The Obese Adrenals

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Abstract

Obesity is a complex disorder with systemic and endocrine implications. Recent insights highlight the adrenal gland as both a target and contributor in obesity-related metabolic dysfunction. Obesity-induced changes in adrenal morphology and hormone dynamics—particularly involving cortisol, aldosterone, and catecholamines—reinforce insulin resistance, visceral adiposity, and cardiovascular risk. Additionally, adrenal-driven conditions such as Cushing's syndrome, primary aldosteronism, and pheochromocytoma may present with obesity or metabolic syndrome, often underrecognized. This review explores the emerging concept of "obese adrenals," emphasizing the bidirectional relationship between adiposity and adrenal activity and the importance of recognizing endocrine subtypes within the broader spectrum of obesity.

Keywords: Adrenal, Cushings, obesity, overweight, pheochromocytoma

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Introduction

Obesity represents a rising global health crisis. In 2022, over 2.5 billion adults aged 18 years and older were classified as overweight, including 890 million living with obesity.[1] Globally, 43% of adults were overweight and 16% were obese.[1] This multifactorial disease results from an interplay of genetic, behavioural, and environmental factors, driven by endocrine and metabolic dysregulation. The adrenal glands, through their secretion of adrenal hormones play a central role in energy homeostasis, stress response, and fat distribution. Obesity can lead to overt as well as sub-clinical dysregulation of adrenal function. Chronic low-grade inflammation and metabolic stress in obesity are known to activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, both of which influence adrenal morphology and function.

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Adrenal Morphology in Obesity

The adrenal gland consists of two distinct regions: an outer cortex, which synthesizes steroid hormones such as mineralocorticoids, glucocorticoids, and androgens; and an inner medulla, responsible for the production of catecholamines. Obesity induced morphological changes in adrenal gland have been observed with studies demonstrating an increased adrenal gland volume.[2] Animal studies have demonstrated increased adrenal gland weight in obese mice on high fat diet compared to controls.[3]

Histological examinations in rodent models of obesity have demonstrated a distinct lipidomic profile, zona fasciculata changes, increased lipid droplet accumulation, and enhanced steroidogenic enzyme activity.[4,5] Radiological studies in obese patients have shown increased adrenal volume, particularly in the zona fasciculata.[6]

Specific histological changes in the adrenal medulla in obesity are not well-defined, however some animal studies in obese mice with hypothalamic obesity describe alterations in chromaffin cells.[7]

Adrenal Function in Obesity

Cortisol and Aldosterone Axis Dysregulation

Chronic low-grade inflammation is a hallmark of both obesity and stress. A bidirectional relationship exists between Inflammatory cytokines and the hypothalamic-pituitary-adrenal (HPA) axis, creating a dynamic feedback loop between cortisol and inflammatory mediators. Increased abdominal adiposity has been linked to dysregulation of the HPA axis. This is evident through exaggerated cortisol responses upon waking and during acute stress.[8] Adipocyte studies reveal increased local cortisol production, primarily driven by elevated expression of the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).

Catecholamine Hyperactivity

Obesity is frequently accompanied by heightened sympathetic nervous system (SNS) activity. This is implicated in the development of obesity-related comorbidities and end-organ damage.[9] SNS hyperactivity may represent a compensatory response to curb excess energy by promoting thermogenesis, thereby limiting further fat accumulation.[10]

Adrenal Androgen Dysfunction

Adrenal androgens, including dehydroepiandrosterone, DHEA-sulfate, and androstenedione, play significant roles in obesity, exhibiting a sex dichotomy with distinct patterns in men and women. Obese women often exhibit a state of functional hyperandrogenism, characterized by elevated androgen activity without overt endocrine disorders.[11] In contrast, obese men typically exhibit reduced testosterone levels and an attenuated luteinizing hormone (LH) secretory pattern, reflecting HPA dysregulation. The "metabolic valley of death" refers to a shared range of circulating testosterone levels where both men and women exhibit elevated metabolic risk—though due to opposing hormonal disturbances. In this overlapping zone, both low testosterone in men and excess androgens in women are linked to increased cardiometabolic complications.[12]

Metabolic Implications

Obesity-induced alterations in adrenal morphology and function contribute significantly to metabolic dysregulation. Increased adipose tissue is associated with exaggerated activity of the HPA axis, leading to elevated local cortisol production, particularly via upregulated 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in adipose tissue.[10] Additionally, obesity is linked to elevated aldosterone levels, which can impair glucose metabolism and exacerbate insulin resistance.[13] Furthermore, alterations in adrenal medullary function, including reduced epinephrine secretion, have been observed in obese individuals, potentially affecting energy expenditure and lipid metabolism.[14] Increased local cortisol, catecholamines, and aldosterone contribute to insulin resistance, endothelial dysfunction, and low-grade inflammation. Overall, these changes establish a feed-forward loop where adrenal dysfunction both results from and contributes to the metabolic complications of obesity.

Adrenal Driven Obesity

Cushing's Syndrome

Cushing's syndrome represents the prototypical form of adrenal-driven obesity, characterized by chronic cortisol excess leading to centripetal fat accumulation, insulin resistance, and a range of cardiometabolic complications. Unlike lifestyle-driven obesity, this phenotype is hormonally mediated and often improves with correction of cortisol excess. Notably, the fat distribution in Cushing's syndrome is more disproportionate with centripetal fat accumulation, particularly in the face, neck, and trunk, providing a clinical clue for differential diagnosis.[15] Table elucidates the distinguishing features between Cushing's Syndrome and Exogenous Obesity.

