



Fresh insights into glucocorticoid-induced diabetes mellitus and new therapeutic directions

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Abstract | Glucocorticoid hormones were discovered to have use as potent anti-inflammatory and immunosuppressive therapeutics in the 1940s and their continued use and development have successfully revolutionized the management of acute and chronic inflammatory diseases. However, long-term use of glucocorticoids is severely hampered by undesirable metabolic complications, including the development of type 2 diabetes mellitus. These effects occur due to glucocorticoid receptor activation within multiple tissues, which results in inter-organ crosstalk that increases hepatic glucose production and inhibits peripheral glucose uptake. Despite the high prevalence of glucocorticoid-induced hyperglycaemia associated with their routine clinical use, treatment protocols for optimal management of the metabolic adverse effects are lacking or underutilized. The type, dose and potency of the glucocorticoid administered dictates the choice of hypoglycaemic intervention (non-insulin or insulin therapy) that should be provided to patients. The longstanding quest to identify dissociated glucocorticoid receptor agonists to separate the hyperglycaemic complications of glucocorticoids from their therapeutically beneficial anti-inflammatory effects is ongoing, with selective glucocorticoid receptor modulators in clinical testing. Promising areas of preclinical research include new mechanisms to disrupt glucocorticoid signalling in a tissue-selective manner and the identification of novel targets that can selectively dissociate the effects of glucocorticoids. These research arms share the ultimate goal of achieving the anti-inflammatory actions of glucocorticoids without the metabolic consequences.

Cortisol is a human glucocorticoid hormone that is essential for survival under periods of stress¹. In 1949, exogenous glucocorticoid supplementation for patients with rheumatoid arthritis was shown to provide pain relief². This discovery led to the recognition that glucocorticoids have potent anti-inflammatory and immunosuppressive effects and fuelled their use as therapeutics in a variety of immune-associated disorders and to prevent organ transplant rejection³. At present, ~1% of the general population receive oral glucocorticoids, with this prevalence increasing to 2.5% among older adults aged 70–79 years^{4,5}. Glucocorticoid use has gained prominence during the COVID-19 pandemic as dexamethasone, one of the most potent glucocorticoid drugs available on the market, is effective in the treatment of patients with severe COVID-19 (REF.⁶) (BOX 1).

Despite excellent therapeutic efficacy for the treatment of inflammatory disorders, long-term glucocorticoid therapy is limited by a wide range of adverse effects⁷. Relevant to this Review, glucocorticoids precipitate the

development of hyperglycaemia, insulin resistance, dyslipidaemia, central adiposity and hepatic steatosis. Over time, these metabolic effects result in diabetes mellitus (alternately referred to as ‘steroid diabetes’), one of the most well-established adverse effects of hyperglucocorticoidism⁸. Globally, oral glucocorticoid use is linked to 2% of cases of new-onset diabetes mellitus⁹. When glucocorticoids were administered for 1–7 days to healthy individuals, insulin resistance and impaired glucose homeostasis were observed^{10,11}. Furthermore, a meta-analysis found that, in patients without pre-existing diabetes mellitus who were treated with glucocorticoids for more than 1 month, the incidence of glucocorticoid-induced hyperglycaemia is ~32% and the incidence of diabetes mellitus is 19%¹². In patients with pre-existing diabetes mellitus, hyperglycaemia can be exacerbated by starting glucocorticoid treatment¹³. Of note, in Cushing syndrome, endogenous overproduction of cortisol produces similar complications to those of iatrogenic hypercortisolism¹⁴.

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Key points

- Glucocorticoid drugs are widely prescribed to treat inflammatory diseases and to prevent organ transplant rejection yet they promote hyperglycaemia and diabetes mellitus.
- Glucocorticoid-induced hyperglycaemia manifests directly via glucocorticoid signalling in metabolic organs and tissues (liver, adipose tissue, muscle, bone and pancreatic β -cells) and indirectly via inter-organ hormone and metabolite flux.
- No single consensus exists with respect to optimal screening frequency for glucocorticoid-induced hyperglycaemia due to context-dependent factors, although analysis of postprandial glucose (not fasting glucose) is recommended.
- Hypoglycaemic agents (such as insulin sensitizers and insulin) can provide satisfactory glucose control but need to be tailored for differences in the dose and type of glucocorticoid used.
- Developing selective glucocorticoid modulators that dissociate the diabetogenic from the anti-inflammatory effects of glucocorticoids continues to be challenging; however, new pharmacological targets that prevent diabetogenic effects are on the horizon.

The prevalence of diabetes mellitus among patients with endogenous Cushing syndrome is 20–45%, with an additional 10–30% of patients exhibiting impaired glucose tolerance¹⁵.

Despite the widespread use of glucocorticoids and their tight association with hyperglycaemia and diabetes mellitus, a firm understanding of the underlying mechanisms and strategies to mitigate and manage these adverse effects are lacking. The actions of glucocorticoids are predominately mediated by the glucocorticoid receptor, which is localized in the cytoplasm of target tissues¹⁶. Upon glucocorticoid binding, the glucocorticoid receptor translocates to the nucleus and can directly bind to a homodimer to DNA sequences called glucocorticoid-response elements (GREs), which are located throughout the genome¹⁷. This binding to GREs is facilitated by co-regulatory proteins and histone modifiers. In addition, the ligand-bound glucocorticoid receptor can tether to other transcription factors to indirectly upregulate or downregulate gene expression¹⁸. Studies into mechanisms and treatments to minimize or prevent glucocorticoid-induced diabetes mellitus are ongoing and eagerly anticipated to improve the clinical experience of glucocorticoid users¹³.

In this Review, we summarize the epidemiology of glucocorticoid-induced hyperglycaemia and our current understanding of the diabetogenic actions of glucocorticoids within different organs that contribute to the development of glucocorticoid-induced diabetes mellitus. We then discuss current diagnostic criteria and treatment options based on the type and schedule

of glucocorticoid and the degree of hyperglycaemia established. Finally, we provide novel insights into promising preclinical approaches and potential targets on the horizon that could eliminate the diabetogenic effects of glucocorticoid drugs while preserving their anti-inflammatory effects.

Epidemiology

Exposure to even a single dose of exogenous glucocorticoids is associated with an abnormal elevation in blood concentrations of glucose in patients with or without pre-existing diabetes mellitus^{19,20}. Indeed, glucocorticoids exacerbate hyperglycaemia in a dose-dependent manner irrespective of prior history of diabetes mellitus^{21,22}. A retrospective review reported that 56% of hospitalized patients without a history of diabetes mellitus experienced at least one episode of hyperglycaemia (defined as blood glucose levels ≥ 200 mg/dl) after corticosteroid treatment²³. In patients treated with glucocorticoids for respiratory disease²⁴, renal disease²⁵, cancer²⁶, solid organ transplant²⁷ and rheumatoid arthritis²⁸, the incidence of new-onset glucocorticoid-induced diabetes mellitus ranges between 15% and 40%. Moreover, the incidence of glucocorticoid-induced hyperglycaemia might be underestimated because of a reliance on fasting blood levels of glucose for diagnosis (discussed later).

Effects of drug type and dosing regimen

The relative risk of any individual developing glucocorticoid-induced hyperglycaemia and diabetes mellitus is difficult to predict owing to the combination of doses, variable glucocorticoid potencies, routes of administration and duration of treatment that are used for different diseases. For the purpose of this Review, we use the following definitions: acute treatment, up to 24 h; short-term treatment, between 24 h to 2 weeks; long-term treatment, 2 weeks to 6 months or longer). Glucocorticoid preparations on the market vary in their pharmacological properties and duration of anti-inflammatory action²⁹. Relative to short-acting hydrocortisone (half-life of 8 h), intermediate-acting prednisolone (half-life of 16–36 h) and methylprednisolone (half-life of 18–40 h), which are the most commonly used glucocorticoids, are 4–5-fold more potent in their anti-inflammatory effect^{13,29}. The long-acting dexamethasone and betamethasone (both with a half-life of 36–54 h) are 25-fold more potent than hydrocortisone^{13,29}.

All common routes of administration for glucocorticoids (oral, inhalation and topical) are linked to an increased risk of hyperglycaemia when prescribed at high doses^{22,30–32}, yet oral corticosteroids confer the greatest risk due to their systemic exposure³³. Local injections of glucocorticoids (intra-articular or intra-lesional) also increase hyperglycaemia in patients with controlled diabetes mellitus^{34,35}. Glucocorticoids exert dose-dependent effects as demonstrated by odds ratios for eventual hypoglycaemic intervention (over a 90-day period) that ranged between 1.7 and 10.3 for daily oral hydrocortisone-equivalent doses starting at 20 mg per day and increasing to ≥ 120 mg per day, respectively²². In patients who underwent an organ transplant, the

Box 1 | Dexamethasone therapy for the treatment of severe COVID-19

Results reported by the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial and other clinical trials have highlighted the beneficial anti-inflammatory effect of dexamethasone (6 mg daily) in reducing the mortality of patients hospitalized with COVID-19 (REFS^{6,203}). However, reports have also indicated that COVID-19 increases the risk of developing incident diabetes mellitus²⁰⁴ and exacerbates hyperglycaemia in patients with diabetes mellitus, prediabetes and/or obesity²⁰⁵, which in turn will worsen overall COVID-19 disease progression²⁰⁶. The prevalence of glucocorticoid-induced hyperglycaemia in patients with COVID-19 is unknown, as yet. However, the development of hyperglycaemia as a result of dexamethasone therapy is anticipated to negatively influence the outcomes of patients with COVID-19 (REF. ²⁰⁷).

