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Chronic cortisol elevation impairs insulin sensitivity and glucagon-mediated fasting glycaemia

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Abstract

Background: Chronic cortisol elevation, from prolonged stress, Cushing's syndrome, or therapeutic glucocorticoids, disrupts glucose homeostasis by impairing insulin signalling and enhancing hepatic glucose production, yet integrated hormonal mechanisms remain incompletely characterized [1,2]. **Objective:** This work aims to systematically review how chronic hypercortisolism affects: (I) peripheral insulin sensitivity; (II) compensatory glucagon secretion and hepatic sensitivity; and (III) fasting glycaemia maintenance in adult populations [2,3]. **Methods:** Systematic search (MEDLINE, Scopus, 2014–2025) of human studies reporting chronic cortisol/glucocorticoid exposure (endogenous or iatrogenic) and fasting metabolic outcomes. Inclusion criteria: adults (≥18 years) with measurements of fasting glycaemia, hepatic glucose production, insulin sensitivity, glucagon levels, or counterregulatory responses. Exclusion criteria: paediatric studies, pregnancy/lactation, animal/*in vitro* models, or studies lacking fasting measures or cortisol/glucagon data [4]. Thirteen peer-reviewed articles were synthesized. **Results:** Chronic excess of cortisol consistently impairs peripheral insulin sensitivity through post-receptor signalling defects and enhanced lipolysis, reducing insulin-dependent glucose uptake by skeletal muscle and adipose tissue [1,4]. Simultaneously, cortisol attenuates insulin's suppression of glucagon and increases hepatic glucagon receptor sensitivity, amplifying hepatic glucose production and gluconeogenesis [3]. These dual defects, diminished insulin efficacy combined with exaggerated glucagon actions, sustain fasting hyperglycaemia [2]. Central neural dysregulation and disrupted circadian feedback loops further destabilize basal glucose control, particularly in populations with obesity or prediabetes [3,5]. **Conclusions:** Chronic hypercortisolism triggers coordinated insulin–glucagon axis imbalance, impairing fasting glycaemia maintenance through combined peripheral resistance and enhanced hepatic glucose output [1]. Targeting hypothalamic–pituitary–adrenal (HPA) axis modulation and stress reduction may prevent glucocorticoid-related dysglycemia [2]. Standardized prospective cohort studies with detailed biomarker kinetics and longitudinal follow-up are essential to establish glucocorticoid-induced prediabetes risk profiles and evidence-based intervention strategies [4,5].

Keywords: cortisol; insulin resistance; glucagon; fasting glycaemia; glucocorticoids

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