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# Glucose Metabolism in Cushing Syndrome

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## Abstract

**Purpose of review—**Impairment of glucose metabolism is commonly encountered in Cushing's syndrome. It is the source of significant morbidity and mortality even after successful treatment of Cushing's. This review is to understand the recent advances in understanding the pathophysiology of diabetes mellitus from excess cortisol.

**Recent findings—***In vitro* studies have led to significant advancement in understanding the molecular effects of cortisol on glucose metabolism. Some of these findings have been translated with human data. There is marked reduction in insulin action and glucose disposal with a concomitant, insufficient increase in insulin secretion. Cortisol has a varied effect on adipose tissue, with increased lipolysis in subcutaneous adipose tissue in the extremities, and increased lipogenesis in visceral and subcutaneous truncal adipose tissue.

**Summary—**Cushing's syndrome results in marked impairment in insulin action and glucose disposal resulting in hyperglycemia. Further studies are required to understand the effect on incretin secretion and action, gastric emptying, and its varied effect on adipose tissue.

### Keywords

Glucose metabolism; secondary diabetes; diabetes mellitus; Cushing's syndrome; cortisol

## Introduction

Glucose metabolism is frequently impaired (43%–84%)[1–3] in Cushing's syndrome (CS) [2,4] resulting in an increased risk of metabolic syndrome[4] and cardiovascular death[5,6]. Individuals with CS have twice as high mortality compared to controls (HR 2.3, 95% CI 1.8–2.9) with persistence of impaired glucose metabolism[7] and increased risk for myocardial infarction even after treatment for CS (HR 4.5 the year after diagnosis, decreasing to HR 3.7 during long term follow up)[6]. In fact, even in mild autonomous cortisol excess (or subclinical ACTH independent CS), the prevalence of diabetes mellitus was 18.1% with an

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increased risk of cardiovascular events compared to nonfunctioning adrenal tumors (15.5% vs 6.4% respectively)[8]. This highlights the importance of understanding the cardiovascular risks associated with cortisol excess and the need to institute early treatment to decrease excess mortality.

Glucose metabolism is a complex biochemical process that requires multiple interacting factors to function effectively in order to achieve euglycemia. Insulin secretion is defined as the β-cell secretory response to the circulating glucose concentration. Equally important is insulin action, which is commonly referred to as insulin sensitivity or insulin resistance. This is defined as the ability of insulin to remove glucose from the blood stream by stimulation of uptake into peripheral tissues, suppression of lipolysis and decreasing endogenous glucose production. Physiologically, cortisol plays a small role in stimulating gluconeogenesis and inhibiting glycogenesis thereby preventing hypoglycemia[9]. In addition cortisol stimulates lipolysis and proteolysis which provides oxidative substrates for metabolism [10]. Excess cortisol amplifies these processes, in addition to impairing insulin secretion and action with resultant hyperglycemia.

In this review, we will describe the pathophysiology of impaired glucose metabolism in CS which is summarized in Table 1. Given the rarity of CS (0.2–5 people/million per year[11,12]), most of our in-depth understanding of how cortisol affects glucose metabolism stems from exogenous glucocorticoid data.

## Insulin Secretion

Insulin secretion is primarily controlled by glucose. Glucose transporter 2 (GLUT2) serves as the β-cell's glucose sensor. Once glucose enters the β-cell, it is phosphorylated by glucokinase and enters several pathways to increase insulin gene transcription, insulin gene translation with formation of insulin secretory granules and insulin granule exocytosis [13]. Approximately 7% of insulin granules are "docked" or linked to the β-cell plasma membrane and are readily available to be released in response to glucose [14]. The rest of insulin granules require mobilization to the plasma membrane, priming and fusion for release [15]. These are referred to as "undocked" and belong to the reserve pool.

