

## The Pathogenetic Role of Cortisol in the Metabolic Syndrome: A Hypothesis

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**Context:** The metabolic syndrome (MetS) is a cluster of metabolic abnormalities that increase the risk for type 2 diabetes mellitus and vascular disease. The common characteristics of MetS and hypercortisolemic conditions such as Cushing's syndrome (CS) suggest that the pathogenesis of MetS and central obesity might involve prolonged and excessive exposure to glucocorticoids. The present review summarizes the evidence on the potential role of cortisol in the pathogenesis of MetS and discusses new therapeutic approaches for these patients.

**Evidence Acquisition:** Using PubMed, we searched for publications during the last 20 yr regarding the possible pathogenetic role of cortisol in the development of MetS.

**Evidence Synthesis:** Emerging data suggest that patients with MetS show hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which leads to a state of "functional hypercortisolism." The cause for this activation of the HPA axis remains uncertain but may be partly associated with chronic stress and/or low birth weight, which are both associated with increased circulating cortisol levels and greater responsiveness of the HPA axis. Increased exposure to cortisol contributes to increased fat accumulation in visceral depots. However, cortisol metabolism is not only centrally regulated. The action of 11 $\beta$ -hydroxysteroid dehydrogenase-1 at the tissue level also modulates cortisol metabolism. Increased 11 $\beta$ -hydroxysteroid dehydrogenase-1 activity in adipose tissue and liver might contribute to the development of several features of the MetS.

**Conclusions:** MetS shares many characteristics of CS, and cortisol might play a role in the development of MetS at both a central and a peripheral level. (*J Clin Endocrinol Metab* 94: 2692–2701, 2009)

The metabolic syndrome (MetS) is a cluster of common abnormalities including hyperglycemia, abdominal obesity, reduced high-density lipoprotein cholesterol (HDL-C) levels, and elevated triglycerides (TG) and blood pressure (BP) (1, 2). MetS was originally described by Reaven in 1988 as "syndrome X" or "insulin resistance syndrome" (3). The components of MetS are associated with endothelial dysfunction and atherosclerosis and increase the risk for type 2 diabetes mellitus

(T2DM) as well as vascular morbidity and mortality (1, 2, 4–6). It is estimated that about one fourth of the world's adult population has MetS (5, 7, 8).

Despite the increasing prevalence of MetS worldwide, there is still a lack of uniformly accepted diagnostic criteria, and there is controversy regarding the pathogenesis of MetS. Different organizations have provided their own definitions of MetS (9). The most widely applied is based on the National Cholesterol Edu-

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Abbreviations: BP, Blood pressure; CHD, coronary heart disease; CS, Cushing's syndrome; CVD, cardiovascular disease; ET, endothelin; GR, glucocorticoid receptor(s); HDL-C, high-density lipoprotein cholesterol; HPA, hypothalamic-pituitary-adrenal; 11 $\beta$ -HSD, 11 $\beta$ -hydroxysteroid dehydrogenase; 11 $\beta$ -HSD1, 11 $\beta$ -HSD type 1; 11 $\beta$ -HSD2, 11 $\beta$ -HSD type 2; IGT, impaired glucose tolerance; MetS, metabolic syndrome; NO, nitric oxide; PPAR, peroxisome proliferator-activated receptor; SCS, subclinical CS; SUA, serum uric acid; T2DM, type 2 diabetes mellitus; TG, triglyceride(s).

cation Program (NCEP) Adult Treatment Panel-III (ATP-III) criteria (7, 8). According to this definition, MetS is diagnosed when three or more of the following parameters are present: waist circumference greater than 102 cm in men and greater than 88 cm in women, TG of at least 150 mg/dl ( $\geq 1.7$  mmol/liter), HDL-C less than 40 mg/dl ( $< 1.04$  mmol/liter) in men and less than 50 mg/dl ( $< 1.29$  mmol/liter) in women, BP of at least 130/85 mm Hg, and fasting glucose of at least 110 mg/dl ( $\geq 6.1$  mmol/liter) (2).

