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

Panagiotis Anagnostis, Vasilios G. Athyros, Konstantinos Tziomalos, Asterios Karagiannis, and Dimitri P. Mikhailidis

Endocrinology Clinic (P.A.), Hippokration Hospital, GR-546 42 Thessaloniki, Greece; Second Propedeutic Department of Internal Medicine (V.G.A., A.K.), Medical School, Aristotle University of Thessaloniki, Hippokration Hospital, GR-546 42 Thessaloniki, Greece; and Departments of Clinical Biochemistry (Vascular Prevention Clinic) and Surgery (K.T., D.P.M.), Royal Free Hospital Campus, University College Medical School, University College London, London NW3 2QG, United Kingdom

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 11β-hydroxysteroid dehydrogenase-1 at the tissue level also modulates cortisol metabolism. Increased 11β-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-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2009-0370 Received February 17, 2009. Accepted May 19, 2009.
First Published Online May 26, 2009

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; 11β-HSD, 11β-hydroxysteroid dehydrogenase; 11β-HSD1, 11β-HSD type 1; 11β-HSD2, 11β-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 (≥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 (≥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 ≤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 *Bcl*I 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 *Bcl*I 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 glucocorticoid-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 α 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). However, 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).

11β-Hydroxysteroid Dehydrogenase (11β-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 increased 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 11β-hydroxysteroid dehydrogenase (11β-HSD) appears to play an important role in the interplay between cortisol and adiposity. 11β-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 11β-HSD isoforms have been described: 11β-HSD type 1 (11β-HSD1) and 11β-HSD type 2 (11β-HSD2). 11β-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 11β-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 11β-HSD2 in mice results in hypertension and hypokalemia, along with suppressed plasma renin and aldosterone levels (114).

11β-HSD1 acts predominantly as a reductase (converting inactive cortisone to active cortisol) rather than a dehydrogenase (in the opposite direction). Thus, 11β-HSD1 facilitates the action of glucocorticoids in key targets such as liver and adipose tissue. 11β-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 11β-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, 11β-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 11β-HSD1 expression or activity increases the risk for several components of MetS, including visceral adiposity, hypertension, and insulin resistance. Overexpression of 11β-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, 11β-HSD1 knockout mice have reduced risk for obesity and MetS (120). Interestingly, wild-type mice show a down-regulation of 11β-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 11β-HSD1 is associated with enhanced expression of GRa in adipose tissue and increased intracellular conversion of cortisone to cortisol (121, 122). A recent study also suggested that adipocyte-derived cytokines, including TNF-α and IL-1β, may stimulate the transcriptional activity of the 11β-HSD1 gene (123). The overtranscription of 11β-HSD1 gene in adipose tissue is associated with obesity, insulin resistance, and increased levels of leptin, resistin, TNF-α, and IL-6 (123, 124). Overall, the role of 11β-HSD1 in cortisol metabolism seems to be complex. Interestingly, hepatic 11β-HSD1 activity was reduced in obese patients in some studies, suggesting a divergent regulation of 11β-HSD1 in different tissues (121, 125). Of note, there was no difference in 11β-HSD1 mRNA levels between

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

Future Treatments

11β-HSD1 might represent a promising therapeutic target in obesity and MetS. Studies in diabetic and obese rodents indicate that pharmacological inhibition of 11β-HSD1 activity ameliorates insulin resistance and glucose levels and induces weight loss (127–136). In humans, peroxisome proliferator-activated receptor (PPAR)-γ agonists used as antidiabetic drugs (known as thiazolidinediones) appear to inhibit the transcriptional activity of 11β-HSD1 in adipose tissue and to decrease the tissue-specific concentration of glucocorticoids (110, 122, 127). PPAR-γ 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 11α-HSD1 in the adipose tissue (129). The decrease of 11β-HSD1 expression in adipocytes by rosiglitazone was also demonstrated in mice (130). Clofibrate—a PPAR-α agonist that is used in patients with hypertriglyceridemia—and metformin also inhibit 11β-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 11β-HSD1 gene expression, resulting in a decrease in the intracellular concentration of glucocorticoids in the liver. In contrast to the beneficial effects of 11β-HSD1 inhibition, 11β-HSD2 inhibition results in activation of the mineralocorticoid receptor by cortisol, leading to hypertension (115).

Inhibitors of 11β-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 11β-HSD1 in adipose tissue (131). Potent and selective inhibitors of 11β-HSD1 have been developed and include arylsulfonamidothiazoles (132), adamantyl triazoles (133), and anilinothiazolones (134). Arylsulfonamidothiazoles and particularly the diethylamide 2a derivative potently inhibit human 11β-HSD1, whereas the 2b analog inhibits only the murine 11β-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 11β-ÇSD1 in rats (134). Three other novel selective inhibitors of 11β-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
11β-HSD1 hyperactivity	Rosiglitazone (PPAR-γ agonist)
	Clofibrate (PPAR-α 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.