Glucocorticoids affect insulin secretion directly and indirectly. The effect is also dependent on the dose of glucocorticoids as well as, the duration of exposure[16]. In vitro studies show a direct inhibition of insulin secretion possibly due to decreased transcription of factors required to activate the secretory process in response to cytoplasmic $Ca^{2+}$ [17]. In vivo studies, however, reveal compensatory mechanisms in response to glucocorticoid exposure. While there is decreased production of NADP, cAMP and inositol phosphate production [17], there is concomitant upregulation of parallel cAMP signaling pathways[18] and increased number of docked secretory granules[19]. Interestingly, pancreatic islets express 11beta-hydroxysteroid dehydrogenase type 1 (11β-Hsd1) which influences both insulin[20] and glucagon secretion[21]. The main action of glucagon is stimulation of hepatic glucose output via increased gluconeogenesis and glycogenolysis with concomitant suppression of glycolysis and glycogenesis. Glucagon secretion is regulated by intra-islet glucose concentration, intra-islet insulin signaling, paracrine stimulation of somatostatin via insulin, with minor contributions

by incretins and the autonomic nervous system [22–24]. Dexamethasone treated rats were found to have increased α-cell mass, higher glucagon receptor content with resultant hyperglucagonemia [25]. The hyperglycemia found was reversed with blockade of the glucagon receptor [25] suggesting a potential role for targeting glucagon and its receptor in the treatment of hyperglycemia in CS.

In an attempt to understand the effect of cortisol under human physiologic conditions, Kamba et al[26] performed a population based study in Japan to investigate the association between cortisol and β cell function. Utilizing the homeostasis model assessment (HOMA) they calculated crude estimates for insulin secretion (HOMA-β) and insulin resistance (HOMA-R). Higher cortisol levels were associated with decreased insulin secretion (p=0.03). In contrast, when a supra-physiological dose of glucocorticoid was administered (prednisolone 30 mg daily for 15 days), insulin secretion was increased as measured by the insulinogenic index after a meal[27]. In addition, glucocorticoids increase hepatic insulin extraction which is more evident during an intravenous glucose challenge compared to an oral glucose challenge [28]. Page et al[29] performed the most robust study comparing 7 individuals with Cushing's disease (CD) to 10 healthy participants utilizing the minimal model analysis with a frequently sampled insulin modified intravenous glucose tolerance test (FSIGTT). While first phase insulin secretion was similar, second phase insulin secretion was found to be enhanced in CD [29]. This increase, however, was not appropriate for the prevailing decrease in insulin action [29].

## Insulin Action

The compensatory increase in insulin secretion found in long term glucocorticoid exposure is likely in response to the profound decrease in insulin action. Glucocorticoids impair insulin sensitivity at multiple sites in the liver, muscle and adipose tissue[30].

When insulin binds to hepatocytes, it decreases hepatic glucose output or endogenous glucose production (EGP) via inhibition of gluconeogenesis. Glucocorticoids upregulate forkhead box O1 (FOXO1) with increased expression of MAP kinase phosphatase-3 (MKP-3)[31]. This results in activation of hepatic gluconeogenesis by increased transcription of key regulatory enzymes (phosphoenolpyruvate[32] and glucose-6-phosphatase (G6P) [33]). Human studies, however, show a more complex interaction between glucocorticoids and EGP. Rooney et al performed a human study utilizing the euglycemic glucose clamp with glucose tracers to study the effect of cortisol on G6P[34]. EGP was suppressed with high insulin infusion despite increased G6P cycle activity. Hyperglycemia was thought to result from impaired glucose disappearance. This study was then replicated in 8 individuals with Cushing's disease which confirmed the finding of impaired insulin action due to reduced glucose disposal [35].

Glucocorticoids also indirectly increase hepatic glucose output through elevated free fatty acid concentrations (FFA). As mentioned above, glucocorticoids upregulate FOXO1. This enhances hepatocyte lipid accumulation via several pathways (MKP-3, PPAR-γ, FAS, SCD1 and ACC2)[36,37] leading to hepatic steatosis. Newly synthesized lipids are converted to

diacylglycerol[38] and ceramides[39], both being implicated in the development of decreased hepatic insulin action.

The direct effect of glucocorticoids on adipose tissue vary depending on the duration of exposure, concentration and the location of adipose tissue being studied (visceral vs subcutaneous). A pathognomonic physical finding in CS is increased truncal adipose tissue mass with atrophy of both muscle and fat in the extremities. The exact underlying molecular difference between the effects of glucocorticoids on visceral as opposed to subcutaneous adipose tissue is yet to be fully determined. Glucocorticoids stimulate lipolysis in subcutaneous adipose tissue [40,41] but induces lipogenesis in visceral adipose tissue, with its action augmented by insulin [42–44]. This seemingly site specific variation in activity is likely linked to its actions on intracellular hormone sensitive lipase [45], intravascular lipoprotein lipase [45], and AMP-activated protein kinase (AMPK) [46]. The result is overall increase in free fatty acid turnover with an overall decrease in insulin action.