It is unclear whether a single primary abnormality triggers a cascade of diverse events that lead to the manifestation of the components of MetS. Because the diagnostic features of MetS are shared by Cushing's syndrome (CS), which results from endogenous or exogenous hypercortisolism, it was proposed that cortisol contributes to the pathogenesis of both states although only mild hypercortisolism occurs in MetS in contrast with CS (10, 11). It was also suggested that inhibiting cortisol action could provide a novel therapeutic approach for MetS (10, 11). Indeed, preliminary data suggest that circulating cortisol concentrations are higher in patients with MetS compared with healthy subjects, both in basal conditions and during dynamic stimulation (12–16). This difference is more evident in patients with MetS and hypertension or impaired glucose tolerance (IGT) (12–16). Furthermore, weight loss normalizes cortisol levels and improves insulin resistance (17). Despite the fact that cortisol levels are within the normal range, there is evidence of increased activity of cortisol in the periphery and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (11, 12). Differences between CS and MetS also need to be emphasized; in CS, once the tumor is removed, symptoms improve; in the MetS, weight loss reverses both hypercortisolism and phenotypic abnormalities (1, 2, 4–6, 17).

## Shared Features between MetS and CS

### Diagnostic features of MetS

#### Abdominal obesity

CS is characterized by a redistribution of adipose tissue from peripheral to central sites of the body, mainly in the truncal region and visceral depots (10). Similarly, central obesity is one of the main components of the MetS (2). Cortisol appears to play a role in adiposity in MetS. Indeed, an increase in urinary free cortisol excretion was reported in patients with MetS (18, 19), although a study that assessed the role of cortisol in body fat distribution and total fat in obese women did not confirm this finding (13). However, there was an increased urinary cortisone/cortisol ratio in women with increased abdominal fat compared with those with peripheral fat distribution, suggesting an increase in the peripheral metabolism of cortisol (13). Interestingly, cortisol clearance seems to be inversely correlated with insulin sensitivity, and this correlation is independent of body fat (20). It is also well documented that glucocorticoids promote the differentiation and proliferation of human adipocytes and that their receptors are more abundant in visceral than in sc adipose tissue (21). They also redistribute adiposity from peripheral to central depots, increase the size and number of fat cells, and

activate lipolysis and the release of free fatty acids into the circulation (22). The positive association of cortisol excess with intraabdominal fat was also shown in another study in which central fat distribution was evaluated using magnetic resonance imaging (15). A single morning cortisol measure was used to explore the correlation between HPA axis activity and MetS. Some researchers reported no relationship between cortisol and waist circumference (14) in contrast with the findings of earlier studies (23–26). Nevertheless, the link between obesity and cortisol levels remains the subject of debate.

Increased cortisol (urinary free and serum overnight) levels are also associated with insulin resistance (assessed using the homeostasis model assessment) (15–17, 26). Higher cortisol concentrations were related to a reduced insulin secretion, a finding consistent with *in vivo* and *in vitro* data showing that glucocorticoids regulate insulin secretion (27). Furthermore, a study conducted in obese children with or without insulin resistance (homeostasis model assessment  $> 4$  or  $\leq 4$ , respectively) showed that body weight reduction reduced both cortisol levels and insulin resistance in the insulin-resistant group. This was not shown in children without insulin resistance (17).

Several studies showed an increased responsiveness of the HPA axis to different stimuli in patients with abdominal obesity. These stimuli included food intake (28), low-dose tetracosactide (29), and CRH-arginine vasopressin (30, 31). Furthermore, abdominal adiposity appears to be associated with attenuated negative feedback in the HPA axis (32, 33) and with reduced diurnal variation in cortisol levels (33). Overall, there appears to be a hyperactivity of the HPA axis in patients with visceral obesity (Table 1).

