

# Metabolic Syndrome in Cushing's Syndrome

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## Key Words

Metabolic syndrome · Diabetes mellitus · Cardiovascular risk · Growth hormone deficiency · Cushing's syndrome · Glucocorticoids

## Abstract

Although the concept of metabolic syndrome (MetS) as a disease entity continues to be debated, it provides a means by which patients at risk for diabetes and cardiovascular disease can be identified and categorized with routinely available criteria. Insulin resistance plays a central role in these abnormalities. Risk factors include central obesity, elevated fasting glucose, hypertension, elevated serum triglycerides, and low high-density-lipoprotein cholesterol. Various definitions of MetS have been proposed since 1998. Recently, a joint statement by several major organizations concluded that three abnormal values in a series of five criteria determined whether a person had MetS, and that elevated waist circumference was not an obligatory feature. A single set of cutoff points was proposed, except for waist circumference, which should be defined according to population and ethnic group. Cushing's syndrome (CS) represents an archetype of MetS. High glucocorticoid levels lead to muscle, liver and adipocyte insulin resistance. Almost all patients with CS are obese or overweight, and have abdominal visceral adiposity. Many also have glucose metabolism abnormalities (21–60% and 20–47% of the patients have impaired glucose tolerance

and diabetes, respectively), hypertension (more than 70% of the patients), and elevated triglyceride levels (20% of the patients). Almost two thirds of CS patients fulfill at least three criteria for MetS. The elevated incidence of diabetes and premature atherosclerosis (directly related to the length of exposure to hypercortisolism), and the increased mortality (particularly cardiovascular mortality) relative to the general population (2 to 4 times higher) show that the predictive value of MetS is also valid in CS. Effective treatment of hypercortisolism improves each of the five MetS components, but MetS and carotid atherosclerosis persist in most patients, and the cardiovascular risk therefore remains elevated. This calls for aggressive treatment of comorbidities and for very long-term follow-up.

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## What Is Metabolic Syndrome?

Metabolic syndrome (MetS) is defined as a complex of interrelated risk factors, including obesity (particularly central obesity), elevated fasting glucose (FG), hypertension, elevated serum triglycerides (TG), and low high-density-lipoprotein cholesterol (HDL-C). The tendency of these factors to cluster was discovered many years ago. Insulin resistance is considered to be the factor linking these different metabolic abnormalities, but the pathogenesis of MetS is unclear. MetS is common in industrial-

**Table 1.** Clinical diagnostic criteria for metabolic syndrome [from ref. 8]

Measure	Categorical cut-points
Elevated waist circumference	population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥150 mg/dl (1.7 mmol/l)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	<40 mg/dl (1.0 mmol/l) in males <50 mg/dl (1.3 mmol/l) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	systolic ≥130 and/or diastolic ≥85 mm Hg
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	>100 mg/dl (5.5 mmol/l)

ized countries (32% in the USA, 26% in Europe), due to obesity and sedentary lifestyles. Whether MetS is a true syndrome or a chance association of unrelated phenotypes is controversial, but there is general agreement that obesity and its complications, including MetS, are associated with an increased risk to health. In particular, MetS is associated with a twofold risk of developing cardiovascular disease after 5–10 years, and with a fivefold risk of developing diabetes mellitus [1].

