JAK/STAT pathway inhibition (JAK1/2/3)	Tofacitinib Baricitinib Upadacitinib Filgotinib Peficitinib	Enable reduction of cumulative glucocorticoid exposure through steroid-sparing regimens and decrease cytokine-driven insulin resistance and systemic metabolic burden.	(Kameda, 2023; Kubo et al., 2023)
Nano- or Tissue-Targeted GC Delivery Systems	Targeted drug delivery and reduced systemic exposure	Various nano-formulations	Improve tissue-specific bioavailability while minimizing systemic toxicity and widespread metabolic adverse effects.	(Cui et al., 2025)

In conclusion, although GC therapy remains indispensable due to its clinical benefits, its dose- and duration-dependent spectrum of adverse effects necessitates careful patient selection, early monitoring, preventive strategies and rigorous assessment of emerging pharmacological approaches. Furthermore, innovations such as SEGRAMs, 11β-HSD1 inhibitors and tissue-targeted formulations require extensive long-term safety and efficacy studies across broader indications.

CONCLUSION

This review has comprehensively examined the complex and multifaceted regulatory mechanisms of glucocorticoids on hepatic gluconeogenesis. Our analysis demonstrates how GCs control hepatic glucose production through both genomic and non-genomic pathways. At the genomic level, activated GR directly stimulates gene expression of key enzymes such as PEPCK and G6Pase, constituting the fundamental regulatory mechanism of gluconeogenesis. Synergistic interactions with transcription factors and coactivators, including PGC-1α, FOXO1 and HNF-4α, amplify the regulatory effects of GCs, enhancing metabolic pathway efficiency.

The effects of GCs on gluconeogenesis extend beyond enzyme expression to encompass substrate mobilization from peripheral tissues. Stimulation of protein breakdown in skeletal muscle and lipolysis in adipose tissue ensures delivery of essential precursors to the liver, meeting the substrate requirements of the metabolic pathway. However, the antagonistic effects of GCs on insulin signaling can lead to metabolic imbalances, particularly during chronic exposure. Suppression of IRS-1 and IRS-2 expression and inhibition of the PI3K/Akt signaling pathway play critical roles in insulin resistance development.

The modulation of tissue-level GC activity by the 11β-HSD1 enzyme provides an important mechanism for local control of hepatic glucocorticoid signaling. While overexpression of this enzyme enhances gluconeogenesis, its inhibition improves metabolic parameters. The rapid metabolic adaptations provided by non-genomic effects through the cAMP/PKA/CREB pathway underscore the critical role of GCs in acute stress situations.

Metabolic complications resulting from excessive GC activation in pathological conditions highlight the necessity for tight control of these hormones. The

glucose intolerance and type 2 diabetes development observed in Cushing's syndrome demonstrate the serious consequences of glucocorticoid signaling imbalance. These findings emphasize the importance of close monitoring of metabolic side effects during long-term glucocorticoid therapy.

Importantly, chronic or high-dose GC exposure can also disturb peripheral insulin sensitivity, promote lipolysis-driven substrate overload and induce muscle proteolysis, collectively worsening hepatic gluconeogenic responses. These adverse metabolic outcomes have encouraged the development of clinical monitoring strategies and steroid-sparing regimens in parallel with pharmacological innovations designed to reduce GC-associated toxicity.

From a therapeutic perspective, novel approaches, including 11β-HSD1 inhibitors, selective glucocorticoid receptor modulators and gluconeogenic enzyme inhibitors, show promising results. These strategies hold potential for reducing metabolic side effects while preserving the anti-inflammatory properties of GCs. The development of selective GR modulators particularly suggests that safer glucocorticoid therapies may be possible in the future.

In conclusion, the central role of glucocorticoids in hepatic gluconeogenesis regulation demonstrates the physiological importance of these hormones while showing that excessive activation can lead to metabolic diseases. Future research should focus on more selective modulation of GC signaling, development of tissue-specific targeting strategies and personalized treatment approaches. The findings presented in this review provide an important foundation for developing therapeutic strategies targeting glucocorticoid signaling in the prevention and treatment of metabolic diseases.