#### High TG and low HDL-C levels

Hypertriglyceridemia and low HDL-C concentration are a common finding in both CS and MetS (2, 34, 35). Higher cortisol (both urinary free and serum overnight) levels have been associated with high TG and low HDL-C levels (12–16, 26, 34). Genetic variations in the glucocorticoid receptors (GR) also affect the activity of the HPA axis and lipid metabolism (36). The GR belong to the superfamily of nuclear receptors that are present in the cytoplasm and act as transcription factors to regulate gene expression. After cortisol binding, a conformational change occurs in GR leading to the dissociation of the receptor from a large complex of proteins, among which the heat shock protein 90 is the most important (37). The activated, ligand-bound GR translocates to the nucleus, where it exerts multiple actions (38). Polymorphisms of GR appear to modulate the sensitivity to endogenous glucocorticoids. In particular, the N363S and *BclI* polymorphisms are associated with hypersensitivity to glucocorticoids, whereas the ER22/23EK polymorphism is associated with a relative resistance to glucocorticoids (38). The N363S variant was recently associated with coronary heart disease (CHD), independently of obesity, as well as with increased total cholesterol and TG levels and total cholesterol/HDL-C ratio. Both the N363S and *BclI* polymorphisms may predispose to obesity. In contrast, carriers of the ER22/23EK variant appear to have reduced vascular risk (39).

**TABLE 1.** Evidence supporting the role of cortisol in the pathogenesis of MetS and obesity

Variables	Features of MetS	First author, date (Ref.)
Higher fasting cortisol levels	Central obesity	Brunner, 2002 (42)
	Waist circumference	Epel, 2000 (23); Pasquali, 2000 (24); Marniemi, 2002 (25); Ward, 2003 (26)
	TG levels	Phillips, 1998 (15); Ward, 2003 (26); Friedman, 1996 (34)
	BP, fasting glucose	Sen, 2008 (12); Duclos, 2005 (13); Weigensberg, 2008 (14); Phillips, 1998 (15); Brunner, 2002 (42)
	Insulin resistance	Phillips, 1998 (15); Reinehr, 2004 (17); Ward, 2003 (26)
Increased urinary free cortisol excretion	Central obesity	Marin, 1992 (18); Pasquali, 1993 (19); Misra, 2008 (16)
	High TG and low HDL-C levels	Garrapa, 2001 (50); Misra, 2008 (16)
Increased cortisol response to food intake	Central obesity	Korbonits, 1996 (28)
Increased cortisol response to low-dose ACTH test	Central obesity	Duclos, 2001 (29)
Increased cortisol response to CRH-arginine vasopressin test	Central obesity	Pasquali, 1996 (30); Pasquali, 2000 (24)
Resistance to low oral dexamethasone suppression test	Central obesity	Pasquali, 2002 (32); Rosmond, 1998 (33)
Loss of diurnal cortisol variation	Central obesity	Rosmond, 1998 (33)

### Hypertension

Hypertension is one of the most distinguishing features of CS because it is present in about 80% of adult patients and in almost half of children and adolescent patients (40). Many studies reported an association between cortisol and systolic and diastolic BP levels (12–16). This correlation might be attributed to the effect of stress, which is associated with the activation of the HPA axis and sympathetic nervous system (41). Indeed, patients with MetS and hypertension appear to have higher urine levels of both cortisol and catecholamine metabolites than healthy individuals (42). Another possible mechanism by which glucocorticoids elevate BP seems to be an increased responsiveness to vasoconstrictors along with a decreased vasodilator production because some studies have shown that a reduction in nitric oxide (NO; a vasodilator) production or bioavailability contributes to glu-

cocorticoid-induced hypertension (43). In addition, the endothelin (ET) system (especially ET-1, a major vasoconstrictor) is activated in CS, leading to elevated plasma ET-1 levels that probably play a role in the pathogenesis of early atherosclerosis in this disorder (44). It has been suggested that in MetS hyperinsulinemia and insulin resistance induce ET-1 release, which further contributes to renal injury that is frequently observed in these patients and provides another pathway to hypertension (45). Insulin exerts both pressor (through increased sympathetic neural flow) and depressor (through vasodilatation) actions, which cause no change or a slight rise in BP in normal subjects. In insulin resistance-hyperinsulinemia state, there is an imbalance between these two different effects (46).