Acknowledgments

Address all correspondence and requests for reprints to: Dimitri P. Mikhailidis, M.D., FFPM, FRCP, FRCPath, Academic Head, Department of Clinical Biochemistry, Royal Free Hospital Campus, University College Medical School, University College London, Pond Street, London NW3 2QG, United Kingdom. E-mail: MIKHAILIDIS@aol.com.

Disclosure Summary: The authors have nothing to declare.

References

1. **Obunai K, Jani S, Dangas GD** 2007 Cardiovascular morbidity and mortality of the metabolic syndrome. Med Clin North Am 91:1169–1184, x
2. 2002 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report 2002. Circulation 106:3143–3421
3. **Reaven GM** 1988 Role of insulin resistance in human disease. Diabetes 37: 1595–1607
4. **Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT** 2002 The metabolic syndrome and total and cardiovascular disease mortality in middle aged men. JAMA 288:2709–2716
5. **Kolovou GD, Anagnostopoulou KK, Salpea KD, Mikhailidis DP** 2007 The prevalence of metabolic syndrome in various populations. Am J Med Sci 333:362–371
6. **Athyros VG, Mikhailidis DP, Papageorgiou AA, Didangelos TP, Ganotakis ES, Symeonidis AN, Daskalopoulou SS, Kakafika AI, Elisaf M; METS-GREECE Collaborative Group** 2004 Prevalence of atherosclerotic vascular disease among subjects with the metabolic syndrome with or without diabetes mellitus: the METS-GREECE Multicentre Study. Curr Med Res Opin 20: 1691–1701
7. **Athyros VG, Ganotakis ES, Elisaf M, Mikhailidis DP** 2005 The prevalence of the metabolic syndrome using the National Cholesterol Educational Program and International Diabetes Federation definitions. Curr Med Res Opin 21: 1157–1159
8. **Athyros VG, Ganotakis ES, Elisaf MS, Liberopoulos EN, Goudevenos IA, Karagiannis A; GREECE-METS Collaborative Group** 2007 Prevalence of vascular disease in metabolic syndrome using three proposed definitions. Int J Cardiol 117:204–210
9. **Daskalopoulou SS, Athyros VG, Kolovou GD, Anagnostopoulou KK, Mikhailidis DP** 2006 Definitions of metabolic syndrome: where are we now? Curr Vasc Pharmacol 4:185–197
10. **Pasquali R, Vicennati V, Cacciari M, Pagotto U** 2006 The hypothalamic-pituitary-adrenal axis activity in obesity and the metabolic syndrome. Ann NY Acad Sci 1083:111–128
11. **Walker BR** 2006 Cortisol—cause and cure for metabolic syndrome? Diabet Med 23:1281–1288
12. **Sen Y, Aygun D, Yilmaz E, Ayar A** 2008 Children and adolescents with obesity and the metabolic syndrome have high circulating cortisol levels. Neuro Endocrinol Lett 29:141–145
13. **Duclos M, Marquez Pereira P, Barat P, Gatta B, Roger P** 2005 Increased cortisol bioavailability, abdominal obesity, and the metabolic syndrome in obese women. Obes Res 13:1157–1166
14. **Weigensberg MJ, Toledo-Corral CM, Goran MI** 2008 Association between the metabolic syndrome and serum cortisol in overweight Latino youth. J Clin Endocrinol Metab 93:1372–1378
15. **Phillips DI, Barker DJ, Fall CH, Seckl JR, Whorwood CB, Wood PJ, Walker BR** 1998 Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? J Clin Endocrinol Metab 83: 757–760
16. **Misra M, Bredella MA, Tsai P, Mendes N, Miller KK, Klibanski A** 2008 Lower growth hormone and higher cortisol are associated with greater visceral adiposity, intramyocellular lipids, and insulin resistance in overweight girls. Am J Physiol Endocrinol Metab 295:E385–E392
17. **Reinehr T, Andler W** 2004 Cortisol and its relation to insulin resistance before and after weight loss in obese children. Horm Res 62:107–112
18. **Mårin P, Darin N, Amemiya T, Andersson B, Jern S, Björntorp P** 1992 Cortisol secretion in relation to body fat distribution in obese premenopausal women. Metabolism 41:882–886
19. **Pasquali R, Cantobelli S, Casimirri F, Capelli M, Bortoluzzi L, Flamia R, Labate AM, Barbara L** 1993 The hypothalamic-pituitary-adrenal axis in obese women with different patterns of body fat distribution. J Clin Endocrinol Metab 77:341–346
20. **Holt HB, Wild SH, Postle AD, Zhang J, Koster G, Umpleby M, Shojaee-Moradie F, Dewbury K, Wood PJ, Phillips DI, Byrne CD** 2007 Cortisol clearance and associations with insulin sensitivity, body fat and fatty liver in middle-aged men. Diabetologia 50:1024–1032