AUTHOR CONTRIBUTION STATEMENT

Y.A.A.: Literature research, Conceptualization, Preparing the study text; E.C. Conceptualization, Reviewing the text

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Agius, L. (2007). New hepatic targets for glycaemic control in diabetes. *Best Practice and Research in Clinical Endocrinology and Metabolism*, *21*(4), 587-605. doi:10.1016/j.beem.2007.09.001

Alexaki, V. I., & Henneicke, H. (2021). The Role of Glucocorticoids in the Management of COVID-19. *Hormone and Metabolic Research*, *53*(1), 9-15. doi:10.1055/a-1300-2550

Anderson, A., & Walker, B. R. (2013). 11β-HSD1 inhibitors for the treatment of type 2 diabetes and cardiovascular disease. *Drugs*, *73*(13). doi:10.1007/s40265-013-0112-5

Barker, H. L., Morrison, D., Llano, A., Sainsbury, C. A. R., & Jones, G. C. (2023). Practical Guide to Glucocorticoid Induced Hyperglycaemia and Diabetes. *Diabetes Therapy*, *14*(5), 937. doi:10.1007/S13300-023-01393-6

Barnes, P. J. (2011). Glucocorticosteroids: Current and future directions. *British Journal of Pharmacology*, *163*(1), 29-43. doi:10.1111/j.1476-5381.2010.01199.x

Beaupere, C., Liboz, A., Fève, B., Blondeau, B., & Guillemain, G. (2021). Molecular mechanisms of glucocorticoid-induced insulin resistance. *International Journal of Molecular Sciences*, *22*(2), 623. doi:10.3390/ijms22020623

Becker, D. E. (2013). Basic and clinical pharmacology of Glucocorticosteroids. *Anesthesia Progress*, *60*(1). doi:10.2344/0003-3006-60.1.25

Boldizsar, F., Talaber, G., Szabo, M., Bartis, D., Palinkas, L., Nemeth, P., & Berki, T. (2010). Emerging pathways of non-genomic glucocorticoid (GC) signalling in T cells. *Immunobiology*, *215*(7), 521-526. doi:10.1016/j.imbio.2009.10.003

Chapman, K., Holmes, M., & Seckl, J. (2013). 11β-hydroxysteroid dehydrogenases intracellular gate-keepers of tissue glucocorticoid action. *Physiological Reviews*, *93*(3). doi:10.1152/physrev.00020.2012

Choi, G. E., Lee, S. J., Lee, H. J., Ko, S. H., Chae, C. W., & Han, H. J. (2017). Membrane-associated effects of glucocorticoid on BACE1 upregulation and Aβ generation: Involvement of lipid raft-mediated CREB activation. *Journal of Neuroscience*, *37*(35). doi:10.1523/JNEUROSCI.0074-17.2017

Clark, A. R., & Belvisi, M. G. (2012). Maps and legends: The quest for dissociated ligands of the glucocorticoid receptor. *Pharmacology and Therapeutics*, *134*(1), 54-67. doi:10.1016/j.pharmthera.2011.12.004

Clark, R. (2008). Glucocorticoid Receptor Antagonists. *Current Topics in Medicinal Chemistry*, *8*(9). doi:10.2174/156802608784535011

Compston, J. (2018). Glucocorticoid-induced osteoporosis: an update. *Endocrine, 61*(1), 7-16. doi:10.1007/s12020-018-1588-2

Cui, L., Yang, Y., Hao, Y., Zhao, H., Zhang, Y., Wu, T., & Song, X. (2025). Nanotechnology-Based Therapeutics for Airway Inflammatory Diseases. *Clinical Reviews in Allergy & Immunology*, *68*(1). doi:10.1007/S12016-024-09019-W

Dang, U. J., Damsker, J. M., Guglieri, M., Clemens, P. R., Perlman, S. J., Smith, E. C., … Hoffman, E. P. (2024). Efficacy and Safety of Vamorolone Over 48 Weeks in Boys With Duchenne Muscular Dystrophy: A Randomized Controlled Trial. *Neurology*, *102*(5), e208112. doi:10.1212/WNL.0000000000208112/SUPPL_FILE/SUPPLEMENTARY_DATA1.PDF

De Bosscher, K., Haegeman, G., & Elewaut, D. (2010). Targeting inflammation using selective glucocorticoid receptor modulators. *Current Opinion in Pharmacology*, *10*(4), 497-504. doi:10.1016/j.coph.2010.04.007

De Guia, R. M., Rose, A. J., & Herzig, S. (2014). Glucocorticoid hormones and energy homeostasis. *Hormone Molecular Biology and Clinical Investigation*, *19*(2), 117-128. doi:10.1515/hmbci-2014-0021