Box 2 | Risk factors for glucocorticoid-induced hyperglycaemia

- Type and dosage of glucocorticoids (strong and/or high dose)^{13,22,29,36}
- Route of administration (intravenous, oral and injectable glucocorticoids confer greater risk than inhaled ones)^{22,30–33}
- Dosing regimen (continuous)^{23,37}
- Advanced age (>60 years)^{24,25,38}
- High BMI (>25 kg/m²), abdominal obesity and/or hypertriglyceridaemia^{25,38,39}
- Prior history of impaired glucose tolerance, decreased insulin sensitivity and/or impaired fasting glucose^{40–43}
- HbA_{1c} (≥6.0%)⁴⁴
- Family history of diabetes mellitus^{45–48}
- Specific single-nucleotide polymorphisms⁴⁹
- Impaired renal function (estimated glomerular filtration rate <40 ml/min/1.73 m²)^{44,47}
- History of hypertension⁵⁰
- Cytomegalovirus infection³⁶
- Smoking³⁸
- Race and ethnicity (Black American individuals have increased risk)⁵¹
- Concomitant immunosuppressive (mycophenolate mofetil or calcineurin inhibitors) or diuretic (furosemide) medication^{36,50}

risk of developing post-transplant diabetes mellitus was also found to increase by 5% per 0.01 mg/kg per day increase in prednisolone dose administered by intravenous injection³⁶. Inhaled corticosteroids used at high doses (fluticasone at ≥1,000 µg per day) increased the incidence of diabetes mellitus by 34% in patients with respiratory disease³⁰. A positive correlation was also observed between the relative potency of a prescribed topical glucocorticoid and the incidence of diabetes mellitus in case–control studies of adults in Denmark and the UK³¹. Dosing regimen also contributes substantially to the precipitation of diabetes mellitus as the incidence of hyperglycaemia was 50% more frequent in patients with haematological diseases who received long-term continuous administration of glucocorticoids over 6-weeks compared with cyclic administration (5 days on, 15 days off)³⁷. Patients without a history of diabetes mellitus who experienced multiple episodes of hyperglycaemia after glucocorticoid therapy were found to be on comparatively longer corticosteroid regimens than those who experienced ≤1 episode of hyperglycaemia²³.

Other risk factors

Many factors are associated with the susceptibility of patients on glucocorticoid therapy to develop hyperglycaemia and diabetes mellitus (BOX 2). Older age (>60 years) is tightly linked to an increased risk of glucocorticoid-induced diabetes mellitus due to declining pancreatic β-cell function and increased glucose intolerance with age^{24,25,38}. High BMI (>25 kg/m²)³⁸, abdominal obesity and hypertriglyceridaemia³⁹ are other independent risk factors that contribute to glucocorticoid-induced diabetes mellitus²⁵. In addition, prior reductions in insulin sensitivity or deficient glucose-stimulated insulin secretion (GSIS)^{40,41}, prior glucose intolerance or impaired fasting levels of glucose^{42,43}, and high HbA_{1c} values (≥6.0%)⁴⁴ are further indicators of increased risk of glucocorticoid-induced diabetes mellitus.

The extent to which a family history of diabetes mellitus contributes to new-onset glucocorticoid-induced diabetes mellitus is still not clear. Several studies do report a positive link to a family history of diabetes mellitus^{45–47}. In a study that compared a cohort of patients with glucocorticoid-induced diabetes mellitus to

patients with type 2 diabetes mellitus (T2DM), a family history of diabetes mellitus was found in 35% versus 65% of patients, respectively⁴⁸. In 2021, specific single-nucleotide polymorphisms were shown to correlate with the development of hyperglycaemia in children receiving dexamethasone for the treatment of acute lymphoblastic leukaemia⁴⁹. Mechanistically, the single-nucleotide polymorphisms modified the genomic binding of the glucocorticoid receptor to metabolic genes in adipose and liver cells⁴⁹. Although these data are intriguing, they will need to be replicated in larger cohorts.

Other less well-studied risk factors include impaired renal function (estimated glomerular filtration rate <40 ml/min/1.73 m²)^{44,47}, presence of hypertension⁵⁰, cytomegalovirus infection³⁶, current smoking³⁸, and race and ethnicity⁵¹. No consistent sex differences were observed in glucocorticoid-induced insulin resistance in healthy individuals⁵² or hospital inpatients⁴⁴. However, a trend was observed towards an increased incidence of glucocorticoid-induced hyperglycaemia in hospitalized men³⁸. The incidence of glucocorticoid-induced hyperglycaemia might also be confounded by the use of concomitant immunosuppressive or diuretic medications^{36,50}. Patients who underwent an organ transplant and received calcineurin inhibitors concurrent with glucocorticoid therapy would be expected to show more severe glucose intolerance than those not on calcineurin inhibitors due to the suppressive effect of calcineurin inhibitors on insulin production⁴⁸. Similarly, the concurrent use of the immunosuppressant mycophenolate mofetil with high-dose prednisolone treatment (≥1 mg/kg per day) in patients with systemic lupus erythematosus was associated with the development of diabetes mellitus, possibly explained by pancreatic β-cell dysfunction and impaired insulin secretion⁵⁰. Thus, several predictors beyond glucocorticoid potency, dose and dosing schedule should be considered when estimating the risk of developing glucocorticoid-induced diabetes mellitus.

Pathophysiology

The development of glucocorticoid-induced hyperglycaemia involves stimulation of hepatic glucose production and increased adipose tissue lipolysis followed by the development of whole-body insulin resistance as well as impaired production and secretion of insulin by pancreatic β-cells. Many of these effects are mediated by direct actions of the glucocorticoid receptor, which binds to specific target genes and controls their transcriptional expression. As described in this section, the tissue-specific effects of glucocorticoids contribute to amplifying their whole-body diabetogenic effect in vivo through inter-organ signalling (FIG. 1).

Liver

Hepatic gluconeogenesis. The liver serves as a central node that links nutritional and hormonal cues to whole-body glucose homeostasis. When circulating glucose is scarce, the liver maintains euglycaemia by increasing gluconeogenesis and glycogenolysis. During a period of stress, glucocorticoids promote increased liver glucose output to ensure that the organism has enough glucose to fuel the brain and survive⁵³. In response to increased

circulating levels of glucocorticoids, the liver upregulates enzymes involved in de novo glucose synthesis. Actions of glucocorticoids on other tissues accelerate the shuttling of gluconeogenic precursors to the liver through protein catabolism in skeletal muscle⁵⁴ and lipolysis in white adipose tissue (WAT)⁵⁵, which further drive hepatic gluconeogenesis.

At the molecular level, the glucocorticoid–glucocorticoid receptor complex binds DNA in hepatocytes to activate gene networks involved in the hepatic metabolism of carbohydrates. For gluconeogenesis, GREs are located in the respective promoters of the genes encoding two critical enzymes, phosphoenolpyruvate carboxykinase (PEPCK, encoded by *PCK1*) and glucose-6-phosphatase (G6Pase, encoded by *G6PCI*)^{56,57}. Activation of these glucocorticoid receptor target genes is only maximized when there is concurrent recruitment of other factors to the regulatory regions on DNA. For example, the co-regulator peroxisome proliferator-activated receptor coactivator 1 α (PGC1 α) and transcription factor Forkhead box protein O1 (FOXO1) are both directly regulated by glucocorticoids and synergistically potentiate activation of PEPCK^{53,58}.

Hepatic insulin resistance. A second key pathway contributing to glucocorticoid-induced hyperglycaemia is the development of hepatic insulin resistance. Under normal physiological conditions, insulin potently suppresses hepatic gluconeogenesis⁵⁹. However, in the presence of glucocorticoids, hepatic insulin resistance occurs, which enables gluconeogenesis to proceed unopposed due to the loss of insulin-mediated repression^{53,60}. Mechanistically, the phosphorylation of downstream signalling messengers of the insulin cascade (that is, insulin receptor substrates (IRSs), phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PKB)–AKT) was found to be impaired in rats treated with glucocorticoids⁶¹. Despite glucocorticoid-induced insulin resistance occurring within the gluconeogenic pathway, the pro-lipogenic effect of insulin remains intact⁶². Compensatory hyperinsulinaemia occurs in response to glucocorticoid-induced hyperglycaemia and, when this condition is paired with increased hepatic glucose delivery (from glucocorticoid-induced peripheral insulin resistance), synergistic stimulation of de novo lipogenesis and subsequent hepatic steatosis occurs, which in turn exacerbates hepatic insulin resistance in a vicious feed-forward cycle in both humans and animal models^{63,64}. Increased liver uptake of circulating non-esterified fatty acids (NEFAs) in the presence of glucocorticoids further precipitates gluconeogenesis and hepatic steatosis^{63,64}. Glucocorticoids also stimulate the biosynthesis of ceramide in the liver, a sphingolipid that is highly associated with hepatic insulin resistance⁶⁵.

Skeletal muscle

Muscle insulin signalling and glucose uptake. Skeletal muscle is the primary site where insulin-stimulated glucose uptake and glycogen storage occur postprandially⁶⁶. Glucocorticoids can directly disrupt insulin signalling in skeletal muscle by downregulating the expression and phosphorylation of IRS1, PI3K and PKB–AKT as shown