21. **Rebuffé-Scrive M, Walsh UA, McEwen B, Rodin J** 1992 Effect of chronic stress and exogenous glucocorticoids on regional fat distribution and metabolism. Physiol Behav 52:583–590
22. **Rebuffé-Scrive M, Krotkiewski M, Elfverson J, Björntorp P** 1988 Muscle and adipose tissue morphology and metabolism in Cushing's syndrome. J Clin Endocrinol Metab 67:1122–1128
23. **Epel ES, McEwen B, Seeman T, Matthews K, Castellazzo G, Brownell KD, Bell J, Ickovics JR** 2000 Stress and body shape: stress-induced cortisol secretion is consistently greater among women with central fat. Psychosom Med 62:623–632
24. **Pasquali R, Vicennati V** 2000 Activity of the hypothalamic-pituitary-adrenal axis in different obesity phenotypes. Int J Obes Relat Metab Disord 24(Suppl 2):S47–S49
25. **Marniemi J, Kronholm E, Aunola S, Toikka T, Mattlar CE, Koskenvuo M, Rönnemaa T** 2002 Visceral fat and psychosocial stress in identical twins discordant for obesity. J Intern Med 251:35–43
26. **Ward AM, Fall CH, Stein CE, Kumaran K, Veena SR, Wood PJ, Syddall HE, Phillips DI** 2003 Cortisol and the metabolic syndrome in South Asians. Clin Endocrinol (Oxf) 58:500–505
27. **Delaunay F, Khan A, Cintra A, Davani B, Ling ZC, Andersson A, Ostenson CG, Gustafsson J, Efendic S, Okret S** 1997 Pancreatic β-cells are important targets for the diabetogenic effects of glucocorticoids. J Clin Invest 100:2094–2098
28. **Korbonits M, Trainer PJ, Nelson ML, Howse I, Kopelman PG, Besser GM, Grossman AB, Svec F** 1996 Differential stimulation of cortisol and dehydroepiandrosterone levels by food in obese and normal subjects: relation to body fat distribution. Clin Endocrinol (Oxf) 45:699–706
29. **Duclos M, Gatta B, Corcuff JB, Rashedi M, Pehourcq F, Roger P** 2001 Fat distribution in obese women is associated with subtle alterations of the hypothalamic-pituitary-adrenal axis activity and sensitivity to glucocorticoids. Clin Endocrinol (Oxf) 55:447–454
30. **Pasquali R, Anconetani B, Chattat R, Biscotti M, Spinucci G, Casimirri F, Vicennati V, Carcello A, Labate AM** 1996 Hypothalamic-pituitary-adrenal axis activity and its relationship to the autonomic nervous system in women with visceral and subcutaneous obesity: effects of the corticotropin-releasing factor/arginine-vasopressin test and of stress. Metabolism 45:351–356
31. **Pasquali R, Vicennati V** 2000 The abdominal obesity phenotype and insulin resistance are associated with abnormalities of the hypothalamic-pituitary-adrenal axis in humans. Horm Metab Res 32:521–525
32. **Pasquali R, Ambrosi B, Armanini D, Cavagnini F, Uberti ED, Del Rio G, de Pergola G, Maccario M, Mantero F, Marugo M, Rotella CM, Vettor R; Study Group on Obesity of the Italian Society of Endocrinology** 2002 Cortisol and ACTH response to oral dexamethasone in obesity and effects of sex, body fat distribution, and dexamethasone concentrations: a dose-response study. J Clin Endocrinol Metab 87:166–175
33. **Rosmond R, Dallman MF, Björntorp P** 1998 Stress-related cortisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. J Clin Endocrinol Metab 83:1853–1859
34. **Friedman TC, Mastorakos G, Newman TD, Mullen NM, Horton EG, Costello R, Papadopoulos NM, Chrousos GP** 1996 Carbohydrate and lipid metabolism in endogenous hypercortisolism: shared features with metabolic syndrome X and NIDDM. Endocr J 43:645–655
35. **Colao A, Pivonello R, Spiezia S, Faggiano A, Ferone D, Filippella M, Marzullo P, Cerbone G, Siciliani M, Lombardi G** 1999 Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure. J Clin Endocrinol Metab 84:2664–2672
36. **Björntorp P, Rosmond R** 1999 Hypothalamic origin of the metabolic syndrome X. Ann NY Acad Sci 892:297–307
37. **Pratt WB, Toft DO** 1997 Steroid receptor interactions with heat shock protein and immunophilinchaperones. Endocr Rev 18:306–360
38. **Schaaf MJ, Cidlowski JA** 2003 Molecular determinants of glucocorticoid receptor mobility in living cells: the importance of ligand affinity. Mol Cell Biol 23:1922–1934
39. **van Rossum EF, Lamberts SW** 2004 Polymorphisms in the glucocorticoid receptor gene and their associations with metabolic parameters and body composition. Recent Prog Horm Res 59:333–357
40. **Magiakou MA, Smyrnaki P, Chrousos GP** 2006 Hypertension in Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 20:467–482