## Glucose disappearance

Glucose disappearance refers to the ability of peripheral tissue to uptake circulating glucose for metabolism. Muscle is the primary source for glucose disposal, accounting for 70–80% of the body's glucose use [36]. Cortisol plays an important role in the myocyte's ability to clear glucose. Physiologically, glucocorticoids are important in maintaining euglycemia during fasting or starvation by increased proteolysis which releases amino acids that serve as precursors for hepatic gluconeogenesis. In addition, there is impaired recruitment of GLUT4 to the cell surface resulting in decreased glucose uptake. In the presence of excess glucocorticoids, these processes are amplified.

Glucocorticoids decrease phosphorylation of the insulin receptor which is required for it to bind to insulin receptor substrate 1 (IRS1) to activate insulin receptor signaling[47]. Downstream signaling is also impaired by decreasing the activity of phosphinositide-3-kinase (PI3K)[48] resulting in disruption of glycogen synthase activity [49]. Glucocorticoids decrease GLUT4 translocation and exocytosis both directly [50] and indirectly due to defective insulin receptor signaling [51]. The net result of excess cortisol is hyperglycemia due to a significant decrease in glucose disappearance [29,35].

## Glucose Effectiveness

Glucose effectiveness refers to the ability of glucose to stimulate its own uptake and suppress EGP. There is limited data pertaining to effect of glucocorticoids on glucose effectiveness. Nielsen et al studied 8 healthy subjects under a somatostatin and insulin clamp using a glucose infusion to simulate postprandial rise in glucose[52]. Each subject served as their own control (hydrocortisone vs saline infusion). There was a significant decrease in both insulin action and glucose effectiveness implicating both to be significant contributors to hyperglycemia.

## Other Factors Influencing Glucose Metabolism

Targeting incretins and their receptors play an important role in the management of type 2 diabetes mellitus. Pharmacological management targeting incretins potentiate the β-cell response to food intake and hyperglycemia. In addition, there is slowed gastric emptying and decreased appetite. In dexamethasone treated rats, the secretory responsiveness of L cells to a meal was decreased [53]. While there is suggestion that glucocorticoids mildly affect the insulinotropic effect of incretins [54,55], it is unclear what physiologic role incretins play in the regulation of glucose metabolism in CS.

Bone produces several factors that affect glucose homeostasis. Secretion of osteocalcin[56] and expression of thioredoxin-interacting protein (TXNIP) [57] are both altered in the presence of chronic glucocorticoids in mice, contributing to decreased insulin sensitivity. The nervous system also contributes to decreased insulin sensitivity. Neuropeptide Y expression is increased in the presence of glucocorticoids which potentiated impaired insulin action. This impairment was reversed by hepatic sympathetic denervation[58]. Secretion of growth hormone, thyrotropin releasing hormone and gonadotropin hormones are impaired in chronic hypercortisolism. Growth hormone deficiency[59], hypothyroidism[60] and hypogonadism[61] have all been implicated in altered glucose metabolism.

Lastly, expression of 11β-Hsd1 is increased in the presence of chronic glucocorticoid exposure[62]. 11β-Hsd1 converts cortisone to cortisol. In the presence of hydrocortisone, 30 healthy adults showed increased hepatic 11β-Hsd1 activity with impaired suppression of EGP [63]. This suggests that hepatic cortisol exposure exacerbates altered glucose metabolism by a deleterious positive feedback loop. 11β-Hsd1 is also present in adipose tissue. Adipose-specific 11β-Hsd1 knock out mice treated with glucocorticoids were protected from circulating fatty acid excess and hepatic steatosis suggesting a crucial role of adipose tissue 11β-Hsd1 in the development of metabolic derangements in CS [64].

## Treatment

The first-line treatment would be to surgically target the underlying cause of CS. In some cases however, it takes time to locate the source, making treating underlying glucose abnormalities a priority to decrease overall morbidity and mortality. With the exception of pasireotide, and to a lesser extent other somatostatin analogues (because of their suppression of insulin secretion), all medical therapeutic options that decrease cortisol will aid in improving glycemic control [36]. While there is ongoing research targeting specific defects found in glucocorticoid induced diabetes (e.g. 11β-Hsd1 inhbition[65] and glucocorticoid receptor modulators[66], the current approach should be similar to the stepwise approach adopted for type 2 diabetes: lifestyle modification, metformin, therapies targeting postprandial insulin secretion and action, and specific metabolic derangements (e.g. hypertriglyceridemia and dyslipidemia) [67,68].