Obesity (a common finding in both CS and MetS) is also associated with hypertension. The possible underlying mechanisms include volume expansion, increased cardiac output and systemic vascular resistance, increased sodium reabsorption, increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system, high leptin levels and concurrent leptin resistance, as well as increased ET-1 and decreased NO (46).

### Hyperglycemia

CS subjects frequently have elevated blood glucose levels (34). In patients with MetS, serum cortisol levels are significantly associated with fasting glucose concentration (12–16). The relationship between fasting hyperglycemia and cortisol is due to the glucocorticoid effects on hepatic gluconeogenesis and insulin secretion (47).

### Subclinical CS and the MetS

Clinically silent hypercortisolism, also known as subclinical CS (SCS), can be present in patients with adrenal incidentalomas. These lesions are characterized by autonomous glucocorticoid production without signs or symptoms of CS (48). However, clinically silent hypercortisolism, which is diagnosed with specific suppression tests, is not completely asymptomatic. SCS (as well as CS) is associated with a higher prevalence of insulin resistance, hypertension, obesity, IGT, and dyslipidemia (high TG and low HDL-C levels) (49–54). Moreover, carotid atherosclerosis was more prevalent in SCS subjects compared with healthy controls (51). Central abdominal obesity determined by waist-to-hip ratio and dual-energy x-ray absorptiometry is also more frequent in SCS patients (50, 52). Thus, it can be speculated that SCS may increase the risk for cardiovascular disease (CVD). Of note, all these metabolic abnormalities appear to improve after surgical resection of adrenal incidentalomas (52–54), although in a few studies unilateral adrenalectomy did not lead to significant improvement in CVD risk profile, despite normalization of cortisol levels (55, 56).

### Nondiagnostic features of MetS

#### Endothelial dysfunction and hypercoagulability

As mentioned above, MetS is associated with endothelial dysfunction that significantly predisposes to an increased risk for CVD (1, 2, 4–6). Endothelial dysfunction is also observed in

patients with CS. Brachial artery flow-mediated dilatation is lower in CS compared with healthy controls (57). The decreased levels of NO and the high ET-1 concentrations seen in CS also contribute to the progression of atherosclerosis (43, 44). Furthermore, emerging data suggest that CS is a thrombotic state, as a result of the higher levels of fibrinogen (51, 58) and homocysteine (59) seen in CS patients in comparison with healthy controls. Hypercoagulability is also present in MetS (60). Indeed, elevated fibrinogen and homocysteine concentrations have been observed in MetS patients compared with healthy controls (60, 61). Hyperfibrinogenemia and homocysteinemia seem to be independent risk factors for CVD and venous thrombosis (51). The derangement of hemostasis in CS is further supported by the high activity of factors XII, XI, IX, and VIII, as well as plasminogen and  $\alpha$  2-antiplasmin that is probably induced by cortisol excess (62). Increased levels of von Willebrand factor seen in CS, another marker of endothelial dysfunction, accompanied by heightened thrombin and plasmin generation, resolve after successful surgical management of CS (63). Finally, CS is also associated with impaired fibrinolysis due to the high levels of plasminogen activator inhibitor-1 observed in this state (64). The defective fibrinolytic potential contributes to hypercoagulability in CS.

### Uric acid

Elevated serum uric acid (SUA) levels are shared by MetS and CS (65, 66). High SUA levels are regarded as a predictor of cardiac and overall mortality in patients with CHD or stroke (67, 68). Elevated SUA is also associated with higher risk of stroke in patients with or without CHD (69). We demonstrated that statin (mainly atorvastatin) therapy is associated with a reduction in SUA levels along with an increase in estimated glomerular filtration rate in CHD patients with MetS (70, 71). This effect on renal function is perhaps due to an amelioration of endothelial function and renal blood flow (70). On the other hand, patients with CS may have higher SUA and urinary uric acid excretion than healthy subjects (66). This is probably a consequence of the hypercatabolic CS state and is independently correlated with increased body weight (66). However, a study evaluating the metabolic features in subjects with CS and nonsecretory adrenal incidentaloma in comparison with healthy controls did not find any difference in SUA between the three groups (50).