41. **Folkow B** 1997 Physiological aspects of the "defense" and "defeat" reactions. Acta Physiol Scand Suppl 640:34–37
42. **Brunner EJ, Hemingway H, Walker BR, Page M, Clarke P, Juneja M, Shipley MJ, Kumari M, Andrew R, Seckl JR, Papadopoulos A, Checkley S, Rumley A, Lowe GD, Stansfeld SA, Marmot MG** 2002 Adrenocortical, autonomic, and inflammatory causes of the metabolic syndrome: nested case-control study. Circulation 106:2659–2665
43. **Mitchell BM, Webb RC** 2002 Impaired vasodilation and nitric oxide synthase activity in glucocorticoid-induced hypertension. Biol Res Nurs 4:16–21
44. **Kirilov G, Tomova A, Dakovska L, Kumanov P, Shinkov A, Alexandrov AS** 2003 Elevated plasma endothelin as an additional cardiovascular risk factor in patients with Cushing's syndrome. Eur J Endocrinol 149:549–553
45. **Sarafidis PA, Lasaridis AN** 2008 Insulin resistance and endothelin: another pathway for renal injury in patients with the cardiometabolic syndrome? J Cardiometab Syndr 3:183–187
46. **Karagiannis A, Mikhailidis DP, Athyros VG, Kakafika AI, Tziomalos K, Liberopoulos EN, Florentin M, Elisaf M** 2007 The role of renin-angiotensin system inhibition in the treatment of hypertension in metabolic syndrome: are all the angiotensin receptor blockers equal? Expert Opin Ther Targets 11: 191–205
47. **Lambillotte C, Gilon P, Henquin JC** 1997 Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. J Clin Invest 99:414–423
48. **Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR** 2004 The clinically inapparent adrenal mass: update in diagnosis and management. Endocr Rev 25:309–340
49. **Terzolo M, Pia A, Alì A, Osella G, Reimondo G, Bovio S, Daffara F, Procopio M, Paccotti P, Borretta G, Angeli A** 2002 Adrenal incidentaloma: a new cause of the metabolic syndrome? J Clin Endocrinol Metab 87:998–1003
50. **Garrapa GG, Pantanetti P, Arnaldi G, Mantero F, Faloia E** 2001 Body composition and metabolic features in women with adrenal incidentaloma or Cushing's syndrome. J Clin Endocrinol Metab 86:5301–5306
51. **Tauchmanovà L, Rossi R, Biondi B, Pulcrano M, Nuzzo V, Palmieri EA, Fazio S, Lombardi G** 2002 Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J Clin Endocrinol Metab 87:4872–4878
52. **Rossi R, Tauchmanova L, Luciano A, Di Martino M, Battista C, Del Viscovo L, Nuzzo V, Lombardi G** 2000 Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J Clin Endocrinol Metab 85:1440–1448
53. **Reincke M, Nieke J, Krestin GP, Saeger W, Allolio B, Winkelmann W** 1992 Preclinical Cushing's syndrome in adrenal "incidentalomas": comparison with adrenal Cushing's syndrome. J Clin Endocrinol Metab 75:826–832
54. **Barzon L, Fallo F, Sonino N, Boscaro M** 2002 Development of overt Cushing's syndrome in patients with adrenal incidentaloma. Eur J Endocrinol 146:61–66
55. **Erbil Y, Ademoðlu E, Ozbey N, Barbaros U, Yanik BT, Salmaslioðlu A, Bozbora A, Ozarmaðan S** 2006 Evaluation of the cardiovascular risk in patients with subclinical Cushing syndrome before and after surgery. World J Surg 30:1665–1671
56. **Faggiano A, Pivonello R, Spiezia S, De Martino MC, Filippella M, Di Somma C, Lombardi G, Colao A** 2003 Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J Clin Endocrinol Metab 88:2527–2533
57. **Baykan M, Erem C, Gedikli O, Hacihasanoglu A, Erdogan T, Kocak M, Durmu° I, Korkmaz L, Celik S** 2007 Impairment of flow-mediated vasodilatation of brachial artery in patients with Cushing's Syndrome. Endocrine 31:300–304
58. **Ambrosi B, Sartorio A, Pizzocaro A, Passini E, Bottasso B, Federici A** 2000 Evaluation of haemostatic and fibrinolytic markers in patients with Cushing's syndrome and in patients with adrenal incidentaloma. Exp Clin Endocrinol Diabetes 108:294–298
59. **Terzolo M, Allasino B, Bosio S, Brusa E, Daffara F, Ventura M, Aroasio E, Sacchetto G, Reimondo G, Angeli A, Camaschella C** 2004 Hyperhomocysteinemia in patients with Cushing's syndrome. J Clin Endocrinol Metab 89: 3745–3751
60. **Kakafika AI, Liberopoulos EN, Karagiannis A, Athyros VG, Mikhailidis DP** 2006 Dyslipidaemia, hypercoagulability and the metabolic syndrome. Curr Vasc Pharmacol 4:175–183
61. **Bellia C, Bivona G, Scazzone C, Ciaccio M** 2007 Association between homocysteinemia and metabolic syndrome in patients with cardiovascular disease. Ther Clin Risk Manag 3:999–1001