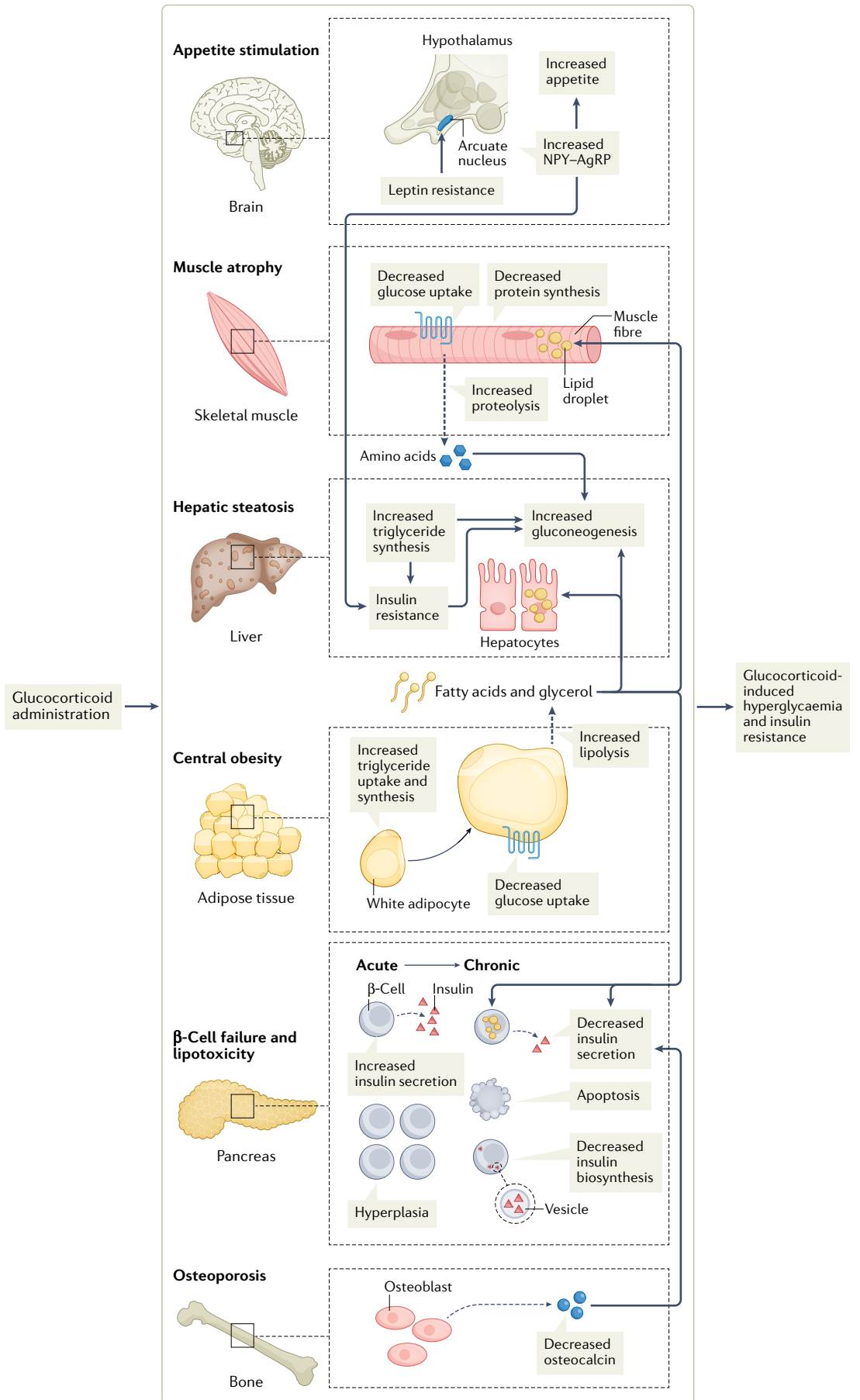
in rats^{67–69}. This effect results in concomitant inhibition of insulin-induced recruitment of glucose transporter 4 (GLUT4) to the cell surface of skeletal muscle⁷⁰. In mouse myotubes, GREs were identified in numerous genes that affect insulin signalling (such as *Pik3r1*, which encodes the p85 α subunit of PI3K⁷¹). Increases in p85 α abundance disrupt its normal interaction with IRS1. This disruption in insulin signalling indirectly decreases glycogen synthase kinase 3 phosphorylation⁶⁹, which clinically manifests as decreased levels of muscle glycogen occurring in patients who receive glucocorticoids after transplantation⁷². Thus, glucocorticoid exposure dampens skeletal muscle insulin sensitivity and glucose uptake, which contributes to the development of glucocorticoid-induced diabetes mellitus.

Development of myopathy. Patients under long-term exposure to glucocorticoid drugs (the length of time until muscle effects occur depends on dose but is generally 2–4-weeks) experience extensive skeletal muscle atrophy that results in the development of myopathy⁷³. Muscle mass is reduced by the combined effect of glucocorticoids to promote protein degradation within skeletal muscle while blunting protein synthesis⁵⁴. Glucocorticoids act by abolishing the transport of amino acids into muscle and also inhibit myogenesis by downregulating myogenin, therefore limiting protein synthesis⁵⁴. Furthermore, the stimulatory actions of insulin and insulin-like growth factor 1 (IGF1) on muscle anabolism are repressed by glucocorticoids through the inhibition of PKB–AKT phosphorylation and mammalian target of rapamycin (mTOR) phosphorylation^{54,74}. Synchronously, proteolysis is facilitated by glucocorticoid-mediated upregulation of atrophy-related gene networks in C2C12 mouse myoblasts, including *Fbxo32* (encoding atrogen 1)⁷⁵ and *Trim63* (encoding MuRF1)⁷⁶, members of the ubiquitin–proteasome system. Myostatin, a secreted factor that promotes muscle catabolism, is concurrently upregulated by glucocorticoids and attenuates the proliferation and differentiation of myoblasts⁵⁴. The effects of glucocorticoids on skeletal muscle were verified in healthy individuals who were treated for 3–6 days with high doses of glucocorticoid; in these individuals, serum levels of amino acids were elevated due to enhanced muscle proteolysis and blunted protein anabolism^{77,78}.

Increases in circulating levels of amino acids also indirectly hinder insulin-stimulated glucose transport and glycogen synthesis in muscle tissue⁷⁹. As described later, glucocorticoids also increase the circulation of NEFAs from adipose tissue lipolysis⁵⁵ and the ectopic accumulation of NEFAs in skeletal muscle further exacerbates insulin resistance⁸⁰. Moreover, the elevation of serum amino acids and NEFAs from glucocorticoid exposure provides substrates to the liver for gluconeogenesis.

White adipose tissue

Aberrant adipose tissue distribution and truncal obesity are hallmark clinical characteristics of patients with hypercortisolism⁸¹. Lipid redistribution from peripheral to abdominal adipose depots suggests that



◀ Fig. 1 | **The pathophysiology of glucocorticoid-induced hyperglycaemia and insulin resistance involves multi-organ crosstalk.** Glucocorticoids increase appetite and promote the intake of high-calorie (high-fat and/or high-sugar) 'comfort food', which indirectly promotes obesity and diabetes mellitus. Glucocorticoids upregulate the transcriptional and functional activity of neuropeptide Y (NPY)-agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus and promote leptin resistance. Skeletal muscle atrophy results from glucocorticoid-mediated protein degradation and decreased protein synthesis in myocytes, and glucocorticoids also decrease glucose uptake into these cells. In the liver, glucocorticoids act directly to upregulate enzymes involved in gluconeogenesis and promote hepatic insulin resistance, which together accelerate the development of hyperglycaemia. Furthermore, glucocorticoids synergize with insulin to stimulate non-esterified fatty acid (NEFA) uptake by hepatocytes and triglyceride synthesis in the liver, which causes hepatic steatosis. In adipose tissue, glucocorticoids increase adipogenesis, de novo lipogenesis and triglyceride synthesis as well as lipid uptake and storage. Concurrently, glucocorticoids facilitate lipolysis, which promotes the futile cycling of lipids. Glucocorticoids also decrease glucose uptake into adipocytes. Acute exposure of pancreatic β -cells to glucocorticoids can stimulate insulin secretion and β -cell hyperplasia to counterbalance glucocorticoid-induced insulin resistance and to maintain plasma levels of glucose within the physiological range. However, long-term exposure to glucocorticoids can interfere with insulin biosynthesis and secretion and induce β -cell apoptosis. Osteocalcin is secreted by osteoblasts and circulating osteocalcin from bone promotes insulin secretion by β -cells. Glucocorticoids suppress the expression of osteocalcin, thereby indirectly inhibiting insulin secretion. The increase in circulating levels of amino acids from muscle breakdown and NEFAs and glycerol from adipose tissue lipolysis provide substrates to the liver for gluconeogenesis. High plasma levels of NEFAs also accumulate ectopically in skeletal muscle, liver and β -cells, which further exacerbates insulin resistance. Thick solid arrows indicate effects; thin solid arrows indicate a transition in time; dashed arrows indicate secreted factors.

glucocorticoids induce depot-dependent adipose tissue breakdown and expansion, although the mechanisms are not fully understood⁸². Central obesity is linked to insulin resistance and the development of T2DM due to the anatomical location of hypertrophic WAT near the liver and direct drainage of NEFAs and pro-inflammatory factors into the portal circulation⁸³. Glucocorticoids promote adipogenesis, triglyceride synthesis and adipose hypertrophy, preferentially in the abdominal adipose depot⁸⁴. Of note, glucocorticoids are also an essential component of the differentiation cocktail used to transform preadipocytes into mature adipocytes *in vitro*⁸⁴. In mouse 3T3-L1 adipocytes, GREs are present near a wide range of genes involved in adipogenesis, de novo lipogenesis, triglyceride synthesis, and lipid transport and storage⁸⁵. In addition, the transcription factor Forkhead box A3 (a direct target of glucocorticoid receptor) binds to promoters of glucocorticoid receptor-regulated genes related to lipid metabolism and facilitates glucocorticoid receptor binding via chromatin remodelling, which leads to adipose expansion⁸⁶.

Lipid metabolism. Although de novo lipogenesis is only a minor contributor to the overall pool of triglycerides in adipose tissue⁸⁷, glucocorticoids can amplify lipogenesis in the presence of insulin⁸⁸. The additive or synergistic effect of glucocorticoids and insulin has also been shown to increase the expression and activity of lipoprotein lipase, an enzyme that hydrolyses circulating triglyceride-rich lipoproteins and provides local free fatty acids that are taken up by adipocytes⁸². Glucocorticoids have a greater effect on lipoprotein lipase in visceral versus subcutaneous adipose depots, thereby promoting lipid accumulation specifically in the abdominal region⁸⁴.