### Adipokines

Adipose tissue is recognized as an important endocrine organ that secretes a variety of bioactive peptides, termed adipokines (72, 73). These molecules exert multiple effects and play a key role in glucose and lipid metabolism, insulin sensitivity, BP, and angiogenesis. The major components of this family of proteins are adiponectin and leptin, which are mainly produced by adipose tissue (72–74). Both these proteins exert an insulin-sensitizing effect through fatty-acid oxidation and, in addition, adiponectin is associated with antiatherogenic, antidiabetic, and antiinflammatory properties. In obesity, insulin resistance has been linked to leptin resistance, elevated leptin, and low adiponectin levels, which are associated with higher CVD risk (72–74). Resistin is expressed in abdominal fat and is also associated with increased risk of central obesity-related diabetes (73). How-

ever, resistin may not be an “adipokine” because in humans it is mainly produced by monocytes, and its link with central obesity is debated (73). Excess adiposity leads to dysregulation of adipokine production, which in turn promotes a state of low-level systemic chronic inflammation predisposing to atherosclerosis (74).

Emerging data suggest a role of adipokines in CS. Glucocorticoids negatively regulate adiponectin mRNA in human visceral adipose tissue (75). A significant increase in adiponectin and a decrease in leptin levels after adrenalectomy and concomitant normalization of cortisol values have been reported in a patient with CS (76). Interestingly, in other reports adiponectin was lower in nonobese CS subjects than in nonobese controls, although its levels were not different in obese CS patients compared with obese controls (77). The data on leptin levels in CS are controversial. Some investigators reported normal concentrations (78, 79), whereas others reported elevated concentrations (80, 81). Finally, a study assessing the levels of adiponectin, leptin, and resistin in CS patients concluded that only resistin was significantly higher in female subjects than in control subjects. However, curative surgery only significantly reduced leptin values (79).

### The Role of Stress and Sleep Duration

Diverse stressful situations, including low socioeconomic status, chronic work stress (82, 83), anxiety, and depression (84, 85), may stimulate neuroendocrine responses. The HPA axis (together with the sympathetic nervous system) mediates the effects of stress on different organs and may induce insulin resistance via excessive cortisol production (86). Some studies showed elevated cortisol levels in situations such as work stress and unemployment (82, 83). Others reported that chronic life stress results in subtle hyperactivity of HPA axis leading to intraabdominal adiposity and development of MetS (23, 36, 84). Patients with MetS appear to have higher urinary excretion of cortisol metabolites compared with healthy subjects. The former also have increased excretion of normetanephrine and elevated levels of IL-6 and C-reactive protein. In a multifactorial analysis, psychological factors explained 5–37% of these differences between patients with MetS and controls (18).

Chronically activated HPA axis was associated with decreased diurnal variability of cortisol levels (87). It was also proposed that central fat distribution is related to greater psychological vulnerability to stress and greater cortisol reactivity (20), although some authors did not confirm these findings (88). Animal studies showed a dose-dependent increase in visceral fat during chronic stress (21, 90). *In vitro*, cortisol appears to increase lipoprotein lipase levels (a fat-storing enzyme) in adipose tissue and particularly in visceral fat (91). Furthermore, genetics may play a role in the relationship between stress and central fat. Genetics can account for up to 50% of the variance in fat distribution (92). There are also genetic influences on psychological coping with stress (93) and on cortisol reactivity (94). It is therefore possible that stress reactivity and central fat are genetically linked. More studies are needed to further determine whether stress and central obesity are causally related.