62. **Patrassi GM, Dal Bo Zanon R, Boscaro M, Martinelli S, Girolami A** 1985 Further studies on the hypercoagulable state of patients with Cushing's syndrome. Thromb Haemost 54:518–520
63. **Fatti LM, Bottasso B, Invitti C, Coppola R, Cavagnini F, Mannucci PM** 2000 Markers of activation of coagulation and fibrinolysis in patients with Cushing's syndrome. J Endocrinol Invest 23:145–150
64. **Patrassi GM, Sartori MT, Viero ML, Scarano L, Boscaro M, Girolami A** 1992 The fibrinolytic potential in patients with Cushing's disease: a clue to their hypercoagulable state. Blood Coagul Fibrinolysis 3:789–793
65. **Tsouli SG, Liberopoulos EN, Mikhailidis DP, Athyros VG, Elisaf MS** 2006 Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander? Metabolism 55:1293–1301
66. **Faggiano A, Pivonello R, Melis D, Filippella M, Di Somma C, Petretta M, Lombardi G, Colao A** 2003 Nephrolithiasis in Cushing's disease: prevalence, etiopathogenesis, and modification after disease cure. J Clin Endocrinol Metab 88:2076–2080
67. **Bickel C, Rupprecht HJ, Blankenberg S, Rippin G, Hafner G, Daunhauer A, Hofmann KP, Meyer J** 2002 Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. Am J Cardiol 89:12–17
68. **Karagiannis A, Mikhailidis DP, Tziomalos K, Sileli M, Savvatianos S, Kakafika A, Gossios T, Krikis N, Moschou I, Xochellis M, Athyros VG** 2007 Serum uric acid as an independent predictor of early death after acute stroke. Circ J 71: 1120–1127
69. **Milionis HJ, Kalantzi KJ, Goudevenos JA, Seferiadis K, Mikhailidis DP, Elisaf MS** 2005 Serum uric acid levels and risk for acute ischaemic non-embolic stroke in elderly subjects. J Intern Med 258:435–441
70. **Athyros VG, Mikhailidis DP, Liberopoulos EN, Kakafika AI, Karagiannis A, Papageorgiou AA, Tziomalos K, Ganotakis ES, Elisaf M** 2007 Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. Nephrol Dial Transplant 22:118–127
71. **Athyros VG, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Milionis HJ, Mikhailidis DP; GREACE Study Collaborative Group** 2004 Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Am J Kidney Dis 43:589–599
72. **Guerre-Millo M** 2004 Adipose tissue and adipokines: for better or worse. Diabetes Metab 30:13–19
73. **Inadera H** 2008 The usefulness of circulating adipokine levels for the assessment of obesity-related health problems. Int J Med Sci 5:248–262
74. **Bakhai A** 2008 Adipokines-targeting a root cause of cardiometabolic risk. Q J Med 101:767–776
75. **Halleux CM, Takahashi M, Delporte ML, Detry R, Funahashi T, Matsuzawa Y, Brichard SM** 2001 Secretion of adiponectin and regulation of apM1 gene expression in human visceral adipose tissue. Biochem Biophys Res Commun 288:1102–1107
76. **Ashizawa N, Takagi M, Seto S, Suzuki S, Yano K** 2007 Serum adiponectin and leptin in a patient with Cushing's syndrome before and after adrenalectomy. Intern Med 46:383–385
77. **Fallo F, Scarda A, Sonino N, Paoletta A, Boscaro M, Pagano C, Federspil G, Vettor R** 2004 Effect of glucocorticoids on adiponectin: a study in healthy subjects and in Cushing's syndrome. Eur J Endocrinol 150:339–344
78. **Widjaja A, Schürmeyer TH, Von zur Mühlen A, Brabant G** 1998 Determinants of serum leptin levels in Cushing's syndrome. J Clin Endocrinol Metab 83:600–603
79. **Krsek M, Silha JV, Jezkovα J, Hána V, Marek J, Weiss V, Stepán JJ, Murphy LJ** 2004 Adipokine levels in Cushing's syndrome; elevated resistin levels in female patients with Cushing's syndrome. Clin Endocrinol (Oxf) 60:350–357
80. **Leal-Cerro A, Considine RV, Peino R, Venegas E, Astorga R, Casanueva FF, Dieguez C** 1996 Serum immunoreactive-leptin levels are increased in patients with Cushing's syndrome. Horm Metab Res 28:711–713
81. **Schafroth U, Godang K, Ueland T, Berg JP, Bollerslev J** 2000 Leptin levels in relation to body composition and insulin concentration in patients with endogenous Cushing's syndrome compared to controls matched for body mass index. J Endocrinol Invest 23:349–355
82. **Eller NH, Netterstrøm B, Hansen AM** 2006 Psychosocial factors at home and at work and levels of salivary cortisol. Biol Psychol 73:280–287
83. **Maier R, Egger A, Barth A, Winker R, Osterode W, Kundi M, Wolf C, Ruediger H** 2006 Effects of short- and long-term unemployment on physical work capacity and on serum cortisol. Int Arch Occup Environ Health 79: 193–198
84. **Chrousos GP** 2000 The role of stress and the hypothalamic-pituitary-adrenal

axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int J Obes Relat Metab Disord 24(Suppl 2):S50–S55
85. **Kinder LS, Carnethon MR, Palaniappan LP, King AC, Fortmann SP** 2004 Depression and the metabolic syndrome in young adults: findings from the Third National Health and Nutrition Examination Survey. Psychosom Med 66:316–322
86. **Björntorp P** 1999 Neuroendocrine perturbations as a cause of insulin resistance. Diabetes Metab Res Rev 15:427–441
87. **Kyrou I, Chrousos GP, Tsigos C** 2006 Stress, visceral obesity, and metabolic complications. Ann NY Acad Sci 1083:77–110
88. **Davis MC, Twamley EW, Hamilton NA, Swan PD** 1999 Body fat distribution and hemodynamic stress responses in premenopausal obese women: a preliminary study. Health Psychol 18:625–633
89. **Gardin JM, Schumacher D, Constantine G, Davis KD, Leung C, Reid CL** 2000 Valvular abnormalities and cardiovascular status following exposure to dexfenfluramine or phentermine/fenfluramine. JAMA 283:1703–1709
90. **Jayo JM, Shively CA, Kaplan JR, Manuck SB** 1993 Effects of exercise and stress on body fat distribution in male cynomolgus monkeys. Int J Obes Relat Metab Disord 17:597–604
91. **Rebuffe-Scrive M** 1991 Neuroendocrine regulation of adipose tissue: molecular and hormonal mechanisms. Int J Obes 15(Suppl 2):83–86
92. **Sellers TA, Drinkard C, Rich SS, Potter JD, Jeffery RW, Hong CP, Folsom AR** 1994 Familial aggregation and heritability of waist-to-hip ratio in adult women: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 18:607–613
93. **Busjahn A, Faulhaber HD, Freier K, Luft FC** 1999 Genetic and environmental influences on coping styles: a twin study. Psychosom Med 61:469–475
94. **Kirschbaum C, Wüst S, Faig HG, Hellhammer DH** 1992 Heritability of cortisol responses to human corticotropin-releasing hormone, ergometry, and psychological stress in humans. J Clin Endocrinol Metab 75:1526–1530
95. **Spiegel K, Leproult R, Van Cauter E** 1999 Impact of sleep debt on metabolic and endocrine function. Lancet 354:1435–1439
96. **Hall MH, Muldoon MF, Jennings JR, Buysse DJ, Flory JD, Manuck SB** 2008 Self reported sleep duration is associated with the metabolic syndrome in midlife adults. Sleep 31:635–643
97. **Ayas NT, White DP, Manson JE, Stampfer MJ, Speizer FE, Malhotra A, Hu FB** 2003 A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med 163:205–209
98. **Chaput JP, Després JP, Bouchard C, Tremblay A** 2008 The association between sleep duration and weight gain in adults: a 6-year prospective study from the Quebec Family Study. Sleep 31:517–523
99. **Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB** 2005 Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep 28:1289–1296
100. **Gottlieb DJ, Punjabi NM, Newman AB, Resnick HE, Redline S, Baldwin CM, Nieto FJ** 2005 Association of sleep time with diabetes mellitus and impaired glucose tolerance. Arch Intern Med 165:863–867
101. **Cappuccio FP, Stranges S, Kandala NB, Miller MA, Taggart FM, Kumari M, Ferrie JE, Shipley MJ, Brunner EJ, Marmot MG** 2007 Gender-specific associations of short sleep duration with prevalent and incident hyper-tension: the Whitehall II Study. Hypertension 50:693–700
102. **Reynolds RM, Walker BR, Syddall HE, Andrew R, Wood PJ, Whorwood CB, Phillips DI** 2001 Altered control of cortisol secretion in adult men with low birth weight and cardiovascular risk factors. J Clin Endocrinol Metab 86:245–250
103. **Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS** 1993 Fetal nutrition and cardiovascular disease in adult life. Lancet 341:938–941
104. **Economides DL, Nicolaides KH, Linton EA, Perry LA, Chard T** 1988 Plasma cortisol and adrenocorticotrophin in appropriate and small for gestational age fetuses. Fetal Ther 3:158–164
105. **Clark PM, Hindmarsh PC, Sheill AW, Law CM, Honour JW, Barker DJ** 1996 Size at birth and adrenocortical function in childhood. Clin Endocrinol (Oxf) 45:721–726
106. **Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD** 1991 Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 303:1019–1022
107. **Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y, Meade TW** 1995 Fetal and infant growth and cardiovascular risk factors in women. BMJ 310:428–432
108. **Barbazanges A, Piazza PV, Le Moal M, Maccari S** 1996 Maternal glucocorticoid secretion mediates long-term effects of prenatal stress. J Neurosci 16:3943–3949
109. **Reul JM, Stec I, Wiegers GJ, Labeur MS, Linthorst AC, Arzt E, Holsboer F** 1994 Prenatal immune challenge alters the hypothalamic-pituitary-adrenocortical axis in adult rats. J Clin Invest 93:2600–2607