Intriguingly, despite contributing to lipid expansion, glucocorticoids concurrently increase triglyceride hydrolysis through upregulation of hormone-sensitive lipase and monoacylglycerol lipase, which promotes the futile cycling of lipids^{85,89}. The expression of genes involved in lipolysis is regulated by the direct binding of glucocorticoid receptors to GREs within these genes or indirectly via other transcription factors, including FOXO1 and FOXO3 (REFS^{82,85}). Glucocorticoids also promote lipolysis through upregulation of *ANGPTL4*, which encodes angiopoietin-like 4, an adipokine that stimulates the production of intracellular cAMP in adipocytes⁸². NEFA release is amplified by the permissive action of glucocorticoids on β -adrenergic-stimulated lipolysis, which occurs concurrently with the loss of insulin-mediated inhibition of lipolysis due to insulin resistance⁸⁴. Although some discrepant results have been reported in the literature (probably due to the concentration, duration of glucocorticoid treatment, adipose depot and/or species differences), short-term infusions of glucocorticoids (6–11 h) in humans increase serum levels of NEFA and glycerol^{90,91}. Increased levels of NEFA and glycerol promote hyperglycaemia by accelerating hepatic gluconeogenesis and impairing liver and muscle insulin sensitivity from ectopic lipid accumulation.

Insulin sensitivity. The effects of glucocorticoids on adipose tissue insulin sensitivity are species dependent. In rodent models, glucocorticoids decrease the phosphorylation of factors downstream of insulin receptor (IRS1, PI3K and PKB-AKT) and decrease insulin-receptor stimulated GLUT4 translocation^{92,93}. By contrast, increased insulin signalling and glucose uptake were observed with short-term (from 24 h to 7 days) glucocorticoid administration to human subcutaneous adipocytes^{94,95}. Notably, in humans, the subcutaneous adipose depot is comparatively sensitive to insulin relative to the insulin-resistant visceral adipose depot, independent of glucocorticoid use^{84,96}.

Glucocorticoids also indirectly affect whole-body insulin sensitivity by regulating the levels of adipokines secreted by WAT. For example, leptin and resistin are upregulated by glucocorticoids in WAT and promote insulin resistance^{8,84}.

WAT inflammation. Another consideration is the effect of glucocorticoids on adipose tissue inflammation. Adipose tissue macrophages are associated with insulin resistance in obesity⁹⁷. As glucocorticoids are globally anti-inflammatory, it is interesting that glucocorticoid treatment induces adipocyte hypertrophy and insulin resistance without increasing M1-like pro-inflammatory macrophage infiltration in adipose tissue under conditions of high-fat diet-induced obesity in mice⁹⁷. Interestingly, glucocorticoids were shown to influence mouse primary peritoneal macrophage polarization *in vitro*, increasing M2-like macrophage markers (*Cd206*) and decreasing M1-like macrophage markers (*Il6*)⁹⁸. In line with this observation, corticosterone treatment in mice promoted M2-macrophage infiltration into visceral (but not subcutaneous) adipose tissue, which was linked to impaired insulin sensitivity under a normal chow diet⁹⁸.

Further studies are warranted to better understand the mechanism of this macrophage–adipose tissue crosstalk.

Other adipose depots

Thermogenic adipose tissue. Brown adipocytes in brown adipose tissue (BAT) differ morphologically and functionally from white adipocytes in WAT by the presence of a high number of mitochondria, which promote non-shivering thermogenesis through the expression of UCP1. A third type of adipocyte, known as beige (or 'brite') adipocytes, is derived from the white adipocyte lineage and located within WAT, yet also expresses UCP1 (REF.⁹⁹).

A growing body of evidence, primarily from animal models, has demonstrated the potential of targeting BAT and the browning of WAT to combat obesity and T2DM⁹⁹. In rodents, glucocorticoids are known inhibitors of BAT and beige adipose tissue function that act, in part, to suppress energy expenditure by downregulating *Ucp1* (REFS^{100,101}). Suppression of *Ucp1* is enhanced by the overexpression of 11 β -HSD1 in mouse primary brown adipocytes¹⁰². This suppressive action of glucocorticoids is mediated by a regulatory region between –4 kb and 0 kb upstream of the *Ucp1* transcription start site as shown in mouse primary brown adipocytes¹⁰³. Glucocorticoids can also indirectly suppress *Ucp1* by inhibiting adrenocorticotrophic hormone (ACTH) secretion via feedback inhibition on the hypothalamic–pituitary–adrenal axis, and ACTH has been found to promote UCP1-dependent respiration in mouse primary brown adipocytes¹⁰⁴. Whether the glucocorticoid-mediated downregulation of *Ucp1* gene expression translates to a true decrease in the thermogenic capacity of BAT remains to be clarified¹⁰³. Intriguingly, acute glucocorticoid treatment in humans (three doses over 24 h) increased BAT activation (assessed by measuring supraclavicular skin temperature and cold-induced ¹⁸F-fluorodeoxyglucose uptake in BAT depots assessed by PET–CT), whereas long-term treatment (>2 weeks) suppressed glucose uptake in BAT compared with control individuals¹⁰⁵. Whether reversing glucocorticoid-associated suppression of BAT and WAT browning is sufficient to improve insulin sensitivity and obesity in humans remains to be determined.

Bone marrow adipose tissue. Adipocytes residing within the bone marrow have gained attention in the past decade as they were found to have a permissive role in contributing to metabolic diseases. Bone marrow adipose tissue (BMAT) is hypothesized to be metabolically distinct from BAT and WAT and accounts for ~70% of bone marrow volume, where BMAT critically functions to fill the long bone cavities in adult humans¹⁰⁶. However, the metabolic contribution of BMAT to whole-body metabolism remains poorly understood. Lipid content in bone marrow of premenopausal women is inversely correlated with whole-body insulin sensitivity¹⁰⁷. Moreover, decreased BMAT insulin responsiveness was reported in patients with obesity and T2DM¹⁰⁸. Glucocorticoids promote BMAT lipid accumulation without affecting glucose uptake into BMAT adipocytes, re-emphasizing the site-specific actions of glucocorticoids in adipose

depots¹⁰⁹. A better understanding of the effect of glucocorticoids in BMAT remains an exciting avenue for further investigation.

Pancreatic β -cells

Pancreatic β -cell dysfunction underlies the progression to T2DM¹¹⁰. Under acute physiological and/or pathological stress, where the demand for insulin is increased, β -cells adapt by enhancing their functional capacity to maintain euglycaemia within a narrow range. Long-term β -cell stress can result in systemic insulin resistance, which is later superseded by β -cell failure and consequent hyperglycaemia¹¹⁰. Studies that investigate the effects of glucocorticoids in isolated primary islets or in vitro systems are therefore unable to account for the adaptive responses observed in vivo.

In vitro and ex vivo studies. An inhibitory role of glucocorticoids on β -cell function was demonstrated using in vitro cell lines and rodent-derived pancreatic islets after acute (minutes to hours) treatment with glucocorticoids^{111,112}. In rat insulinoma INS-1E cells, glucocorticoids had a minimal effect on basal insulin release but GSIS was greatly reduced¹¹². The underlying mechanism is unclear as evidence of direct inhibition of the insulin secretory cascade is still under debate¹¹³. Under physiological conditions, the uptake of glucose by β -cells causes an increase in intracellular ATP levels that triggers closure of the ATP-sensitive K⁺ channels followed by depolarization of the β -cell membrane. This change in voltage enables the influx of Ca²⁺ and subsequent exocytosis of insulin granules¹¹⁴. Glucocorticoids are thought to interfere at several stages in this process by limiting glucose uptake and oxidation, facilitating futile cycling of glucose, repolarizing the β -cell membrane by enhancing K⁺ channel activity and in turn attenuating Ca²⁺ influx, and amplifying α 2-adrenergic signalling^{74,113,115}.

Apart from directly reducing insulin secretion, glucocorticoids also elicit inhibitory effects on insulin biosynthesis by inducing endoplasmic reticulum stress, which ultimately triggered apoptosis of INS-1E cells treated with glucocorticoids¹¹². Glucocorticoids might also increase cytotoxicity by accelerating the production of reactive oxygen species, which can also induce β -cell apoptosis¹¹⁶. Despite the potential for glucocorticoid-induced β -cell apoptosis, glucocorticoid-induced diabetes mellitus in humans was found to be more related to insulin resistance and β -cell dysfunction rather than to decreased β -cell mass¹¹⁷.

In vivo studies. Studies to identify the direct effects of glucocorticoids in vivo are particularly challenging to interpret owing to compensatory factors induced by long-term glucocorticoid exposure. A single oral dose of glucocorticoids acutely impaired insulin secretion in healthy individuals, whereas short-term treatment (up to 2 weeks) resulted in hyperinsulinaemia along with subtle changes in glycaemia^{111,118}. Healthy β -cells can increase insulin secretion to counterbalance glucocorticoid-induced insulin resistance as shown by increased β -cell function in rodent islets after in vivo glucocorticoid challenge (13 days)¹¹¹. Dexamethasone

treatment of rats (5 days) also increases Ca^{2+} -dependent protein kinase C α (PKC α) signalling in islets, enhances GSIS capacity, and increases docking and exocytosis of preformed insulin granules¹¹⁹. Hyperinsulinaemia induced by dexamethasone treatment in rats (5 days) is accompanied by the expansion of β -cell mass in a dose-dependent manner¹²⁰. However, in susceptible populations (such as those with obesity or a family history of T2DM), where β -cells are already overworked, the compensation by β -cells to a glucocorticoid challenge is lost^{41,46,121}. Short-term (2–5 days) exposure to glucocorticoids in these individuals decreases β -cell insulin secretion and whole-body glucose disposal^{41,46,121}. In agreement with these findings, GSIS was impaired with long-term (24 days) glucocorticoid treatment of obese Wistar and Zucker (fa/fa) rats, which led to the development of hyperglycaemia^{74,122}.

Interpreting the long-term effects of glucocorticoids on β -cells can also be confounded by the effect of the underlying inflammatory condition that the glucocorticoids are prescribed to treat^{74,123}. Intriguingly, high serum levels of cortisol (still within physiological range) are positively associated with β -cell defects and suppressed insulin secretion in the general population and in patients with Cushing syndrome^{124,125}. In addition to these mechanisms by which glucocorticoids directly induce β -cell failure, glucocorticoids also indirectly promote β -cell lipotoxicity due to high plasma levels of NEFAs⁷⁴.