There is cumulative evidence that sleep duration is associated with MetS/CS states. In particular, increased cortisol levels have been reported in individuals with sleep deprivation (95). On the other hand, short sleep duration has been linked to increased risk of MetS and CVD (96, 97). Indeed, cross-sectional studies in adults have repeatedly found an association between reduced sleep and obesity (98, 99). A proposed mechanism is based on a neuroendocrine dysregulation of the appetite, and, in particular, on decreased levels of leptin (an anorexigenic hormone-adipokine) and increased levels of the orexigenic hormone ghrelin (98). Furthermore, sleep shortage has been linked to increased risk of glucose intolerance and T2DM (95, 100) as well as hypertension (101) and increased TG (98). Thus, it can be speculated that the elevated cortisol levels caused by shorter sleep duration may have a pathogenetic mechanism in the generation of the MetS/CS phenotype. We must also state that there is evidence linking long sleep duration (>8 h) with MetS and glucose intolerance, although the exact mechanism is not clarified and evidence providing association with CVD risk is mixed (98).

### Low Birth Weight

Several studies showed that low birth weight is associated with increased prevalence of MetS and vascular disease in adult life. Although the exact mechanisms are not known, resetting of major hormonal axes controlling growth and development might explain this association (15, 102, 103). Recent studies suggested that subtle abnormalities of the HPA axis might be of particular importance in the association between reduced fetal growth and the development of MetS in adult life. Fetal malnutrition results in glucocorticoid overproduction, and low birth weight babies have elevated umbilical cord blood cortisol concentrations, as well as elevated excretion of glucocorticoid metabolites during childhood (104, 105).

A study carried out in 60- to 70-yr-old men suggested that fasting plasma cortisol concentrations are inversely related to birth weight independently of age and body mass index (15). Both birth and infant weights appear also to be inversely associated with the prevalence of IGT and T2DM (106, 107). This relationship was independent of known risk factors for T2DM, including body mass index during adulthood (106, 107). These data are in accordance with experimental studies in pregnant rats, where exposure to a variety of stressful stimuli (low-protein diet, restraint and nonabortive infections) induced corticosteroid secretion in adult life (108, 109).

### 11 $\beta$ -Hydroxysteroid Dehydrogenase (11 $\beta$ -HSD)

Overall, it appears that relative hypercortisolemia may contribute to the development of different features of MetS. However, it is not clear whether glucocorticoids play a role the pathogenesis of obesity. Circulating cortisol levels are not always elevated in obese subjects, and in some studies they are lower than lean subjects (110–112). This might be partly explained by enhanced metabolic clearance of cortisol because obese patients show in-

creased urinary excretion of free cortisol and metabolites (13, 112). Indeed, there are other determinants of cortisol action besides the circulating levels. In this context, the local expression of 11 $\beta$ -hydroxysteroid dehydrogenase (11 $\beta$ -HSD) appears to play an important role in the interplay between cortisol and adiposity. 11 $\beta$ -HSD catalyzes the conversion of the hormonally active C11-hydroxylated glucocorticoids (cortisol, corticosterone) to their inactive C11-keto metabolites (cortisone, 11-dehydrocorticosterone) (113, 114). Two 11 $\beta$ -HSD isoforms have been described: 11 $\beta$ -HSD type 1 (11 $\beta$ -HSD1) and 11 $\beta$ -HSD type 2 (11 $\beta$ -HSD2). 11 $\beta$ -HSD2 is a high-affinity nicotinamide adenine dinucleotide-dependent dehydrogenase that protects the mineralocorticoid receptor in renal tubules from excess stimulation by cortisol. It has also been identified in the colon, salivary glands, and placenta (113, 114). Mutations in the 11 $\beta$ -HSD2 gene cause an inherited form of hypertension, the syndrome of “apparent mineralocorticoid excess,” in which cortisol acts as a potent mineralocorticoid (115). Moreover, homozygous deletion of 11 $\beta$ -HSD2 in mice results in hypertension and hypokalemia, along with suppressed plasma renin and aldosterone levels (114).