The RECOVERY Collaborative Group. (2021). Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine*, *384*(8). doi:10.1056/nejmoa2021436

Di Dalmazi, G., Pagotto, U., Pasquali, R., & Vicennati, V. (2012). Glucocorticoids and type 2 diabetes: From physiology to pathology. *Journal of Nutrition and Metabolism*, *2012*. doi:10.1155/2012/525093

Doggrell, S. (2003). Is AL-438 likely to have fewer side effects than the glucocorticoids? *Expert Opinion on Investigational Drugs*, *12*(7), 1227–1229. doi:10.1517/13543784.12.7.1227

Drebert, Z., Bracke, M., & Beck, I. M. (2015). Glucocorticoids and the non-steroidal selective glucocorticoid receptor modulator, compound A, differentially affect colon cancer-derived myofibroblasts. *The Journal of Steroid Biochemistry and Molecular Biology*, *149*, 92–105. doi:10.1016/j.jsbmb.2015.02.002

Duma, D., Jewell, C. M., & Cidlowski, J. A. (2006). Multiple glucocorticoid receptor isoforms and mechanisms of post-translational modification. *Journal of Steroid Biochemistry and Molecular Biology*, *102*(1-5), 11-21. doi:10.1016/j.jsbmb.2006.09.009

Echeverria, P. C., & Picard Didier, D. (2010). Molecular chaperones, essential partners of steroid hormone receptors for activity and mobility. *Biochimica et Biophysica Acta - Molecular Cell Research*, *1803*(6), 641-649. doi:10.1016/j.bbamcr.2009.11.012

Exton, J. H., Friedmann, N., Wong, E. H., Brineaux, J. P., Corbin, J. D., & Park, C. R. (1972). Interaction of glucocorticoids with glucagon and epinephrine in the control of gluconeogenesis and glycogenolysis in liver and of lipolysis in adipose tissue. *Journal of Biological Chemistry*, *247*(11). doi:10.1016/s0021-9258(19)45180-6

Finn, P. F., & Dice, J. F. (2006). Proteolytic and lipolytic responses to starvation. *Nutrition*, *22*(7-8), 830-844. doi:10.1016/j.nut.2006.04.008

Friedman, J. E. (1994). Role of glucocorticoids in activation of hepatic PEPCK gene transcription during exercise. *American Journal of Physiology - Endocrinology and Metabolism*, *266*(4 Pt 1), E560-566. doi:10.1152/ajpendo.1994.266.4.e560

Hanberg, J. S., & Miloslavsky, E. M. (2023). Steroid sparing in vasculitis: Myth or reality? *Best Practice & Research. Clinical Rheumatology*, *37*(1). doi:10.1016/J.BERH.2023.101843

Heitzer, M. D., Wolf, I. M., Sanchez, E. R., Witchel, S. F., & DeFranco, D. B. (2007). Glucocorticoid receptor physiology. *Reviews in Endocrine and Metabolic Disorders*, *8*(4), 321-330. doi:10.1007/s11154-007-9059-8

Hers, H. G., & Hue, L. (1983). Gluconeogenesis and related aspects of glycolysis. *Annual Review of Biochemistry*, *52*. doi:10.1146/annurev.bi.52.070183.003153

Hu, Z., Wang, H., In, H. L., Du, J., & Mitch, W. E. (2009). Endogenous glucocorticoids and impaired insulin signaling are both required to stimulate muscle wasting under pathophysiological conditions in mice. *Journal of Clinical Investigation*, *119*(10). doi:10.1172/JCI38770

Imai, E., Miner, J. N., Mitchell, J. A., Yamamoto, K. R., & Granner, D. K. (1993). Glucocorticoid receptor-cAMP response element-binding protein interaction and the response of the phosphoenolpyruvate carboxykinase gene to glucocorticoids. *Journal of Biological Chemistry*, *268*(8). doi:10.1016/s0021-9258(18)53327-5

Jakob, F., Hennen, S., Gautrois, M., Khalil, F., & Lockhart, A. (2025). Novel selective glucocorticoid receptor modulator GRM-01 demonstrates dissociation of anti-inflammatory effects from adverse effects on glucose and bone metabolism. *Frontiers in Pharmacology*, *16*. doi:10.3389/fphar.2025.1542351

