Editorial
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The Role of Cortisol in the Pathogenesis of the Metabolic Syndrome

In-Kyung Jeong
Division of Endocrinology & Metabolism, Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea

Metabolic syndrome (MetS) is a constellation of metabolic derangements that includes insulin resistance, hyperglycemia, hypertension, reduced high density lipoprotein cholesterol (HDL-C), elevated triglycerides, and abdominal obesity. It was originally described by Reaven in 1988 as "syndrome X" or "insulin resistance syndrome" [1]. MetS increases the risk for development of type 2 diabetes mellitus as well as cardiovascular disease [2].

The prevalence of MetS has increased worldwide, with an increase from 19.6% in 1998 to 32.4% in 2009, according to the Korean National Health and Nutrition Examination Survey (NHANES) [3]. In spite of the increasing prevalence of MetS, there are no uniformly accepted diagnostic criteria for MetS. Different organizations have suggested their own criteria. The National Cholesterol Education Program (NCEP) Adult Treatment Panel-III (ATP III) guidelines [4] are the most widely used, and require at least three of the following: 1) central obesity (waist circumference ≥90 cm for Asian men or ≥80 cm for Asian women, 2) triglycerides ≥150 mg/dL, or receiving drug treatment for high triglycerides, 3) HDL-C <40 mg/dL for men or <50 mg/dL for women or receiving drug treatment for low HDL-C, 4) systolic/diastolic blood pressure ≥130/85 mm Hg or receiving drug treatment for high blood pressure, and 5) fasting plasma glucose ≥100 mg/dL or receiving drug treatment for high fasting plasma glucose levels. However, according to the International Diabetes Federation (IDF) criteria [5], abdominal obesity (waist circumference ≥90 cm for Asian men or ≥80 cm for Asian women) is a prerequisite for the diagnosis of MetS, in addition to at least two of the following components: 1) triglycerides ≥150 mg/dL or receiving drug treatment for high triglycerides, 2) HDL-C <40 mg/dL for men or <50 mg/dL for women or receiving drug treatment for low HDL-C, 3) systolic/diastolic blood pressure ≥130/85 mm Hg or receiving drug treatment for high blood pressure, and 4) fasting plasma glucose ≥100 mg/dL or receiving drug treatment for high fasting plasma glucose levels. Yoon et al. [6] compared the two criteria. All MetS patients who met the IDF criteria also met the revised NCEP criteria. Patients who met the NCEP criteria but not the IDF criteria were metabolically obese with normal waist circumferences and significantly worse metabolic profiles than the MetS-free group. This illustrates why the revised NCEP criteria are preferred to the IDF criteria for measuring the prevalence of MetS in Korea.

Even though the primary mechanism of MetS is insulin resistance, there is still controversy regarding the pathogenesis of MetS. Because the clinical features of MetS are shared by Cushing's syndrome (CS), mild hypercortisolism was proposed as one of the pathogenic mechanisms of MetS [7]. Shared features between MetS and CS are abdominal obesity, high triglycerides, low HDL-C, hypertension, and hyperglycemia.

Previous studies have evaluated the association between MetS and hypercortisolism by examining fasting plasma cortisol, 24-hour urinary free cortisol, cortisol reactivity to some stimuli, or profiles of cortisol patterns over the day [8-24]. More

Corresponding author: In-Kyung Jeong
Division of Endocrinology & Metabolism, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, 892 Dongnam-ro, Gangdong-gu, Seoul 134-727, Korea
E-mail: jik1016@dreamwiz.com

recently, salivary cortisol measurements have been used [24]. Because lack of circadian rhythmicity is one of the most sensitive indicators of the presence of CS, midnight serum cortisol is very helpful as a low dose dexamethasone suppression test, but it is impractical for screening outpatients [9]. Midnight salivary cortisol, on the other hand, is much more practical for screening. Cortisol circulates in the plasma largely bound to cortisol binding globulin or albumin. Less than 5% of circulating cortisol is free cortisol which is a physiologically active hormone. Since binding proteins are absent from saliva, the concentration of salivary cortisol is in equilibrium with plasma free cortisol [10]. Thus, the salivary cortisol test is a simple, reproducible, stress-free, non-invasive and reliable test [11]. Interestingly, salivary cortisol testing was first reported about 30 years ago. There is some variation in cutoff values for salivary cortisol because different commercially available methods are used, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), and tandem mass spectrometry (LC-MS) [11].