110. **Rask E, Olsson T, Söderberg S, Andrew R, Livingstone DE, Johnson O, Walker BR** 2001 Tissue-specific dysregulation of cortisol metabolism in human obesity. J Clin Endocrinol Metab 86:1418–1421
111. **Walker BR, Soderberg S, Lindahl B, Olsson T** 2000 Independent effects of obesity and cortisol in predicting cardiovascular risk factors in men and women. J Intern Med 247:198–204
112. **Travison TG, O'Donnell AB, Araujo AB, Matsumoto AM, McKinlay JB** 2007 Cortisol levels and measures of body composition in middle-aged and older men. Clin Endocrinol (Oxf) 67:71–77
113. **Stewart PM, Krozowski ZS** 1999 11 β-Hydroxysteroid dehydrogenase. Vitam Horm 57:249–324
114. **Espíndola-Antunes D, Kater CE** 2007 Adipose tissue expression of 11β-hydroxysteroid dehydrogenase type 1 in Cushing's syndrome and in obesity. Arq Bras Endocrinol Metab 51:1397–1403
115. **New MI, Levine LS, Biglieri EG, Pareira J, Ulick S** 1977 Evidence for an unidentified steroid in a child with apparent mineralocorticoid hypertension. J Clin Endocrinol Metab 44:924–933
116. **Bujalska IJ, Kumar S, Stewart PM** 1997 Does central obesity reflect "Cushing's disease of the omentum"? Lancet 349:1210–1213
117. **Terzolo M, Bovio S, Pia A, Osella G, Borretta G, Angeli A, Reimondo G** 2007 Subclinical Cushing's syndrome. Arq Bras Endocrinol Metabol 51:1272–1279
118. **Tomlinson JW, Sinha B, Bujalska I, Hewison M, Stewart PM** 2002 Expression of 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue is not increased in human obesity. J Clin Endocrinol Metab 87:5630–5635
119. **Masuzaki H, Yamamoto H, Kenyon CJ, Elmquist JK, Morton NM, Paterson JM, Shinyama H, Sharp MG, Fleming S, Mullins JJ, Seckl JR, Flier JS** 2003 Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. J Clin Invest 112:83–90
120. **Morton NM, Paterson JM, Masuzaki H, Holmes MC, Staels B, Fievet C, Walker BR, Flier JS, Mullins JJ, Seckl JR** 2004 Novel adipose tissue-mediated resistance to diet-induced visceral obesity in 11 β-hydroxysteroid dehydrogenase type 1-deficient mice. Diabetes 53:931–938
121. **Masuzaki H, Paterson J, Shinyama H, Morton NM, Mullins JJ, Seckl JR, Flier JS** 2001 A transgenic model of visceral obesity and the metabolic syndrome. Science 294:2166–2170
122. **Iwasaki Y, Takayasu S, Nishiyama M, Tsugita M, Taguchi T, Asai M, Yoshida M, Kambayashi M, Hashimoto K** 2008 Is the metabolic syndrome an intracellular Cushing state? Effects of multiple humoral factors on the transcriptional activity of the hepatic glucocorticoid-activating enzyme (11β-hydroxysteroid dehydrogenase type 1) gene. Mol Cell Endocrinol 285:10–18
123. **Wake DJ, Rask E, Livingstone DE, Söderberg S, Olsson T, Walker BR** 2003 Local and systemic impact of transcriptional up-regulation of 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue in human obesity. J Clin Endocrinol Metab 88:3983–3988
124. **Tomlinson JW, Moore J, Cooper MS, Bujalska I, Shahmanesh M, Burt C, Strain A, Hewison M, Stewart PM** 2001 Regulation of expression of 11β-hydroxysteroid dehydrogenase type 1 in adipose tissue: tissue-specific induction by cytokines. Endocrinology 142:1982–1989
125. **Lindsay RS, Wake DJ, Nair S, Bunt J, Livingstone DE, Permana PA, Tataranni PA, Walker BR** 2003 Subcutaneous adipose 11β-hydroxysteroid dehydrogenase type 1 activity and messenger ribonucleic acid levels are associated with adiposity and insulinemia in Pima Indians and Caucasians. J Clin Endocrinol Metab 88:2738–2744
126. **Mariniello B, Ronconi V, Rilli S, Bernante P, Boscaro M, Mantero F, Giacchetti G** 2006 Adipose tissue 11β-hydroxysteroid dehydrogenase type 1 expression in obesity and Cushing's syndrome. Eur J Endocrinol 155:435–441
127. **Alberts P, Engblom L, Edling N, Forsgren M, Klingström G, Larsson C, Rönquist-Nii Y, Ohman B, Abrahmsén L** 2002 Selective inhibition of 11β-hydroxysteroid dehydrogenase type 1 decreases blood glucose concentrations in hyperglycaemic mice. Diabetologia 45:1528–1532
128. **Hermanowski-Vosatka A, Balkovec JM, Cheng K, Chen HY, Hernandez M, Koo GC, Le Grand CB, Li Z, Metzger JM, Mundt SS, Noonan H, Nunes CN, Olson SH, Pikounis B, Ren N, Robertson N, Schaeffer JM, Shah K, Springer MS, Strack AM, Strowski M, Wu K, Wu T, Xiao J, Zhang BB, Wright SD, Thieringer R** 2005 11β-HSD1 inhibition ameliorates metabolic syndrome and prevents progression of atherosclerosis in mice. J Exp Med 202:517–527
129. **Mai K, Andres J, Bobbert T, Maser-Gluth C, Möhlig M, Bähr V, Pfeiffer AF, Spranger J, Diederich S** 2007 Rosiglitazone decreases 11β-hydroxysteroid dehydrogenase type 1 in subcutaneous adipose tissue. Clin Endocrinol (Oxf) 67:419–425
130. **Berger J, Tanen M, Elbrecht A, Hermanowski-Vosatka A, Moller DE, Wright**