Kamagate, A., Qu, S., Perdomo, G., Su, D., Dae, H. K., Slusher, S., … Dong, H. H. (2008). FoxO1 mediates insulin-dependent regulation of hepatic VLDL production in mice. *Journal of Clinical Investigation*, *118*(6). doi:10.1172/JCI32914

Kameda, H. (2023). JAK inhibitors～overview～. *Immunological Medicine*, *46*(3), 108–111. doi:10.1080/25785826.2023.2183594

Krozowski, Z. (1999). The 11β-hydroxysteroid dehydrogenases: Functions and physiological effects. *Molecular and Cellular Endocrinology*, *151*(1–2). doi:10.1016/S0303-7207(98)00256-1

Kubo, S., Nakayamada, S., & Tanaka, Y. (2023). JAK inhibitors for rheumatoid arthritis. *Expert Opinion on Investigational Drugs*, *32*(4), 333–344. doi:10.1080/13543784.2023.2199919

Kuo, T., McQueen, A., Chen, T. C., & Wang, J. C. (2015). Regulation of glucose homeostasis by glucocorticoids. *Advances in Experimental Medicine and Biology*, *872*. doi:10.1007/978-1-4939-2895-8_5

Lecker, S. H., Jagoe, R. T., Gilbert, A., Gomes, M., Baracos, V., Bailey, J., … Goldberg, A. L. (2004). Multiple types of skeletal muscle atrophy involve a common program of changes in gene expression. *The FASEB Journal*, *18*(1). doi:10.1096/fj.03-0610com

Lesovaya, E. A., Chudakova, D., Baida, G., Zhidkova, E. M., Kirsanov, K. I., Yakubovskaya, M. G., & Budunova, I. V. (2022). The long winding road to the safer glucocorticoid receptor (GR) targeting therapies. *Oncotarget*, *13*(1), 408–424. doi:10.18632/ONCOTARGET.28191

Lim, M. A., Kohli, J., & Bloom, R. D. (2017). Immunosuppression for kidney transplantation: Where are we now and where are we going? *Transplantation Reviews*, *31*(1), 10-17. doi:10.1016/j.trre.2016.10.006

Lin, J., Puigserver, P., Donovan, J., Tarr, P., & Spiegelman, B. M. (2002). Peroxisome proliferator-activated receptor γ coactivator 1β (PGC-1β), a novel PGC-1-related transcription coactivator associated with host cell factor. *Journal of Biological Chemistry*, *277*(3). doi:10.1074/jbc.C100631200

Liu, H., Zhou, L., Wang, X., Zheng, Q., Zhan, F., Zhou, L., … Hua, F. (2024). Dexamethasone upregulates macrophage PIEZO1 via SGK1, suppressing inflammation and increasing ROS and apoptosis. *Biochemical Pharmacology*, *222*. doi:10.1016/j.bcp.2024.116050

Magomedova, L., & Cummins, C. L. (2015). Glucocorticoids and metabolic control. *Handbook of Experimental Pharmacology*, *233*. doi:10.1007/164_2015_1

Mao, L., Wei, W., & Chen, J. (2023). Biased regulation of glucocorticoid receptors signaling. *Biomedicine & Pharmacotherapy*, *165*, 115145. doi:10.1016/j.biopha.2023.115145

Morand, E. F., Fernandez-Ruiz, R., Blazer, A., & Niewold, T. B. (2023). Advances in the management of systemic lupus erythematosus. *BMJ*, *383*, e073980. doi:10.1136/bmj-2022-073980

Morgan, S. A., McCabe, E. L., Gathercole, L. L., Hassan-Smith, Z. K., Larner, D. P., Bujalska, I. J., … Lavery, G. G. (2014). 11β-HSD1 is the major regulator of the tissue-specific effects of circulating glucocorticoid excess. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(24). doi:10.1073/pnas.1323681111

Noetzlin, S., Breville, G., Seebach, J. D., & Gastaldi, G. (2022). Short-term glucocorticoid-related side effects and adverse reactions: a narrative review and practical approach. *Swiss Medical Weekly*, *152*, w30088. doi:10.4414/smw.2022.w30088

Noyin, K., Akpinar, E., Cadirci, E., Cinar, I., & Aydin, P. (2018). THE EFFECTS OF VARIOUS DOSES OF PREDNISOLONE ADMINISTRATION ON SERUM VASPIN LEVELS IN RATS. *Acta Endocrinologica (Bucharest, Romania : 2005)*, *14*(3), 320–323. doi:10.4183/AEB.2018.320