11 $\beta$ -HSD1 acts predominantly as a reductase (converting inactive cortisone to active cortisol) rather than a dehydrogenase (in the opposite direction). Thus, 11 $\beta$ -HSD1 facilitates the action of glucocorticoids in key targets such as liver and adipose tissue. 11 $\beta$ -HSD1 is a low-affinity nicotinamide adenine dinucleotide-dependent dehydrogenase, and besides liver and fat, it is also expressed in gonadal tissue and central nervous system (113, 114, 116). The expression of 11 $\beta$ -HSD1 appears to be higher in omental than sc fat. Its activity was further increased *in vitro* when omental adipose stromal cells were treated with cortisol and insulin (116). Thus, 11 $\beta$ -HSD1 results in higher intraadipose cortisol levels in obese subjects (11, 105, 110, 117), although some studies have not confirmed this finding (118).

Genetic studies in mice suggest that increased 11 $\beta$ -HSD1 expression or activity increases the risk for several components of MetS, including visceral adiposity, hypertension, and insulin resistance. Overexpression of 11 $\beta$ -HSD1 in the liver is associated with the development of fatty liver disease and an increase in serum total cholesterol and TG levels (119). In contrast, 11 $\beta$ -HSD1 knockout mice have reduced risk for obesity and MetS (120). Interestingly, wild-type mice show a down-regulation of 11 $\beta$ -HSD1 expression in the adipose tissue in response to high-fat feeding, indicating that this enzyme is subject to regulatory feedback during changes in energy balance (121).

Overactivity of 11 $\beta$ -HSD1 is associated with enhanced expression of GR $\alpha$  in adipose tissue and increased intracellular conversion of cortisone to cortisol (121, 122). A recent study also suggested that adipocyte-derived cytokines, including TNF- $\alpha$  and IL-1 $\beta$ , may stimulate the transcriptional activity of the 11 $\beta$ -HSD1 gene (123). The overtranscription of 11 $\beta$ -HSD1 gene in adipose tissue is associated with obesity, insulin resistance, and increased levels of leptin, resistin, TNF- $\alpha$ , and IL-6 (123, 124). Overall, the role of 11 $\beta$ -HSD1 in cortisol metabolism seems to be complex. Interestingly, hepatic 11 $\beta$ -HSD1 activity was reduced in obese patients in some studies, suggesting a divergent regulation of 11 $\beta$ -HSD1 in different tissues (121, 125). Of note, there was no difference in 11 $\beta$ -HSD1 mRNA levels between

patients with CS and subjects with normal weight. It appears that 11 $\beta$ -HSD1 activity is down-regulated in CS due to the chronic exposure to glucocorticoids, suggesting a negative feedback relationship between 11 $\beta$ -HSD1 and glucocorticoids (126).

## Future Treatments

11 $\beta$ -HSD1 might represent a promising therapeutic target in obesity and MetS. Studies in diabetic and obese rodents indicate that pharmacological inhibition of 11 $\beta$ -HSD1 activity ameliorates insulin resistance and glucose levels and induces weight loss (127–136). In humans, peroxisome proliferator-activated receptor (PPAR)- $\gamma$  agonists used as antidiabetic drugs (known as thiazolidinediones) appear to inhibit the transcriptional activity of 11 $\beta$ -HSD1 in adipose tissue and to decrease the tissue-specific concentration of glucocorticoids (110, 122, 127). PPAR- $\gamma$  is expressed at high levels in adipose tissue and at much lower levels in liver and muscle. It was proposed that the effects of thiazolidinediones on insulin sensitivity may be partly explained by the down-regulation of 11 $\alpha$ -HSD1 in the adipose tissue (129). The decrease of 11 $\beta$ -HSD1 expression in adipocytes by rosiglitazone was also demonstrated in mice (130). Clofibrate—a PPAR- $\alpha$  agonist that is used in patients with hypertriglyceridemia—and metformin also inhibit 11 $\beta$ -HSD1 activity (122). These data suggest that the beneficial effects of these drugs on IGT and dyslipidemia might be partly mediated by the inhibition of 11 $\beta$ -HSD1 gene expression, resulting in a decrease in the intracellular concentration of glucocorticoids in the liver. In contrast to the beneficial effects of 11 $\beta$ -HSD1 inhibition, 11 $\beta$ -HSD2 inhibition results in activation of the mineralocorticoid receptor by cortisol, leading to hypertension (115).