## Conclusion

CS results in impaired glucose metabolism primarily through a decrease in insulin action and reduction in glucose disposal. While there is a compensatory increase in insulin

secretion, it is insufficient to overcome the significant alteration in insulin receptor signaling in the liver and peripheral tissues. Varied effects on adipose tissue results in both lipolysis and lipogenesis accounting for the characteristic body fat distribution noted in CS. More studies are needed to understand the effect of excess cortisol on incretins, gut mobility/metabolism, the nervous system and bone.

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## Abbreviations:

| | |
|---|---|
| **CS** | Cushing's syndrome |
| **CD** | Cushing's disease |
| **ACTH** | Adrenocorticotrophic hormone |
| **HR** | hazard ratio |
| **CI** | confidence interval |
| **NADP** | Nicotinamide adenine dinucleotide phosphate |
| **cAMP** | cyclic adenosine monophosphate |
| **GLUT2** | glucose transporter 2 |
| **GLUT4** | Glucose transporter 4 |
| **HOMA** | Homeostatic Model Assessment |
| **HOMA-β** | Homeostatic Model Assessment of insulin secretion |
| **HOMA-R** | Homeostatic Model Assessment of insulin resistance |
| **FSIGTT** | Frequently sampled intravenous glucose tolerance test |
| **FOXO1** | Forkhead box O1 |
| **G6P** | Glucose 6 phosphate |
| **EGP** | Endogenous glucose production |
| **MKP-3** | MAP kinase phosphatase-3 |
| **PPAR-γ** | Peroxisome proliferator-activated receptor gamma |
| **FAS** | Fatty acid synthase |
| **SCD1** | Stearoyl-CoA desaturase |

| | |
|---|---|
| **ACC2** | Acetyl-CoA carboxylase 2 |
| **AMPK** | AMP-activated protein kinase |
| **FFA** | Free fatty acid |
| **IRS1** | Insulin receptor substrate 1 |
| **PI3K** | phosphinositide-3-kinase |
| **TXNIP** | thioredoxin-interacting protein |
| **11β-Hsd1** | 11beta-hydroxysteroid dehydrogenase type 1 |

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• of special interest

•• of outstanding interest


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**Key Points**

1. Impaired glucose metabolism is prevalent in Cushing's syndrome.
2. Cushing's syndrome causes a significant reduction in insulin sensitivity and glucose disappearance (peripheral uptake of glucose).
3. Excess cortisol induces both lipolysis and lipogenesis.
4. Metabolic derangements from excess cortisol significantly increases overall morbidity and mortality even after successful treatment of Cushing's syndrome.

**Table 1.**

Factors affecting Glucose Metabolism with excess cortisol

| Factor | Organ | Molecular Change |
|---|---|---|
| Insulin Secretion | Pancreas | ↑cAMP signaling |
| | | ↑insulin |
| | | ↑glucagon |
| | Gut | ↓GLP-1 |
| Insulin Action | Liver | ↑MKP-3, ↑FOXO1 |
| | | ↑11β-Hsd1 |
| | Adipose Tissue | ↑MKP-3, ↑FOXO1,↑PPAR-γ |
| | | ↑NADPH |
| | Bone | ↑osteocalcin |
| | | ↑TXNIP |
| | Brain | ↑NPY |
| | Pituitary | ↓GH, ↓TSH, ↓FSH/LH |
| Glucose disappearance | Muscle | ↓insulin receptor signaling |
| | | ↓glycogen synthase |
| | | ↓GLUT4 |
| Glucose effectiveness | Liver | ↓glucose stimulated glucose uptake |
| Glucagon suppression | Pancreas | ↑α-cell mass |
| | | ↑glucagon receptors |
| Gastric emptying | Gut | unknown |

MKP-3 - MAP kinase phosphatase 3; FOXO1 – forkhead box O1; 11β-Hsd1 – 11 β hydroxysteroid type 1; PPAR-γ - peroxisome proliferator-activated receptor gamma; TXNIP - thioredoxin-interacting protein; NPY – neuropeptide Y; GH – growth hormone; TSH – thyrotropin stimulating hormone; FSH – follicle stimulating hormone; LH – luteinizing hormone; GLUT4 – glucose transporter type 4