Oakley, R. H., & Cidlowski, J. A. (2013). The biology of the glucocorticoid receptor: New signaling mechanisms in health and disease. *Journal of Allergy and Clinical Immunology*, *132*(5), 1033-44. doi:10.1016/j.jaci.2013.09.007

Okun, J. G., Conway, S., Schmidt, K. V., Schumacher, J., Wang, X., de Guia, R., … Rose, A. J. (2015). Molecular regulation of urea cycle function by the liver glucocorticoid receptor. *Molecular Metabolism*, *4*(10). doi:10.1016/j.molmet.2015.07.006

Oray, M., Abu Samra, K., Ebrahimiadib, N., Meese, H., & Foster, C. S. (2016). Long-term side effects of glucocorticoids. *Expert Opinion on Drug Safety*, *15*(4), 457-465. doi:10.1517/14740338.2016.1140743

Othonos, N., Pofi, R., Arvaniti, A., White, S., Bonaventura, I., Nikolaou, N., … Tomlinson, J. W. (2023). 11β-HSD1 inhibition in men mitigates prednisolone-induced adverse effects in a proof-of-concept randomised double-blind placebo-controlled trial. *Nature Communications, 14*(1), 1025. doi:10.1038/s41467-023-36541-w

Panettieri, R. A., Schaafsma, D., Amrani, Y., Koziol-White, C., Ostrom, R., & Tliba, O. (2019). Non-genomic Effects of Glucocorticoids: An Updated View. *Trends in Pharmacological Sciences*, *40*(1), 38-49. doi:10.1016/j.tips.2018.11.002

Paterson, J. M., Morton, N. M., Fievet, C., Kenyon, C. J., Holmes, M. C., Staels, B., … Mullins, J. J. (2004). Metabolic syndrome without obesity: Hepatic overexpression of 11β-hydroxysteroid dehydrogenase type 1 in transgenic mice. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(18). doi:10.1073/pnas.0305524101

Peckett, A. J., Wright, D. C., & Riddell, M. C. (2011). The effects of glucocorticoids on adipose tissue lipid metabolism. *Metabolism: Clinical and Experimental*, *60*(11), 1500-1510. doi:10.1016/j.metabol.2011.06.012

Pedersen, K. B., Zhang, P., Doumen, C., Charbonnet, M., Lu, D., Newgard, C. B., … Scott, D. K. (2007). The promoter for the gene encoding the catalytic subunit of rat glucose-6-phosphatase contains two distinct glucose-responsive regions. *American Journal of Physiology - Endocrinology and Metabolism*, *292*(3). doi:10.1152/ajpendo.00510.2006

Pivonello, R., De Leo, M., Vitale, P., Cozzolino, A., Simeoli, C., De Martino, M. C., … Colao, A. (2010). Pathophysiology of diabetes mellitus in Cushing's syndrome. *Neuroendocrinology*, *92*(Suppl 1), 77-81. doi:10.1159/000314319

Pratt, W. B., & Toft, D. O. (1997). Steroid receptor interactions with heat shock protein and immunophilin chaperones. *Endocrine Reviews*, *18*(3), 306-360. doi:10.1210/er.18.3.306

Puigserver, P., Rhee, J., Donovan, J., Walkey, C. J., Yoon, J. C., Oriente, F., … Spiegelman, B. M. (2003). Insulin-regulated hepatic gluconeogenesis through FOXO1-PGC-1α interaction. *Nature*, *423*(6939). doi:10.1038/nature01667

Ratman, D., Vanden Berghe, W., Dejager, L., Libert, C., Tavernier, J., Beck, I. M., & De Bosscher, K. (2013). How glucocorticoid receptors modulate the activity of other transcription factors: A scope beyond tethering. *Molecular and Cellular Endocrinology*, *380*(1-2), 41-54. doi:10.1016/j.mce.2012.12.014

Reichardt, H. M., Tuckermann, J. P., Göttlicher, M., Vujic, M., Weih, F., Angel, P., … Schütz, G. (2001). Repression of inflammatory responses in the absence of DNA binding by the glucocorticoid receptor. *EMBO Journal*, *20*(24). doi:10.1093/emboj/20.24.7168