Inhibitors of 11 $\beta$ -HSD1 must be potent and selective. For example, carbenoxolone, a natural product derived from liquorice, although it improves insulin sensitivity, is neither potent nor selective for 11 $\beta$ -HSD1 in adipose tissue (131). Potent and selective inhibitors of 11 $\beta$ -HSD1 have been developed and include arylsulfonamidothiazoles (132), adamantyl triazoles (133), and anilinothiazolones (134). Arylsulfonamidothiazoles and particularly the diethylamide 2a derivative potently inhibit human 11 $\beta$ -HSD1, whereas the 2b analog inhibits only the murine 11 $\beta$ -HSD1 and reduces glucose levels in diabetic mice (132). The aryl sulfonamide derivatives reduced insulin levels and improved IGT when administered to rodents for 7 d (126). Adamantyl triazoles reduced body weight and delayed the progression of atherosclerosis in mice (128, 133). Anilinothiazolones are also potent inhibitors of 11 $\beta$ -HSD1 in rats (134). Three other novel selective inhibitors of 11 $\beta$ -HSD1 were recently developed: PF-877423, BVT116429, and BVT2733. PF-877423 reduces adipogenesis *in vitro* (particularly in omental depots) (135). Treatment of diabetic mice with BVT116429 reduced blood glucose levels and increased adipokine levels (an insulin-sensitizing adiponectin), whereas BVT2733 improved glycated hemoglobin levels but had no effect on adiponectin (136) (Table 2). It remains for these promising preliminary findings to be confirmed in human studies.

**TABLE 2.** Potential therapeutic interventions based on the putative interplay between cortisol metabolism and development of the MetS

Underlying mechanism	Proposed regimen
Chronic stress	Psychosocial interventions to reduce stress and depression Improvement of working conditions
11 $\beta$ -HSD1 hyperactivity	Rosiglitazone (PPAR- $\gamma$ agonist) Clofibrate (PPAR- $\alpha$ agonist) Metformin Arylsulfonamidothiazoles Anilinothiazolones Adamantyl triazoles PF-877423 BVT116429 BVT2733

Finally, we must report the effect of chronic treatment of d-fenfluramine on rats, which decreased the release of cortisol and fatty acids in response to stress and improved insulin sensitivity. The effects of d-fenfluramine were also evaluated in male rats that are prone to developing atherosclerosis and myocardial infarction. Administration of d-fenfluramine improved insulin sensitivity, decreased TG levels, and decreased myocardial necrosis (137). However, this drug is no longer marketed due to its association with cardiac valve disease and other side effects (89). Therefore, d-fenfluramine is not recommended for clinical studies.

## Conclusions

MetS is a cluster of abnormalities that predispose to the development of diabetes, atherosclerosis, and CVD, although many patients with MetS may already have diabetes and/or vascular disease. Therefore, it is important to always specify whether MetS is or is not accompanied by diabetes. Because MetS shares many characteristics of CS, it was proposed that the pathogenesis of MetS and central obesity involves prolonged and excessive glucocorticoid exposure. Emerging data suggest that patients with MetS are characterized by hyperactivity of the HPA axis, which leads to “functional hypercortisolism.” Stress seems to play an important role in this interplay through an increase in the responsiveness of the HPA axis. Low birth weight was also associated with increased circulating cortisol levels, suggesting that the HPA axis may be permanently dysregulated due to early life events. 11HSD1 is a key enzyme in glucocorticoid metabolism in peripheral tissues (particularly in the adipose tissue and liver). 11HSD1 overexpression in adipocytes is observed in MetS and central obesity and results in increased conversion of cortisone to cortisol and in excessive tissue-specific glucocorticoid activity. Experimental studies with 11HSD1 inhibitors further support the role of 11HSD1 in the pathogenesis of MetS and might provide novel therapeutic approaches in patients with MetS or obesity.

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