Bone

Osteoporosis is one of the most well-established adverse effects of long-term glucocorticoid exposure (>3 months, osteoporosis risk depends on the dose)¹²⁶. Glucocorticoid-induced osteoporosis results from the dual action of glucocorticoids on the suppression of bone-forming osteoblasts and the differentiation and maturation of bone-resorbing osteoclasts¹²⁷. The effects of glucocorticoids on bone might contribute to hyperglycaemia in part due to elevated leptin secretion from adipose tissue as leptin suppresses the expression of osteocalcin, an insulin-sensitizing hormone that is secreted by osteoblasts¹²⁸. Intriguingly, mice that lack osteocalcin develop glucose intolerance and insulin resistance due to impaired pancreatic β -cell proliferation and insulin expression¹²⁹. Indeed, circulating levels of osteocalcin are associated with improved glycaemic control in patients with T2DM¹³⁰. Furthermore, a single dose of glucocorticoid in humans is correlated with reduced serum levels of osteocalcin¹³¹. Mice with decreased glucocorticoid signalling in osteoblasts (achieved through targeted overexpression of 11 β -HSD2 to inactivate endogenous glucocorticoids) had higher levels of circulating osteocalcin and were protected against glucocorticoid-induced glucose and insulin intolerance compared with glucocorticoid-treated wild-type mice¹³². These findings demonstrate a partial role for the skeleton in the regulation of energy metabolism.

Brain

The development of glucocorticoid-induced obesity and diabetes mellitus is also partially mediated through appetite stimulation in the arcuate nucleus

of the hypothalamus¹³³. Glucocorticoids upregulate the mRNA expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP) and increase the firing rate of their respective neurons, which stimulates appetite in rodents^{134,135}. In mice, local administration of glucocorticoids to the arcuate nucleus was shown to induce hepatic insulin resistance through NPY release and signalling via the sympathetic nervous system¹³⁶. Glucocorticoids stimulate leptin release from adipocytes into the circulation¹³⁷. Furthermore, under physiological conditions, leptin suppresses appetite via leptin receptor signalling in NPY–AgRP neurons, which inhibits the release of these orexigenic peptides¹³⁸. However, in rats, glucocorticoids were shown to synergistically antagonize the action of leptin by directly reducing leptin-dependent JAK–STAT signalling in the hypothalamus¹³⁹. Aside from their orexigenic effects, glucocorticoids also promote increased caloric intake by shifting food preference towards high-calorie food that is high in fat or sugar ('comfort food'). Rodents placed under restraint stress preferred lard and sucrose over normal chow¹⁴⁰. Similarly, individuals with elevated circulating levels of cortisol (occurring after a stressful task) prefer high-calorie 'comfort food' over food that is lower in sugar and fat¹⁴¹. Over time, this extra caloric intake could contribute to a substantial increase in adiposity.

Current treatment options

Prior to starting glucocorticoid treatment, patients should be evaluated for risk factors for hyperglycaemia, including age, BMI and family history, and should be screened for pre-existing diabetes mellitus (measurements of fasting plasma glucose and HbA_{1c})^{38,142}. At a minimum, plasma levels of glucose should be monitored 1–3 days after initiation of glucocorticoid treatment^{7,13}. The frequency of monitoring plasma levels of glucose will increase if the patient is in hospital and/or has pre-existing T2DM^{29,143}. Monitoring should continue at regular 3–6 month intervals for a year and then yearly thereafter⁷. The criteria for the diagnosis of glucocorticoid-induced diabetes mellitus are similar to other types of diabetes mellitus: fasting plasma glucose concentration ≥ 7.0 mM, random plasma concentration of glucose ≥ 11.1 mM, HbA_{1c} $\geq 6.5\%$ (48 mmol/mol) or plasma glucose concentration ≥ 11.1 mM 2 h after an oral glucose tolerance test (OGTT)¹⁴⁴. Glucocorticoid exposure has a more notable effect on postprandial glycaemia compared with fasting glucose¹³. Thus, the prevalence of glucocorticoid-induced hyperglycaemia is probably underestimated because fasting plasma glucose is more frequently assessed compared with the more time-consuming OGTT¹⁴⁵. Determination of postprandial glycaemia 2 h after lunch and/or OGTT provides the most ideal measure to diagnose glucocorticoid-induced diabetes mellitus^{13,146}. Treatment should be initiated when plasma levels of glucose are repeatedly ≥ 12 mM according to the management guideline established by the Joint British Diabetes Societies²⁹. The goal of hypoglycaemic treatment in glucocorticoid-induced hyperglycaemia is to achieve glucose levels ≤ 10 mM (REFS^{29,147}).

Table 1 | Hypoglycaemic agents in glucocorticoid-induced hyperglycaemia and diabetes mellitus

Drug class	Advantages	Disadvantages	Evidence in patients with glucocorticoid-induced diabetes mellitus	Suitable for type of glucocorticoid drug ^a
Sulfonylureas	Immediate onset of action	Long acting; high risk of hypoglycaemia; not specific to postprandial glucose	Improved fasting glucose ¹⁵⁰	Intermediate-acting (two or more daily doses) or long-acting glucocorticoids; intra-articular glucocorticoids
Glinides	Immediate onset of action; short acting; targets postprandial glucose; low risk of hypoglycaemia	Frequent dosing; high cost	Improved postprandial glucose ^{152,153} and mean glucose ¹⁵³ ; improved mean HbA _{1c} in combination with other immunosuppressants ¹⁵¹	Short-acting glucocorticoids
Incretin-based therapy: GLP1 receptor agonists	Immediate onset of action; targets postprandial glucose; low risk of hypoglycaemia	Limited evidence; gastrointestinal and renal adverse effects; high cost	Improved mean and postprandial glucose ^{157,158} ; reduced the insulin dose and injection frequency in combination with basal-bolus insulin ²⁰¹	Intermediate-acting or long-acting glucocorticoids
Incretin-based therapy: DPP4is	Immediate onset of action; targets postprandial glucose; low risk of hypoglycaemia	Contradictory evidence; high cost	Improved ^{159,160} or unaffected ^{161,162} postprandial glucose; improved mean glucose ¹⁶⁰ and HbA _{1c} levels ¹⁵⁹	Intermediate-acting or long-acting glucocorticoids
Metformin	Low risk of hypoglycaemia; low cost	Slow onset of action; avoid use in renal impairment	Improved postprandial glucose ¹⁶⁸ ; improved AUC of glucose during OGTT ²⁰² , fasting glucose and HbA _{1c} levels ¹⁶⁹	Intermediate-acting glucocorticoids
Thiazolidinediones	Low risk of hypoglycaemia	Slow onset of action; promotes weight gain (shared adverse effects with glucocorticoids)	Improved AUC of glucose during OGTT and HbA _{1c} levels ¹⁷³ in combination with insulin ¹⁷⁴	Intermediate-acting glucocorticoids
SGLT2is	Immediate onset of action; low risk of hypoglycaemia	Limited evidence; promotes bone fracture (shared adverse effects with glucocorticoids)	No improvement in mean glucose when used as an add-on to other hypoglycaemics ¹⁷⁵	Insufficient data (has not been tested without other hypoglycaemic agents)
α-Glucosidase inhibitors	Immediate onset of action; targets postprandial glucose; low risk of hypoglycaemia	Limited evidence; only provides weak hypoglycaemic effect	Improved postprandial glucose levels in combination with glinides ¹⁵²	Insufficient data (has not been tested without other hypoglycaemic agents)

AUC, area under the curve; DPP4is, dipeptidyl peptidase 4 inhibitors; GLP1, glucagon-like peptide 1; OGTT, oral glucose tolerance test; SGLT2is, sodium-glucose co-transporter type 2 inhibitors. ^aShort acting (for example, hydrocortisone, half-life of 8 h), intermediate acting (for example, prednisolone or methylprednisolone, half-life of 16–40 h), long acting (for example, dexamethasone or betamethasone, half-life of 36–54 h).

Few clinical trials have systematically investigated the efficacy of oral hypoglycaemic agents on glucocorticoid-induced hyperglycaemia. Currently, no one-size-fits-all consensus exists regarding the optimal treatment strategy for this condition owing to the myriad factors involved. Due to the slow onset of action and narrow flexibility in dose titration of many oral hypoglycaemic agents, it is difficult to match the hypoglycaemic agent to the hyperglycaemic oscillation induced by glucocorticoids¹³. Individualized treatments are needed that consider the type, dose, scheme and duration of action of the glucocorticoid used as well as underlying patient comorbidities, concurrent medication use and the severity of hyperglycaemia induced by glucocorticoid administration. Short- and intermediate-acting glucocorticoids (often administered transiently with a high initial dose and tapered over time) can lead to rapid and severe fluctuations in glycaemia, with peaks occurring within 4–8 h of the dose and decreasing during the night^{29,115}. In response to this, hypoglycaemic agents with high potency and rapid onset should be used to avoid the risk of nocturnal hypoglycaemia^{13,29}. For patients on long-acting glucocorticoids or those taking multiple daily doses,

hyperglycaemia can persist over 24 h. As such, treatments are favoured that have a long duration of action and enable flexibility in dose adjustments without exacerbating other glucocorticoid-dependent adverse effects¹⁴⁸. Treatments should be tailored to the pattern of glucocorticoid-induced hyperglycaemia by considering the type of glucocorticoid and the pharmacokinetics and pharmacodynamics of the different hypoglycaemic agents¹⁴⁵.

Non-insulin glucose-lowering therapies

Oral hypoglycaemic drugs are generally reserved for those experiencing mild glucocorticoid-induced hyperglycaemia (fasting plasma concentration of glucose <11.1 mM) without a history of diabetes mellitus or with well-controlled diabetes mellitus^{13,145}. Different hypoglycaemic treatment options have various advantages and disadvantages and considerations for use under different glucocorticoid treatment schemes (TABLE 1).

Sulfonylureas. Sulfonylureas act to increase insulin release from pancreatic β-cells by binding to and inhibiting ATP-sensitive K⁺ channels¹⁴⁹. Their mechanism and immediate onset of action is an asset as an

oral agent for the treatment of glucocorticoid-induced diabetes mellitus¹⁵⁰. However, they target fasting plasma levels of glucose rather than postprandial hyperglycaemia and, if used with short-acting glucocorticoids given as a single morning dose, their long effects and narrow therapeutic window result in a high risk of nocturnal hypoglycaemia¹⁴⁵. Therefore, sulfonylureas are not recommended for the management of glucocorticoid-induced hyperglycaemia and are only considered for patients treated with intermediate-acting or long-acting glucocorticoid preparations in two or more daily doses or intra-articular glucocorticoids^{13,38}.