Roberts, A., James, J., Dhatariya, K., Agarwal, N., Brake, J., Brooks, C., … Winocour, P. (2018). Management of hyperglycaemia and steroid (glucocorticoid) therapy: a guideline from the Joint British Diabetes Societies (JBDS) for Inpatient Care group. *Diabetic Medicine : A Journal of the British Diabetic Association*, *35*(8), 1011–1017. doi:10.1111/DME.13675

Rose, A. J., & Herzig, S. (2013). Metabolic control through glucocorticoid hormones: An update. *Molecular and Cellular Endocrinology*, *380*(1–2). doi:10.1016/j.mce.2013.03.007

Saag, K. G., Furst, D. E., & Barnes, P. J. (2022). Major side effects of inhaled glucocorticoids. *UpToDate*.

Sacta, M. A., Chinenov, Y., & Rogatsky, I. (2016). Glucocorticoid Signaling: An Update from a Genomic Perspective. *Annual Review of Physiology*, *78*, 155-180. doi:10.1146/annurev-physiol-021115-105323

Sakoda, H., Ogihara, T., Anai, M., Funaki, M., Inukai, K., Katagiri, H., … Asano, T. (2000). Dexamethasone-induced insulin resistance in 3T3-L1 adipocytes is due to inhibition of glucose transport rather than insulin signal transduction. *Diabetes*, *49*(10). doi:10.2337/diabetes.49.10.1700

Şengül, E., & Çadirci, E. (2023). Kortikotropin salgılatıcı hormon ve kanser. In H. T. Akkoyun, M. Bayramoğlu Akkoyun, Ş. Melek (Eds.), *Sağlık Bilimleri Alanında Uluslararası Akademik Çalışmalar ve Teorik Bilgiler-I* (pp.15-28). Ankara: İKSAD Yayınevi.

Shah, A., & Wondisford, F. E. (2023). Gluconeogenesis Flux in Metabolic Disease. *Annual Review of Nutrition, 43*, 153-177. doi:10.1146/annurev-nutr-061121-091507

Shah, P., Kalra, S., Yadav, Y., Deka, N., Lathia, T., Jacob, J. J., … Das, S. (2022). Management of Glucocorticoid-Induced Hyperglycemia. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *15*, 1577. doi:10.2147/DMSO.S330253

Sharma, V. K., & Singh, T. G. (2019). Chronic Stress and Diabetes Mellitus: Interwoven Pathologies. *Current Diabetes Reviews*, *16*(6). doi:10.2174/1573399815666191111152248

Shi, Y., Qiao, J., Mu, B., Zuo, B., & Yuan, J. (2017). 3-(2-amino-ethyl)-5-[3-(4-butoxyl-phenyl)-propylidene]-thiazolidine-2,4-dione (K145) ameliorated dexamethasone induced hepatic gluconeogenesis through activation of Akt/FoxO1 pathway. *Biochemical and Biophysical Research Communications*, *493*(1). doi:10.1016/j.bbrc.2017.09.029

Sin, T. K., Yung, B. Y., & Siu, P. M. (2015). Modulation of SIRT1-foxo1 signaling axis by resveratrol: Implications in skeletal muscle aging and insulin resistance. *Cellular Physiology and Biochemistry*, *35*(2), 541-552. doi:10.1159/000369718

Song, I. H., & Buttgereit, F. (2006). Non-genomic glucocorticoid effects to provide the basis for new drug developments. *Molecular and Cellular Endocrinology*, *246*(1–2). doi:10.1016/j.mce.2005.11.012

Storer, C. L., Dickey, C. A., Galigniana, M. D., Rein, T., & Cox, M. B. (2011). FKBP51 and FKBP52 in signaling and disease. *Trends in Endocrinology and Metabolism*, *22*(12), 481-90. doi:10.1016/j.tem.2011.08.001

Sundahl, N., Bridelance, J., Libert, C., De Bosscher, K., & Beck, I. M. (2015). Selective glucocorticoid receptor modulation: New directions with non-steroidal scaffolds. *Pharmacology and Therapeutics*, *152*, 28-41. doi:10.1016/j.pharmthera.2015.05.001

Surjit, M., Ganti, K. P., Mukherji, A., Ye, T., Hua, G., Metzger, D., … Chambon, P. (2011). Widespread negative response elements mediate direct repression by agonist-liganded glucocorticoid receptor. *Cell*, *145*(2). doi:10.1016/j.cell.2011.03.027