Some evidence suggests that circulating cortisol concentrations are higher in patients with MetS compared to healthy control subjects. Higher concentrations of urinary free cortisol were reported in patients with MetS [12,13]. Increased urinary cortisone/cortisol ratios were reported in women with abdominal obesity compared to those with a high proportion of peripheral fat. Cortisol appears to play a role in abdominal adiposity in MetS. Another study [14] did not find any relationship between cortisol and waist circumference, in contrast with findings from earlier studies [15,16]. Other studies measured the response of hypothalamic-pituitary-adrenal (HPA) axis to the various stimuli. Increased response of the HPA axis during a low dose adrenocorticotropic hormone test [17] and corticotropin-releasing hormone-vasopressin test [18] is found in central obesity. Overall there seems to be a hyperactivity of the HPA axis in patients with abdominal obesity. Several reports also show an association between higher fasting cortisol levels and parameters of MetS such as blood pressure, fasting glucose, and high triglycerides [19-21]. Recently Jang et al. [22] reported an association between midnight salivary cortisol and MetS. Even though the sample size was small, their data supported the hypothesis that cortisol plays an important role in the pathogenesis of MetS.

In contrast, circulating cortisol levels are not always elevated in obese subjects, and in some studies, they are lower than in lean subjects [23-25]. DeSantis et al. [25] analyzed the association between salivary cortisol measured 18 times over 3 days and MetS, using data from the Multi-Ethnic Study of Atherosclerosis. The area under the curve of cortisol levels was lower in the MetS group compared with the control group and there was no consistent pattern between MetS components and cortisol levels. This might be partly explained by tissue-specific dysregulation of cortisol metabolism, because plasma cortisol concentration is determined by the rate of secretion, the rate of inactivation, and the rate of excretion of free cortisol.

11β-hydroxysteroid dehydrogenase (11β-HSD) catalyzes the conversion of the hormonally active cortisol to inactive cortisone. There are two isoforms of 11β-HSD. 11β-HSD type 1 (11β-HSD1) converts inactive cortisone to active cortisol in key targets such as liver, adipose tissue, gonadal tissue and the central nervous system. 11β-HSD2 is expressed in a number of tissues and converts cortisol to inactive cortisone. Mutations in the 11β-HSD2 gene cause a syndrome of apparent mineralocorticoid excess, reflecting insufficient inactivation of cortisol in the kidney.

The expression of 11β-HSD1 appears to be higher in omental than subcutaneous fat. Treatment with cortisol and insulin increased the activity of 11β-HSD1 in adipose stromal cells [26], suggesting central obesity may reflect higher 11β-HSD1 activity. Mice overexpressing 11β-HSD1 in adipocytes develop central obesity [27]. Furthermore, 11β-HSD1 knockout mice have a reduced risk of obesity and MetS [28]. However, expression of 11β-HSD1 in adipose tissue is not increased in obese humans. The activity of 11β-HSD1 inversely correlates with body mass index, but increased proliferation of preadipose tissue as a consequence of decreased 11β-HSD1 expression may contribute to increases in visceral adipose tissue in obese humans [29]. Recent studies showed enhanced expression of the 11β-HSD1 gene in adipose tissue is associated with obesity, insulin resistance, and increased levels of leptin, resistin, and cytokines [30]. Therefore, 11β-HSD1 might be a promising therapeutic target in obesity and MetS. Carbenoxolone, a non-selective inhibitor of 11β-HSD1, improves insulin sensitivity [31]. Pharmacological inhibition of 11β-HSD1 by metformin, rosiglitazone, and clofibrate could explain the beneficial effects of these drugs on insulin resistance [32]. Selective and potent inhibitors of 11β-HSD1 have been developed [33]. Experimental studies with 11β-HSD1 inhibitors might support the role of 11β-HSD1 in the pathogenesis of MetS.

In conclusion, MetS is a constellation of metabolic abnormalities which predisposes patients to the development of dia-

betes, atherosclerosis, and cancer. Because MetS shares clinical characteristics of CS, functional hypercortisolism is one of the proposed pathogenic mechanisms of MetS. Increased cortisol production, hyperreactivity of the HPA axis, and dysregulation of 11β-HSD1 seem to contribute to hypercortisolism and MetS. Inhibition of cortisol action might be a new therapeutic target in patients with MetS.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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