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# Functional hypercortisolism, visceral obesity and metabolic syndrome

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Functional hypercortisolism (FH), defined as chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis, is a common finding in many conditions such as major depression, anorexia nervosa, bulimia nervosa, alcoholism, diabetes mellitus, obesity, polycystic ovary syndrome, obstructive sleep apnea syndrome, panic disorder, generalized anxiety disorder, shift work, and end-stage renal disease (1). Compare with Cushing syndrome, functional hypercortisolism is usually mild in terms of biochemical profile and clinical manifestations and probably reversible after the resolution of the underlying condition. Nonetheless, mild state does not necessarily mean harmless. In fact, many clinical observations have suggested an association between functional hypercortisolism and a number of complications. Among these complications, the components of metabolic syndrome, such as visceral obesity, dyslipidemia, type 2 diabetes mellitus, and hypertension are frequently present (1). Indeed, a similar link between mild hypercortisolism and metabolic syndrome was observed in adrenal incidentaloma-related subclinical hypercortisolism, a state caused by autonomous cortisol secretion from adrenal adenomas (2).

Despite numerous clinical studies demonstrating associations of functional hypercortisolism with harmful complications, the findings are not always consistent (1). One of the major confounding factors is the complexity of the complications associated with functional hypercortisolism. It is indeed not an easy task to pinpoint the harmful role of functional hypercortisolism in the setting of the underlying comorbidities. For instance, when a patient presents with depression, metabolic syndrome and functional hypercortisolism, it is difficult to ascertain if his/her metabolic syndrome is solely associated with functional hypercortisolism, since depression itself as well as certain anti-depressant medications can also be culprits. In this issue of *Endocrine Practice*, Tirabassi and colleagues studied the impact of functional hypercortisolism on body composition in patients with type 2 diabetes mellitus-associated late onset hypogonadism (3). Among 32 patients with type 2 diabetes mellitus-associated late onset hypogonadism, they identified 14 patients with functional hypercortisolism, defined as levels of 24 hour urinary free cortisol above the reference range and/or abnormal results of an overnight dexamethasone suppression test with a cortisol value greater than 1.8 mcg/dl. In addition, the presence of Cushing syndrome was ruled out in

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these patients. The other 18 patients had normal cortisol levels based on these tests and serve as the control group. Body composition was measured by whole-body dual energy x-ray absorptiometry (DXA) scanning and linear regression analysis was performed to evaluate the correlation of area-under-curve (AUC) cortisol following CRH stimulation with body composition. The analysis revealed a significant positive association between AUC cortisol and trunk and abdominal fat, and a significant negative association between AUC cortisol and lean leg mass, in the group with functional hypercortisolism, but not in the control group. A significantly higher waist circumference, and significantly higher abdominal fat (but not trunk, arm, leg or total fat) were found in patients with functional hypercortisolism than in the control group. These findings are significant because two major confounding factors, type 2 diabetes mellitus and late onset hypogonadism were effectively excluded because both conditions are present in functional hypercortisolism and control groups. This study reveals a more specific role of functional hypercortisolism in body composition and fat distribution.

The term *metabolic syndrome* was initially proposed after researchers identified that the majority of individuals who develop cardiovascular disease have several risk factors, such as hypertension, dyslipidemia and hyperglycemia, that generally cluster together. Subsequently, a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, including abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance ± glucose intolerance, a proinflammatory state, and a prothrombotic state have become known as the components of metabolic syndrome (4). Surprisingly, or not surprisingly, more than one third of US adults older than 20 years of age meet the criteria for metabolic syndrome (5). Importantly, given the fact that more than one third of the US population are obese, as defined by their body mass index (BMI) ≥30, the impact of obesity on our overall health has caught significant attention. A positive correlation between obesity and cardiovascular disease has been observed in various studies, and moreover, methodical studies have identified that abdominal obesity has the strongest association with cardiovascular disease. Abdominal or visceral obesity, manifest as increased waist circumference, is the type of obesity most closely associated with the metabolic syndrome. A strong association between visceral fat and insulin resistance has been shown in a meta-analysis of 40 observational studies (6). In parallel to the studies of the association between visceral obesity and insulin resistance, visceral fat was also found to be strictly and independently related to atherogenic dyslipidemia (7) and to a proinflammatory and prothrombotic state (8). Visceral obesity was also found at a higher rate in patients with coronary heart disease than that in subjects without coronary heart disease (9).