Primary Aldosteronism (PA)

Although classically associated with hypertension and/or hypokalaemia, PA can contribute to obesity via mineralocorticoid receptor activation, leading to insulin resistance. It is underdiagnosed in obese patients with hypertension. Obesity, particularly visceral adiposity, is associated with increased adipokine secretion—notably leptin—which has been shown to directly stimulate aldosterone production in the adrenal zona glomerulosa.[16] This leptin-aldosterone axis may promote sodium retention, hypertension, and further adipose tissue inflammation. Additionally, elevated aldosterone levels may contribute to insulin resistance and metabolic dysfunction, establishing a bidirectional relationship between excess adiposity and mineralocorticoid activity.

Pheochromocytoma

Although pheochromocytoma is known to be associated with weight loss due to catecholamine-driven hypermetabolism, recent data suggest that a subset of patients may present with overweight or obesity, particularly those with milder or intermittent catecholamine secretion. Chronic catecholamine excess can impair insulin signalling and promote glucose intolerance, potentially contributing to visceral adiposity.[17] These findings highlight the need to consider pheochromocytoma in obese patients with unexplained vasculometabolic presentations.

Pseudo-Cushing States

Pseudo-Cushing syndrome (PCS) or non-neoplastic hypercortisolism include chronic alcoholism, depression, sleep apnoea, and severe obesity which can mimic Cushing's syndrome clinically and biochemically. In obesity,

Table: Cushing's Syndrome vs Exogenous Obesity.

Feature	Cushing's Syndrome	Exogenous Obesity
History	Weight gain with proximal muscle weakness, easy bruisability	Gradual weight gain with high caloric intake, sedentary lifestyle
Physical Exam	Moon face, facial plethora, supraclavicular fat, centripetal obesity, livid purple striae, thin skin, muscle atrophy	Generalized obesity, usually without striae or muscle weakness
Investigations	Abnormal dexamethasone suppression, elevated midnight cortisol/ 24 hour urinary cortisol, altered ACTH levels±imaging	Normal cortisol profile/diurnal rhythm , preserved dexamethasone suppression
Treatment	Surgical resection, steroidogenesis inhibitors, pituitary/adrenal-directed therapy	Lifestyle modification, pharmacotherapy, bariatric surgery if indicated

there is enhanced cortisol reactivity in response to physical and psychosocial stressors as well as increased local cortisol production.[18] These changes create a state of functional hypercortisolism that promotes central adiposity and insulin resistance, mimicking Cushing's syndrome but without true cortisol excess. Careful clinical assessment and dynamic testing are essential for accurate differentiation.

Pseudo-pheochromocytoma

Pseudo pheochromocytoma is a syndrome presenting with paroxysmal hypertension, palpitations, and adrenergic symptoms in the absence of biochemical catecholamine excess.[19] In the context of obesity, especially in individuals with comorbid conditions such as obstructive sleep apnoea, metabolic stress, or emotional dysregulation, heightened sympathetic activity may drive these symptoms. Though it mimics pheochromocytoma clinically, plasma metanephrines and imaging remain normal. Management is supportive and often centers on psychosocial interventions, anxiolytics, and antihypertensives, rather than endocrine surgery or tumor-specific therapy.

Non-Functioning Adrenal Adenoma

Non-functioning adrenal adenomas (NFA) have been linked to increased prevalence of obesity, insulin resistance, and features of the metabolic syndrome. When compared to BMI-matched obese individuals, those with NFA often demonstrate a greater tendency for visceral fat accumulation and reduced insulin sensitivity. Subtle, undetected cortisol excess may underlie these metabolic disturbances. Alternatively, NFA may represent a consequence of chronic insulin resistance rather than its cause.[20]

Diagnostic & Therapeutic Considerations

The clinical overlap between adrenal-mediated obesity and primary obesity poses a diagnostic challenge. Initial adrenal screening may include low-dose dexamethasone suppression test, late-night salivary cortisol, aldosterone-renin ratio, plasma metanephrines, or imaging studies. Distinguishing pseudo-Cushing states from autonomous cortisol excess is particularly challenging and may require dynamic testing and evaluation of diurnal cortisol rhythm. Importantly, incidental adrenal lesions in obese patients (especially NFAs) must be carefully evaluated, even if hormone secretion appears minimal.

Understanding the role of adrenal hormone dynamics in obesity opens up new therapeutic possibilities.[21] In confirmed adrenal disorders, surgical or medical correction (e.g., adrenalectomy, mineralocorticoid receptor antagonists, steroidogenesis inhibitors) can result in definite metabolic improvement. Even in the absence of overt endocrine disease, targetting pathways such as 11β-HSD1 inhibition, sympathetic modulation, or mineralocorticoid receptor blockade may benefit selected patients with adrenal-predominant obesity phenotypes. Personalized treatment strategies, guided by endocrine profiling, may optimize outcomes beyond conventional lifestyle or pharmacologic obesity management. Early identification and intervention in adrenal-driven obesity could reduce long-term cardiovascular and metabolic complications.

Conclusion

The adrenal gland plays a pivotal role in the pathophysiology of obesity. From subtle hormonal alterations to overt endocrine disorders, adrenal dysfunction can drive or exacerbate the metabolic complications associated with excess adiposity. Managing adrenal-mediated obesity phenotypes calls for diagnostic vigilance and therapeutic astuteness. Research should focus on identifying biomarkers that differentiate adrenal-driven obesity from primary forms, and evaluating adreno-targetted therapies. A nuanced understanding of the "obese adrenal" may redefine obesity management.

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