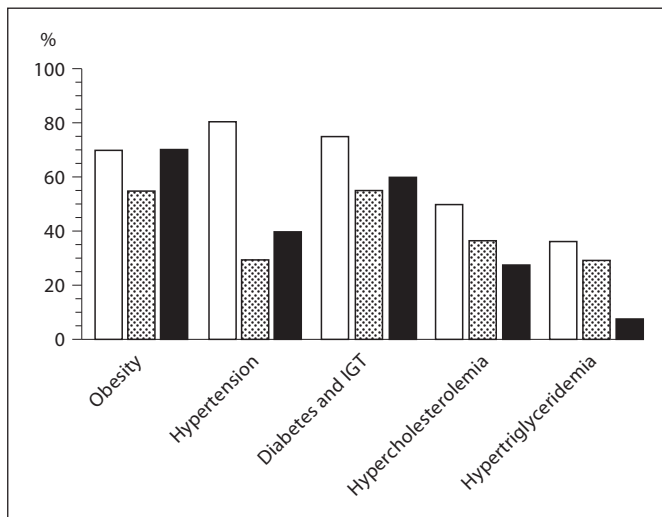
There is also considerable disagreement regarding the diagnostic criteria for MetS. The initial definition emphasized insulin resistance as the major underlying risk factor [2]. In 2001, a new definition of MetS was proposed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) [3]. It required the presence of three of the following five criteria: (1) central obesity measured by waist circumference (WC) (≥102 cm for males, ≥88 cm for females); (2) FG ≥100 mg/dl (≥5.6 mmol/l), or a diagnosis of diabetes, or drug treatment for elevated glucose; (3) TG ≥150 mg/dl (≥1.7 mmol/l); (4) HDL-C <40.0 mg/dl (<1.03 mmol/l) for men and <50.0 mg/dl (<1.29 mmol/l) for women, and (5) blood pressure (BP) ≥130/85 mm Hg or antihypertensive treatment. In 2005, the International Diabetes Federation (IDF) concluded that abdominal obesity was one of the five criteria required for diagnosis, along with two of the other four criteria proposed by NCEP-ATPIII [4]. The IDF also proposed WC cutoffs for abdominal obesity in different populations: ≥94 cm in males and ≥80 cm in females of European ('Europids'), Middle-Eastern/Mediterranean, or sub-Saharan African origin, and ≥90 cm in males and ≥80 cm in females of Ethnic Central and South American or Asian origin. At the same time the American Heart Association/National Heart, Lung and

Blood Institute (AHA-NHLBI) proposed that diagnosis of MetS required three of the five criteria, but that abdominal obesity (defined as ≥102 cm in men and ≥88 cm in women) was not mandatory; the other criteria were the same as in the IDF definition [5].

Recently, a joint meeting of several major organizations (IDF, NHLDI, AHA, WHF, IAS, IASO) attempted to harmonize these criteria. An interim statement proposed that abdominal obesity was not obligatory to diagnose MetS, but that WC remained useful for preliminary screening. According to this interim statement, three abnormal findings out of five would qualify a person for MetS. A single set of cut-points was proposed for fasting blood glucose, triglycerides, HDL-C and BP, while national or regional cutoff points for WC could be used pending further studies [6]. Table 1 summarizes the criteria for clinical diagnosis of MetS listed in this joint statement.

### **Cushing's Syndrome Is an Archetype of Metabolic Syndrome**

Whatever the cut-points used to define MetS, Cushing's syndrome (CS) represents an archetype of MetS. Indeed, a compilation of clinical studies reporting the prevalence of the different clinical signs and symptoms of CS showed that obesity or weight gain was found in 95% of the patients, facial plethora in 90%, hypertension in 75%, and glucose intolerance in 60% [7]. Many patients with CS also have elevated TG concentrations (around 20% of the cases) and low HDL-C levels (36% of the cases) [8, 9]. It has been estimated that almost two thirds of CS patients fulfill three of the five criteria for MetS (fig. 1).



**Fig. 1.** Prevalence of various components of metabolic syndrome in patients with Cushing's disease before treatment (□), 1 year after cure of Cushing's disease (■) and 5 years after cure of Cushing's disease (▨). IGT = Impaired glucose tolerance. Adapted from Pivonello et al. [9].

MetS has been linked to intermediary cardiovascular risk markers such as intima media thickness (IMT) and vascular lumen diameter. Faggiano et al. [8] showed elevated carotid artery IMT and a low systolic lumen diameter, diastolic lumen diameter and distensibility coefficient (DC). Atherosclerotic plaque has been found in around 30% of the patients with active Cushing's disease.

### Central Role of Abdominal Visceral Obesity

#### *Abdominal Visceral Obesity Is a Major Risk Factor*

Abdominal visceral obesity is one of the most prevalent features of CS. Visceral adiposity, defined as an elevated waist-to-hip circumference ratio (WHR) or simply as an elevated WC, is an independent risk factor for cardiovascular disease and diabetes, and it is more predictive than BMI in the general population [10].

While there is no correlation between BMI and metabolic or vascular parameters in CS, WHR correlates with BP, fasting and postglucose glycemia, insulin levels, IMT and DC [8].

#### *Truncal Fat Is the Main Component of Fat Mass in Cushing's Disease*

Studies of fat mass and truncal fat mass in CS have given inconsistent results [11–13]. Ho's group recently

conducted a detailed study of metabolic phenotypes in 18 CS subjects compared to 18 controls [14]. Mean percentage fat mass was 30% higher in the patients, while lean body mass was 15% lower. Moreover, truncal fat represented a larger proportion of total fat mass in the CS patients than in the controls (52 vs. 47%).