While an association between abdominal obesity and metabolic dysfunction has been established, the underlying mechanisms remain to be elucidated. Moreover, the etiological root contributing to visceral adiposity appears multifactorial. Age, gender, genetics, and ethnicity are recognized as causal factors for visceral obesity (10). In terms of the underlying mechanism, a role of local cortisol in visceral adipogenesis was implicated in both animal and human studies. In animal studies, increased local conversion of inactive cortisone to active cortisol by type 1 11β-hydroxysteroid dehydrogenase in adipose tissue was identified as one of the major factors contributing to visceral obesity (11). In human studies, type 1 11β-hydroxysteroid dehydrogenase expression in visceral adipose tissue is positively

associated with visceral obesity (12). Nonetheless, the role of type 1 11β-hydroxysteroid dehydrogenase activity in adipogenesis is not conclusive because inconsistent findings have been reported. A recent study investigated the cortisol levels across the weight spectrum in a group of women with normal weight, overweight/obese or underweight/anorexia nervosa. This study demonstrated a U-shaped curve relationship of cortisol levels with BMI and visceral adipose tissue. Surprisingly, the nadir cortisol level was found in the group with BMI 25–29.9 kg/m$^2$; i.e., overweight (13). The underlying significance of this finding remains to be determined but a recent meta-analysis showed that overweight (BMI of 25–<30) is associated with significantly lower all-cause mortality relative to normal weight (BMI of 18.5–<25) (14). Even though both the underweight state and severe obesity are associated with elevated cortisol levels, the crosstalk between HPA dynamics and visceral adiposity may vary in these two conditions. On one hand, the underweight state as occurs in patients with anorexia nervosa may activate the HPA axis to increase adrenal cortisol production. The elevated cortisol level in the underweight state does not cause visceral adipose accumulation due to the malnutrition-related deficiency of substrates for adipogenesis. On the other hand, the interaction between HPA activation and visceral obesity in subjects with severe obesity may be bidirectional. Functional hypercortisolism may contribute to visceral adipogenesis while the metabolic stress of visceral adiposity may activate the HPA axis.

The observation of marked sexual dimorphism in body fat patterning in humans suggests that sex steroid hormones play a critical role in adipose distribution. In fact, an important role of low androgens in visceral fat accumulation has been observed in clinical studies (15). Among male patients seeking medical care for obesity, the percentage with low serum androgen levels is relatively high. Furthermore, the prevalence of obesity among patients evaluated for male hypogonadism is also higher than in the general population. In contrast, weight loss in obese patients is associated with improvement of testosterone levels in men, while long-term treatment with testosterone in obese hypogonadal men results in weight loss and a decrease in visceral obesity. These clinical observations again suggest that, like the crosstalk between visceral obesity and hypercortisolism, there exist a bidirectional interaction between obesity and hypogonadism. In another words, obesity-related metabolic dysfunction and inflammatory state may inhibit the hypothalamic-pituitary-gonadal axis and lead to hypogonadotropic hypogonadism. Simultaneously, hypogonadism increases visceral fat accumulation.

In conclusion, a link between functional hypercortisolism and metabolic syndrome has been observed in an increasing number of clinical studies, yet some inconsistent and non-specific findings are present. Considering the clearer evidence of an increased rate of metabolic comorbidities from its counterpart, adrenal incidentaloma-related subclinical hypercortisolism, the negative impact of functional hypercortisolism on metabolic and cardiovascular consequences is very likely true and should be addressed. Further studies are needed to understand the optimal management for patients with functional hypercortisolism. In light of the bidirectional interaction between functional hypercortisolism and visceral adiposity, treating the underlying comorbidities may improve underlying conditions as well as functional hypercortisolism. On the other hand, treating functional hypercortisolism is an alternative strategy that remains to be explored. Unlike its counterpart, adrenal tumor-

associated subclinical hypercortisolism, which may be cured by surgical intervention to remove the adrenal tumor, medical management, if applicable, is the only treatment option for functional hypercortisolism. The question is how therapy for hypercortisolism would be best targeted. Although mifepristone, a glucocorticoid and progesterone receptor antagonist, has been approved by the FDA for the treatment of Cushing syndrome-related hyperglycemia, until one or more large scale, randomized clinical trials are performed to investigate the efficacy and adverse effects of glucocorticoid receptor antagonist treatments, the therapy of functional hypercortisolism by antagonizing cortisol action is merely a speculative option.

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