Glinides. Glinides are secretagogues that stimulate insulin secretion while exerting a more rapid onset and shorter duration of action than sulfonylureas³⁸. As such, glinides provide improved flexibility in adapting to glucocorticoid-provoked postprandial hyperglycaemia and their use eliminates the possibility of nocturnal hypoglycaemia¹³. Glinides were shown to effectively manage blood levels of glucose in 14 out of 23 transplant recipients with new-onset diabetes mellitus that occurred after exposure to low dose glucocorticoids in combination with other immunosuppressants¹⁵¹. Retrospective studies further confirmed that glinides improved glucocorticoid-induced postprandial hyperglycaemia regardless of the dose and duration of glucocorticoid treatment (divided dose or high-dose pulse therapy)^{152,153}. However, the frequent required dosing and cost have limited their use and the efficacy of glinides is reduced when insulin resistance is present^{151,154}. Therefore, a combination of glinides with insulin sensitizers (metformin or thiazolidinediones) might be beneficial to control glucocorticoid-induced hyperglycaemia. Interestingly, the insulin-sensitizing thiazolidinediones (described later) induce CYP2C8 and CYP3A4 liver enzyme activity¹⁵⁵. If thiazolidinediones are combined with a glinide, this effect might result in a potential drug–drug interaction due to metabolism by the same enzymes¹⁵⁶.

Incretin-based therapies. Incretin hormones are peptides released by enteroendocrine cells in the gut following nutrient ingestion that stimulate insulin secretion. Glucagon-like peptide 1 (GLP1) receptor agonists and dipeptidyl peptidase 4 inhibitors (DPP4is) are incretin-based therapies that control hyperglycaemia by enhancing insulin secretion and glucose uptake into peripheral tissues, inhibiting glucagon secretion and decreasing gastric emptying¹¹⁵. In particular, DPP4is enable the release of insulin postprandially by elevating the circulating levels of GLP1, thus specifically targeting postprandial glucose levels³⁸. Indeed, exenatide (a GLP1 receptor agonist) has been reported to efficaciously treat glucocorticoid-evoked postprandial hyperglycaemia in both healthy individuals¹⁵⁷ and those with T2DM¹⁵⁸. DPP4is are also effective for the treatment of glucocorticoid-induced new-onset diabetes mellitus, yet contradicting reports exist that question their efficacy to prevent glucocorticoid-augmented postprandial hyperglycaemia^{159–162}. GLP1 receptor agonists are associated with more potent hypoglycaemic

effects compared with DPP4is in patients with T2DM¹⁶³. Of note, injectable GLP1 receptor agonists have substantial gastrointestinal adverse effects, which make them less well tolerated compared with DPP4is¹⁵⁴. GLP1 receptor agonists should be used cautiously in patients with glucocorticoid-induced hyperglycaemia after renal transplantation owing to the potential for acute renal injury that is secondary to plasma volume contraction¹⁶⁴.

The immediate onset of action of incretin-based therapies without risk of hypoglycaemia and their specificity towards controlling postprandial glucose could enable these drugs to become frontline hypoglycaemics for patients with glucocorticoid-induced diabetes mellitus. They are particularly suitable for patients treated with a single daily dose of intermediate-acting or long-acting glucocorticoids, either transiently or over a long-term period¹³. GLP1 agonists also have beneficial effects on body weight reduction and blood pressure, which suggests potential additive benefits towards glucocorticoid-induced secondary complications¹⁶⁵. However, evidence of incretin-based therapies providing long-term efficacy towards glucocorticoid-induced hyperglycaemia remains unclear. Furthermore, potential relapse might occur as observed in patients with T2DM who were treated with sitagliptin (a DPP4i) after 6 months¹⁶⁶. The paucity of evidence confirming the efficacy and safety of the incretin-based therapies in treating glucocorticoid-induced diabetes mellitus has limited their use and thus future studies are essential²⁹.

Insulin-sensitizing therapies

Metformin. Metformin has long been recommended as the first-line therapy for the treatment of T2DM. The drug induces a minimal risk of hypoglycaemia and limits glucocorticoid-induced hepatic and peripheral insulin resistance. Metformin greatly improves hepatic insulin sensitivity by counteracting gluconeogenesis and lipogenesis in the liver while increasing GLP1 secretion and glucose utilization in the gastrointestinal tract, thereby lowering glycaemia¹⁶⁷. Despite widespread use in T2DM, evidence of the effectiveness of metformin to counterbalance glucocorticoid treatment is fairly scarce. Nonetheless, glucocorticoid-mediated postprandial hyperglycaemia¹⁶⁸ and insulin resistance¹⁶⁹ are decreased with metformin use in patients receiving glucocorticoids who do not have diabetes mellitus. Due to its slow onset of action, metformin is considered a favourable option when low doses of intermediate-acting glucocorticoids are administered over the long term¹³. Metformin remains important for combination therapy with other oral hypoglycaemic drugs because it is not metabolized by cytochrome P450 enzymes, has minimal adverse effects and is low cost¹⁷⁰. Of note, metformin is contraindicated in individuals with impaired renal function¹⁷¹, and should therefore be avoided in patients receiving glucocorticoids after renal transplantation.

Thiazolidinediones. Thiazolidinediones are robust insulin sensitizers and therefore affect the action of glucocorticoids on plasma levels of glucose by improving both hepatic and peripheral insulin sensitivity without

inducing hypoglycaemia¹⁴⁸. In addition to improving insulin sensitivity, thiazolidinediones have the ability to preserve β -cell function¹⁷². Similar to metformin, their slow onset of action limits the use of thiazolidinediones for long-term treatment in patients with glucocorticoid-induced hyperglycaemia³⁸. In patients on long-term, low-dose glucocorticoid therapy, 6 months of treatment with pioglitazone statistically significantly reduced plasma glucose concentration 2 h post-OGTT, HbA_{1c} and homeostasis model assessment of insulin resistance (HOMA-IR)¹⁷³. Thiazolidinediones also improve diabetes-related parameters in patients with severe glucocorticoid-induced hyperglycaemia when administered in combination with insulin¹⁷⁴. However, thiazolidinediones are less appealing compared with metformin owing to their overlapping adverse effects with glucocorticoids, including weight gain, increased risk of bone fractures and fluid retention¹⁴⁵. Therefore, the benefits must be balanced against their complications when considering thiazolidinediones as treatment options for managing glucocorticoid-induced hyperglycaemia.

Therapies with other mechanisms of action

Sodium–glucose co-transporter type 2 inhibitors. Sodium–glucose co-transporter type 2 inhibitors (SGLT2is) lower plasma levels of glucose by reducing glucose reabsorption in the kidney. Their immediate onset of action without the risk of hypoglycaemia provides a novel approach to minimizing glucocorticoid-associated diabetes mellitus¹⁴⁵. Additionally, SGLT2is reduce body weight and cardiovascular risk in patients with T2DM, thus theoretically providing the capacity to combat other adverse effects of glucocorticoids³⁸. However, add-on dapagliflozin to existing hypoglycaemic therapy exerted minimal additional glycaemic control in patients with hyperglycaemia or T2DM when they were challenged with a short-term

(5–14 days) high dose of glucocorticoid¹⁷⁵. SGLT2is are also associated with risks of urinary tract and genital infections¹⁷⁶, and this risk could be exacerbated by glucocorticoid-mediated immunosuppression. The risk of glucocorticoid-induced osteoporosis might also be enhanced due to the potential of SGLT2is to enhance bone resorption¹⁷⁷. Finally, whether SGLT2is alone can alleviate glucocorticoid-induced hyperglycaemia remains to be tested.

α -Glucosidase inhibitors. α -Glucosidase inhibitors (AGIs) inhibit the breakdown of complex carbohydrates and delay the absorption of glucose in the gastrointestinal tract, thus reducing postprandial plasma levels of glucose¹⁷⁸. As a second-line intervention to metformin, AGIs are mainly prescribed in combination with other hypoglycaemic agents owing to their non-cytochrome P450-dependent metabolism and weak hypoglycaemic effect when administered alone^{178,179}. The combination of glinides and AGIs was shown to improve glucocorticoid-mediated postprandial hyperglycaemia in patients with rheumatoid arthritis¹⁵².

Insulin

Insulin therapy should be initiated in those patients who are treated with glucocorticoids and have persistent glycaemic oscillations ≥ 10 mM as recommended by the ADA^{143,147}. Insulin should also be used when non-insulin hypoglycaemic therapy fails to adequately control glycaemia in patients treated with glucocorticoids who have pre-existing T2DM¹⁸⁰. Insulin therapy can efficaciously provide immediate targeting of postprandial hyperglycaemia and flexibility in dosing based on food intake¹⁴². Insulin regimens are tailored to glucocorticoid dosing schedules and patient BMI and hyperglycaemic profile¹⁸¹ (TABLE 2). In patients with pre-existing diabetes mellitus who already require insulin, a 20% increment in daily insulin dose is generally required upon the addition of

Table 2 | Insulin therapy in glucocorticoid-induced hyperglycaemia and diabetes mellitus

Insulin schedules	Onset of action	Duration	Advantages	Disadvantages	Suitable for type of glucocorticoid drug ^a
Basal insulin (detemir or glargine)	1–4 h	Long acting, up to 24 h	Low risk of hypoglycaemia	Not specific to postprandial glucose	Intermediate-acting (2 or more daily doses), or long-acting glucocorticoids
Basal insulin (NPH)	1–2 h	Intermediate acting, ≥ 14 h	Activity profile closely resembles glucocorticoid-induced hyperglycaemia	Not specific to postprandial glucose	Intermediate-acting glucocorticoids
Prandial (bolus) insulin	15–60 min	Rapid and short acting, 3–8 h	Immediate onset of action; targets postprandial glucose; can be combined with basal insulin for severe glucocorticoid-induced hyperglycaemia	Limited flexibility in the timing of administration	Short-acting glucocorticoids
Basal-bolus	15–60 min for bolus	Rapid and long acting, up to 24 h	Flexibility in dose adjustment; useful for severe or persistent glucocorticoid-induced hyperglycaemia	Multiple daily injections	Use is based on severity of hyperglycaemia (not on type of glucocorticoid)

NPH, neutral protamine Hagedorn. ^aShort acting (for example, hydrocortisone, half-life of 8 h), intermediate acting (for example, prednisolone or methylprednisolone, half-life of 16–40 h), long acting (for example, dexamethasone or betamethasone, half-life of 36–54 h).