Vander Kooi, B. T., Onuma, H., Oeser, J. K., Svitek, C. A., Allen, S. R., Vander Kooi, C. W., … O'Brien, R. M. (2005). The glucose-6-phosphatase catalytic subunit gene promoter contains both positive and negative glucocorticoid response elements. *Molecular Endocrinology*, *19*(12). doi:10.1210/me.2004-0497

Vandevyver, S., Dejager, L., & Libert, C. (2012). On the Trail of the Glucocorticoid Receptor: Into the Nucleus and Back. *Traffic*, *13*(3), 364-374. doi:10.1111/j.1600-0854.2011.01288.x

Vandewalle, J., Luypaert, A., De Bosscher, K., & Libert, C. (2018). Therapeutic Mechanisms of Glucocorticoids. *Trends in Endocrinology and Metabolism*, *29*(1), 42-54. doi:10.1016/j.tem.2017.10.010

Vegiopoulos, A., & Herzig, S. (2007). Glucocorticoids, metabolism and metabolic diseases. *Molecular and Cellular Endocrinology*, *275*(1-2), 43-61. doi:10.1016/j.mce.2007.05.015

Waddell, D. S., Baehr, L. M., Van Den Brandt, J., Johnsen, S. A., Reichardt, H. M., Furlow, J. D., & Bodine, S. C. (2008). The glucocorticoid receptor and FOXO1 synergistically activate the skeletal muscle atrophy-associated MuRF1 gene. *American Journal of Physiology - Endocrinology and Metabolism*, *295*(4). doi:10.1152/ajpendo.00646.2007

Wang, X. L., Herzog, B., Waltner-Law, M., Hall, R. K., Shiota, M., & Granner, D. K. (2004). The synergistic effect of dexamethasone and all-trans-retinoic acid on hepatic phosphoenolpyruvate carboxykinase gene expression involves the coactivator p300. *Journal of Biological Chemistry*, *279*(33). doi:10.1074/jbc.M403455200

Wu, K., Michalski, A., Cortes, D., Rozenberg, D., & Mathur, S. (2022). Glucocorticoid-induced myopathy in people with asthma: a systematic review. *Journal of Asthma*, *59*(7), 1396–1409. doi:10.1080/02770903.2021.1926488

Wu, M., Liu, C., & Sun, D. (2024). Glucocorticoid-Induced Myopathy: Typology, Pathogenesis, Diagnosis, and Treatment. *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones et Metabolisme*, *56*(5), 341–349. doi:10.1055/A-2246-2900

Xie, Y., Perry, B. D., Espinoza, D., Zhang, P., & Price, S. R. (2018). Glucocorticoid-induced CREB activation and myostatin expression in C2C12 myotubes involves phosphodiesterase-3/4 signaling. *Biochemical and Biophysical Research Communications*, *503*(3). doi:10.1016/j.bbrc.2018.07.056

Xu, C., He, J., Jiang, H., Zu, L., Zhai, W., Pu, S., & Xu, G. (2009). Direct effect of glucocorticoids on lipolysis in adipocytes. *Molecular Endocrinology*, *23*(8). doi:10.1210/me.2008-0464

Yao, F., Chen, L., Fan, Z., Teng, F., Zhao, Y., Guan, F., … Liu, Y. (2017). Interplay between H6PDH and 11β-HSD1 implicated in the pathogenesis of type 2 diabetes mellitus. *Bioorganic and Medicinal Chemistry Letters*, *27*(17). doi:10.1016/j.bmcl.2017.07.043

Yoon, J. C., Puigserver, P., Chen, G., Donovan, J., Wu, Z., Rhee, J., … Spiegelman, B. M. (2001). Control of hepatic gluconeogenesis through the transcriptional coaotivator PGC-1. *Nature*, *413*(6852). doi:10.1038/35093050

Youssef, J., Novosad, S. A., & Winthrop, K. L. (2016). Infection Risk and Safety of Corticosteroid Use. *Rheumatic Disease Clinics of North America*, *42*(1), 157-176. doi:10.1016/j.rdc.2015.08.004

Yuan, C., St. Jean, D. J., Liu, Q., Cai, L., Li, A., Han, N., … Fotsch, C. (2007). The discovery of 2-anilinothiazolones as 11β-HSD1 inhibitors. *Bioorganic and Medicinal Chemistry Letters*, *17*(22). doi:10.1016/j.bmcl.2007.09.070