SD, Thieringer R 2001 Peroxisome proliferator-activated receptor-γ ligands inhibit adipocyte 11β-hydroxysteroid dehydrogenase type 1 expression and activity. J Biol Chem 276:12629–12635

131. **Andrews RC, Rooyackers O, Walker BR** 2003 Effects of the 11 β-hydroxysteroid dehydrogenase inhibitor carbenoxolone on insulin sensitivity in men with type 2 diabetes. J Clin Endocrinol Metab 88:285–291
132. **Barf T, Vallgårda J, Emond R, Häggström C, Kurz G, Nygren A, Larwood V, Mosialou E, Axelsson K, Olsson R, Engblom L, Edling N, Rönquist-Nii Y, Ohman B, Alberts P, Abrahmsén L** 2002 Arylsulfonamidothiazoles as a new class of potential antidiabetic drugs. Discovery of potent inhibitors of the 11β-hydroxysteroid dehydrogenase type I. J Med Chem 45:3813–3815
133. **Olson S, Aster SD, Brown K, Carbin L, Graham DW, Hermanowski-Vosatka A, LeGrand CB, Mundt SS, Robbins MA, Schaeffer JM, Slossberg LH, Szymonifka MJ, Thieringer R, Wright SD, Balkovec JM** 2005 Adamantyl triazoles as selective inhibitors of 11β-hydroxysteroid dehydrogenase type 1. Bioorg Med Chem Lett 15:4359–4362
134. **Yuan C, St Jean Jr DJ, Liu Q, Cai L, Li A, Han N, Moniz G, Askew B, Hungate RW, Johansson L, Tedenborg L, Pyring D, Williams M, Hale C, Chen M, Cupples R, Zhang J, Jordan S, Bartberger MD, Sun Y, Emery M, Wang M, Fotsch C** 2007 The discovery of 2-anilinothiazolones as 11β-HSD1 inhibitors. Bioorg Med Chem Lett 17:6056–6061
135. **Bujalska IJ, Gathercole LL, Tomlinson JW, Darimont C, Ermolieff J, Fanjul AN, Rejto PA, Stewart PM** 2008 A novel selective 11β-hydroxysteroid dehydrogenase type 1 inhibitor prevents human adipogenesis. J Endocrinol 197:297–307
136. **Sundbom M, Kaiser C, Björkstrand E, Castro VM, Larsson C, Selén G, Nyhem CS, James SR** 2008 Inhibition of 11βHSD1 with the S-phenylethylaminothiazolone BVT116429 increases adiponectin concentrations and improves glucose homeostasis in diabetic KKAy mice. BMC Pharmacol 8:3
137. **Brindley DN** 1995 Role of glucocorticoids and fatty acids in the impairment of lipid metabolism observed in the metabolic syndrome. Int J Obes Relat Metab Disord 19(Suppl 1):S69–S75