Box 3 | Clinical candidates under investigation to avoid adverse metabolic effects of glucocorticoids: SEGRAs and SEGRMs

Before mechanisms of glucocorticoid action were characterized at the genome-wide level, glucocorticoids were thought to induce hyperglycaemia by direct binding to DNA, causing transactivation of genes involved in gluconeogenesis, and to inhibit inflammation by indirect binding to genes involved in inflammation, causing transrepression²⁰⁸. This mechanistic separation of effects led to widespread interest in the development of selective glucocorticoid receptor agonists (SEGRAs) and selective glucocorticoid receptor modulators (SEGRMs) to optimize the therapeutically beneficial effects while minimizing the adverse effects of glucocorticoids²⁰⁹. However, genome-wide analyses of glucocorticoid receptor chromatin binding have since shown that glucocorticoid receptors exert their repressive function in part by indirectly tethering pro-inflammatory mediators or by direct binding to negative glucocorticoid-response elements (GREs)^{18,210}. Furthermore, glucocorticoids not only upregulate essential anti-inflammatory genes via transactivation²¹¹; some glucocorticoid-induced complications (for example, osteoporosis) are also controlled by both transactivation and transrepression of certain key genes²⁰⁹. Hyperglycaemia, however, arises predominantly from glucocorticoid transactivation activity.

SEGRMs (such as Compound A) selectively exert anti-inflammatory effects whilst avoiding GRE-driven expression of *PCK1* and *G6PC1*, thereby blunting gluconeogenesis²¹². Nonetheless, intensive research has only guided a few SEGRMs into clinical trials, which highlights the challenge of developing efficacious dissociative agonists^{213–215}. The SEGRA fosdagrocorat (PF-04171327) achieved similar anti-inflammatory efficacy while demonstrating enhanced glycaemic control compared with the same dose of prednisone in healthy individuals²¹⁴. However, its development was discontinued for undisclosed reasons. AZD9567, developed in 2018 (REF. 213), is a SEGRM that also showed promising postprandial glucose improvement in a phase I clinical trial²¹⁶ with a similar efficacy profile to prednisolone in patients with rheumatoid arthritis. Results from an ongoing phase II trial examining the effect of AZD9567 on glycaemic control in patients with type 2 diabetes mellitus are eagerly awaited (NCT04556760)²¹⁷.

glucocorticoid therapy in order to achieve similar glycaemic control¹⁴². Of note, changes to the glucocorticoid dose might not immediately result in corresponding effects on blood levels of glucose, particularly in patients with pre-existing diabetes mellitus²⁹. As such, the insulin dose used should be carefully titrated to match the glycaemic oscillation of individual patients to provide optimal glucose control.

The use of basal and bolus insulin in combination delivers insulin that most closely resembles its physiological pancreatic release to maintain euglycaemia in both fasting and postprandial states¹⁸². For inpatients with severe or persistent hyperglycaemia due to high glucocorticoid doses, multiple daily doses or long-acting

glucocorticoid use, basal-bolus insulin should be initiated^{29,143,148}. These regimens offer great flexibility in dose titration, as hospital staff can make adjustments based on preprandial glycaemic reading, anticipated carbohydrate intake and interpatient insulin sensitivity¹⁸⁰. However, as multiple daily injections are required of long-acting basal insulin and rapid-acting bolus insulin administered preprandially¹⁸³, it is impractical for the outpatient with new-onset glucocorticoid-induced hyperglycaemia to manage once discharged. Education on self-injections, stringent glucose monitoring and concern over nocturnal hypoglycaemia can be major drawbacks for insulin therapy, especially if glucocorticoids are required only over a short term¹⁵⁴.

For outpatients who are treated with long-term, once-daily glucocorticoids, for whom only postprandial glucose is elevated, neutral protamine Hagedorn (NPH) insulin is a preferable option that can be administered at the same time as their glucocorticoid in the morning^{13,154}. These insulin preparations have a closely aligned temporal profile (peak 4–10 h, duration of action ≥ 14 h) with the hyperglycaemic excursion induced by intermediate-acting glucocorticoids¹⁸². When twice-daily intermediate-acting or long-acting glucocorticoids are administered, the total dose of NPH insulin can be divided¹³ or substituted for long-acting basal insulin (insulin detemir or glargine), which can adequately match the pattern of glucocorticoid-evoked hyperglycaemia¹⁵⁴. Oral hypoglycaemic agents can be added to insulin therapy when patients continue to exhibit severe or persistent hyperglycaemia ($\text{HbA}_{1c} > 9\%$)^{13,181}. Insulin sensitizers, such as metformin and thiazolidinediones, are the most frequently prescribed in combination with insulin that can provide further glycaemic benefits under chronic glucocorticoid exposure^{13,182}.

Novel pharmacological targets

The unparalleled efficacy of glucocorticoids for the treatment of inflammatory diseases has led to tremendous interest by pharmaceutical companies to develop compounds that could eliminate their diabetogenic effects while preserving their anti-inflammatory functions. Two such approaches, selective glucocorticoid receptor agonists or selective glucocorticoid receptor modulators (BOX 3) and 11 β -HSD1 inhibitors (BOX 4), have made it to clinical trials; however, neither has yet emerged as being clearly superior to glucocorticoids as currently used in practice. The limited dissociative effects of selective glucocorticoid receptor agonists or selective glucocorticoid receptor modulators and the limited efficacy of 11 β -HSD1 inhibitors have challenged their continued clinical development as they have not achieved clear superiority over conventional glucocorticoids. Discoveries of novel therapeutic targets that can distinguish the beneficial effects of glucocorticoids from their secondary complications have sparked new interest in the field (FIG. 2).

Liver X receptor- β

As members of the nuclear receptor superfamily of transcription factors, liver X receptor- α (LXR α) and LXR β control cholesterol homeostasis by sensing

Box 4 | Clinical candidates under investigation to avoid adverse metabolic effects of glucocorticoids: 11 β -HSD1 inhibitors

11 β -HSD1 is the enzyme that converts glucocorticoids from an inactive to an active form. Increased adipose expression of 11 β -HSD1 in rodents and humans promotes visceral adiposity and glucose intolerance^{84,218,219}, whereas inhibition of 11 β -HSD1 enhances insulin signalling in high-fat diet-fed mice²²⁰. 11 β -HSD1 controls intra-tissue glucocorticoid exposure and is critical to the development of whole-body insulin resistance. 11 β -HSD1 inhibitors have been developed to treat patients with type 2 diabetes mellitus and metabolic syndrome²²¹. Although some 11 β -HSD1 inhibitors in clinical trials reduced fasting glycaemia and improved insulin resistance in patients with type 2 diabetes mellitus already on metformin²²², other inhibitors did not meet this end point or showed lower efficacy compared with metformin alone^{223,224}. The potential of 11 β -HSD1 inhibitors to mitigate hyperglycaemia from exogenous glucocorticoid treatment has been shown in rodents²²¹ but remains to be determined in humans. A phase II clinical trial in healthy volunteers of AZD4017 in combination with prednisolone (20 mg) is ongoing to assess whether the 11 β -HSD1 inhibitor will limit the detrimental adverse effects of prednisolone on glucose disposal (NCT03111810)²²⁵.

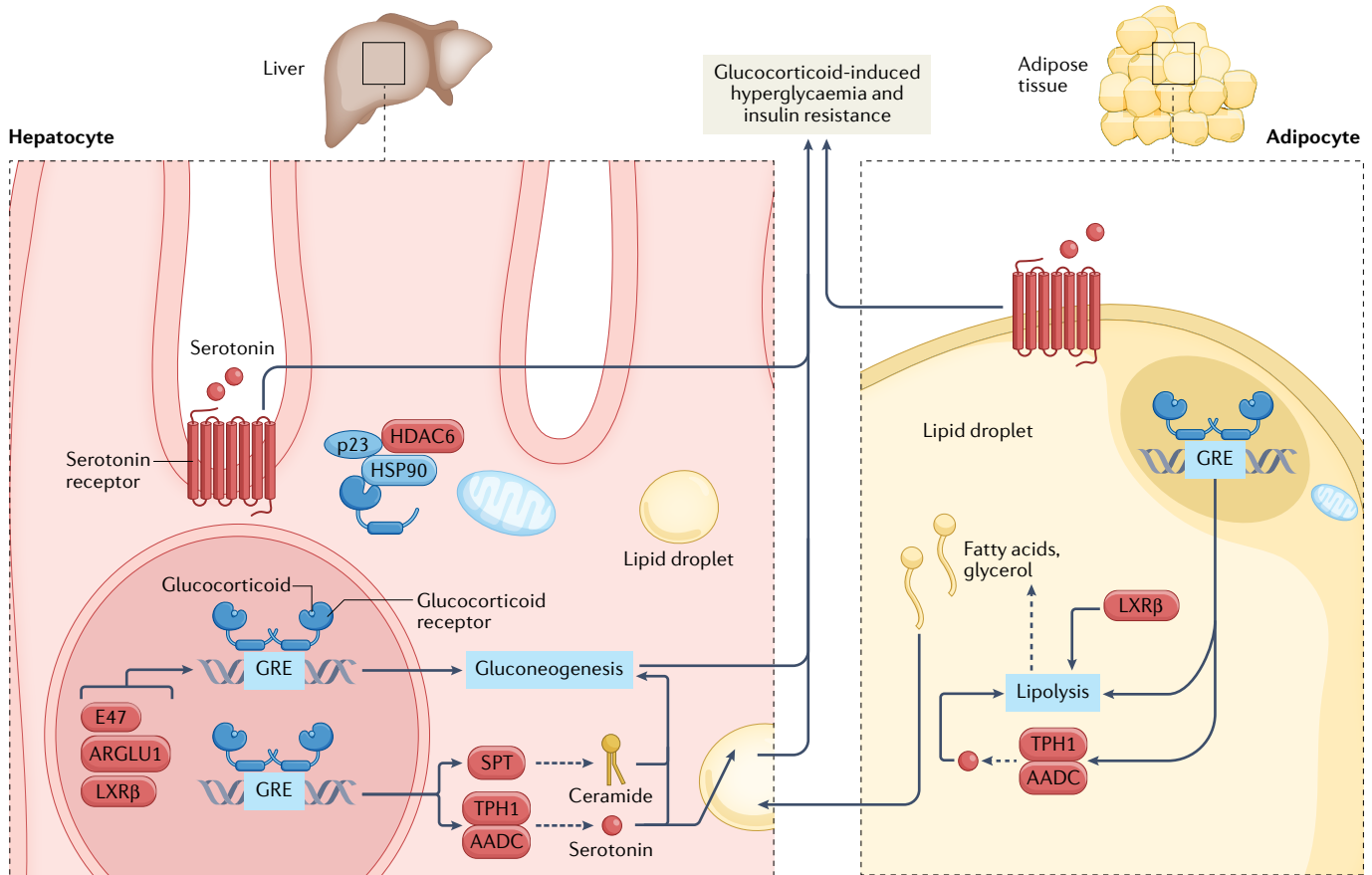


Fig. 2 | Novel pharmacological targets to combat glucocorticoid-induced hyperglycaemia and insulin resistance. In the absence of ligand, glucocorticoid receptor resides in the cytoplasm bound to chaperone proteins, including heat shock protein 90 (HSP90) and p23. Histone deacetylase 6 (HDAC6) deacetylates HSP90, thereby enabling its interaction with the co-chaperone p23, which in turn promotes the proper folding of the glucocorticoid receptor. Inhibition of HDAC6 prevents the interaction of HSP90 with p23, inhibiting glucocorticoid receptor translocation. In the presence of glucocorticoids, the glucocorticoid receptor binds to glucocorticoid-response elements (GREs) in genes related to metabolism in target tissues to exert their metabolic effects. Liver X receptor-β (LXRβ), basic helix-loop-helix transcription factor E47 and the glucocorticoid receptor arginine and glutamate-rich protein 1 (ARGLU1) are required for the full recruitment of the glucocorticoid receptor to target genes involved in

gluconeogenesis. Loss of any of these factors protects against glucocorticoid-induced hyperglycaemia. Elevated ceramide levels in the portal circulation and the liver, occurring as a result of increased gene and protein expression of serine palmitoyltransferase (SPT) induced by glucocorticoids, promote hepatic gluconeogenesis. Likewise, increased serotonin synthesis (from glucocorticoid-induced TPH1 and AADC) and serotonin receptor expression promote gluconeogenesis and steatosis in liver and lipolysis in adipose tissue. LXRβ also promotes glucocorticoid-induced lipolysis increasing the flux of non-esterified fatty acids and glycerol into the liver, which exacerbates hepatic steatosis. Small-molecule inhibitors (HDAC6, SPT, PKC ζ , TPH1 and AADC) or antagonists (LXRβ and serotonin receptor) have been shown to protect against glucocorticoid-induced hyperglycaemia and insulin resistance in mouse models. Thick solid arrows indicate effects; dashed arrows indicate secreted factors.

intracellular cholesterol load¹⁸⁴. Whole-body knock-out of the gene encoding LXRβ (*Nr1h2*) (but not LXRα, encoded by *Nr1h3*) and/or pharmacological inhibition of LXRβ protects mice against hyperglycaemia, hyperinsulinaemia and hepatic steatosis following glucocorticoid treatment via suppression of genes involved in gluconeogenesis^{184,185}. Notably, the immunosuppressive effects of glucocorticoids are unaltered by LXRβ antagonism. Loss of LXRβ specifically in adipose tissue was reported in a 2021 study to attenuate glucocorticoid-induced lipogenesis and lipolysis in mice and improve systemic insulin tolerance by decreasing NEFA shuttling to the liver¹⁸⁶. Limitations of targeting LXRβ to minimize the diabetogenic effects of glucocorticoids include the development of LXRβ isoform-selective inhibitors (owing to high similarity with LXRα) and ensuring no adverse effects occur on

whole-body cholesterol efflux (although this function is mainly mediated by LXRα)¹⁸⁷.

E47

The basic helix-loop-helix transcription factor E47 is required for efficient recruitment of glucocorticoid receptors and coregulators to a subset of lipid and glucose metabolic gene promoters in the liver¹⁸⁸. Loss of E47 specifically from rodent livers abolished the development of glucocorticoid-induced hyperglycaemia and hepatic steatosis¹⁸⁸. Both LXRβ and E47 could plausibly synchronously regulate the recruitment of glucocorticoid receptors to target genes involved in gluconeogenesis such as *Pck1*. Due to the ubiquitous expression of LXRβ and E47, targeting these proteins might necessitate the development of tissue-specific antagonists.

Coregulators of glucocorticoid receptor

The loss of the glucocorticoid receptor coactivator euchromatic histone methyltransferase 2 in the liver was associated with aggravated glucocorticoid-induced hepatic insulin resistance in mice¹⁸⁹. Another coactivator of the glucocorticoid receptor, arginine and glutamate-rich protein 1 (ARGLU1), is critical in mediating the recruitment of glucocorticoid receptors to the gluconeogenic *Pck1* promoter¹⁹⁰. Thus, targeting specific members of the glucocorticoid receptor co-regulator complex remains a fruitful area for future investigation.

Histone deacetylase 6

In the absence of ligand, the glucocorticoid receptor is bound to chaperone proteins in the cytoplasm, including heat shock protein 90 (HSP90)¹⁹¹. Histone deacetylase 6 (HDAC6) deacetylates HSP90, thereby enabling its interaction with the co-chaperone p23, which is essential for the ligand-binding activity of glucocorticoid receptor. Inactivation of HDAC6 results in HSP90 hyperacetylation and decreases ligand binding to the glucocorticoid receptor due to the dissociation of p23 (REF.¹⁹²). Loss of HDAC6 in mice partially ameliorated glucocorticoid-induced hyperglycaemia and insulin resistance by impairing translocation of glucocorticoid receptors and subsequent glucocorticoid receptor-mediated gluconeogenesis in the liver¹⁹³. In 2021, HDAC6 was discovered to deacetylate the histone arginine demethylase PRMT5, which inhibits its activity¹⁹⁴. As PRMT5 increases chromatin accessibility near gluconeogenic promoters¹⁹⁵, this finding could be an additional mechanism by which HDAC6 inhibition constrains glucocorticoid-induced hyperglycaemia.

Serotonin signalling

Plasma levels of serotonin (5-hydroxytryptamine or 5-HT) were found to be elevated in patients with T2DM and seemingly contribute to peripheral vascular disease¹⁹⁶. In rodents, glucocorticoids can promote insulin resistance by upregulating serotonin synthesis and serotonin receptor (5-HT₂R) expression in liver and visceral adipose tissue¹⁹⁷. In rats, treatment with a serotonin synthetic inhibitor and/or 5-HT₂R antagonist reversed glucocorticoid-mediated hepatic gluconeogenesis, steatosis and insulin resistance¹⁹⁸. A key question that remains for therapeutic targeting of the serotonin signalling pathway in this context will be whether inhibition can be achieved without altering serotonin transmission in the central nervous system.

Ceramide synthesis

The ability of glucocorticoids to upregulate the expression of genes involved in ceramide synthesis, such as that encoding serine palmitoyltransferase (*Sptlc2*), provides a novel approach to protect against glucocorticoid-dependent disruption in glucose homeostasis⁶⁵. Ceramide-induced activation of protein kinase C ζ (PKC ζ) promotes hepatic insulin resistance by inhibiting PKB–AKT downstream of the insulin receptor¹⁹⁹. In rodents, pharmacological inhibition of serine palmitoyltransferase by myriocin or PKC ζ by 2-acetyl-1,3-cyclopentanedione limits ceramide biosynthesis and signalling, which in turn reduces glucocorticoid-mediated hepatic glucose output and insulin resistance. Despite the inverse correlation between plasma levels of ceramides and improved glucose homeostasis, ceramides have a wide range of biological functions at several cellular growth checkpoints. Therefore, pharmacological targeting of ceramides will first require prudent examination of the specific roles of different ceramide species²⁰⁰.

Conclusions

Glucocorticoids are indispensable for their powerful immunosuppressive and anti-inflammatory effects. However, the adverse metabolic effects of long-term use, including hyperglycaemia and diabetes mellitus, have diminished their therapeutic value. The underlying molecular mechanisms of glucocorticoid-induced hyperglycaemia are complex and involve multiple organs. Organs and tissues either fail to remain responsive to insulin or promote insulin resistance via inter-organ crosstalk, which makes it difficult to predict which patients will develop adverse metabolic effects. This limitation in knowledge has resulted in the poor clinical management of hyperglycaemia and diabetes mellitus as a result of glucocorticoid exposure. Universal guidelines should be established that consider the variations in glucocorticoid therapy, genetic predisposition, comorbidities and therapeutic tolerance of individual patients. The incorporation of patient education with respect to routine glucose monitoring upon the prescription of glucocorticoids will help combat glucocorticoid-induced hyperglycaemia and diabetes mellitus. Future studies that provide a deeper understanding of the mechanism of action of glucocorticoids could lead to the development of novel therapeutic strategies to minimize the diabetogenic effects while sparing the beneficial immunosuppressive effects of glucocorticoids.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

C.L.C. is a co-inventor on US9428753 patent entitled “Use of LXR antagonists for treatment of side effects of elevated glucocorticoid levels”. J.X.L. declares no competing interests.

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