#### *Link between Glucocorticoids and Abdominal Visceral Fat*

Visceral obesity in CS may have several explanations. Glucocorticoids stimulate appetite [15], adipocyte differentiation [16] and lipoprotein lipase activity more strongly in visceral than in subcutaneous adipocytes [17–19]. A central role of AMP-activated protein kinase (AMPK) has recently been suggested by a study in rodents [20]. AMPK is the sensor of cellular energy status [21]; when AMPK is activated by a low energy state, it switches off anabolic pathways such as fatty acid and protein synthesis and switches on catabolic pathways (glycolysis and fatty acid oxidation). AMPK activity was 70% lower in visceral adipose tissue removed during abdominal surgery from CS patients as compared with normal subjects [22]. As a result, fatty acid synthesis, a downstream target of AMPK, was inhibited. Indeed, RT-PCR revealed up-regulation (240%) of fatty acid synthase (FAS) mRNA in visceral adipose tissue of CS patients as compared with normal subjects, FAS being known to promote lipid storage in abdominal visceral tissue.

Insulin resistance may also play a role in the metabolic abnormalities associated with CS. Glucocorticoid exposure leads to impaired insulin sensitivity in skeletal muscle and adipose tissue by its direct effect on insulin signaling pathways, glucose transport and glucose oxidation, and by an indirect effect on lipid metabolism and protein metabolism [23, 24].

#### *Metabolic Syndrome: A 'Cushing's Syndrome' of Visceral Abdominal Fat?*

The MetS-like features of CS, resulting from endogenous or exogenous glucocorticoid excess, led to the suggestion that cortisol might contribute to the pathogenesis of MetS at two different levels [review in 25]. First, MetS could be associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis, as suggested by the variable degree of HPA hyperactivity in CS patients, which could contribute to abdominal fat accumulation. Chronic stress, decreased sleep duration, and low birth weight have all been implicated in this central activation of the HPA axis, although the precise underlying mechanism remains elusive. Second, modulation of cortisol metabo-

lism may be defective in abdominal tissues of subjects with MetS. Some findings implicate 11 $\beta$ -hydroxysteroid dehydrogenase 1 (11 $\beta$ HSD1), which converts inactive cortisone to cortisol, to be its active metabolite. 11 $\beta$ HSD1 is expressed in liver, adipose tissue, bone and the central nervous system. Mice with 11 $\beta$ HSD1 overexpression or over-activity develop several features of MetS [26], while 11 $\beta$ HSD1 knockout mice have a reduced risk of obesity and MetS [27, 28]. Human data on the relationship between 11 $\beta$ HSD1 expression and parameters of visceral adipose tissue or liver are much more controversial [29]. The development of 11 $\beta$ HSD1 inhibitors will help to clarify the role of this enzyme in MetS.

### **Impact of Treatment for Cushing's Syndrome on Metabolic Syndrome**

In a study of 25 patients, BMI, WC and systolic and diastolic BP were lower 1 year after the effective treatment of Cushing's disease than before treatment but, except for systolic BP, they remained higher than in healthy subjects. In addition, obesity, diabetes, hypertension, hypertriglyceridemia and hypercholesterolemia were still present in 63, 60, 56, 60, and 76% of the patients, respectively [8]. After 5 years, despite some improvement, 33% of the patients were overweight (compared with 20% of matched healthy subjects), 40% were obese (vs. 0%), 27% still had IGT (vs. 10% of sex- and age-matched healthy controls and 27% of IMC-matched controls), 33% had diabetes (vs. 7% of BMI-matched controls), 40% remained hypertensive (vs. 10% of age- and sex-matched controls and 20% of BMI-matched controls, the difference was non significant in this latter case) and 30% were still dyslipidemic [30]. Insulin levels following a glucose load were higher than in controls, suggesting the persistence of insulin resistance [30].

Thus, despite normalization of cortisolemia, MetS persists in a substantial number of CS patients.

### **What Is the Effect of Treatment for Cushing's Syndrome on Cardiovascular Risk?**

#### *Mortality*

The duration of exposure to excess glucocorticoids is a key determinant of cardiovascular risk. As would be expected, mortality is higher among patients who have not received effective treatment for CS than among patients who are cured [31, 32].

Very few studies have compared the mortality rate of cured CS patients with that of the general population. In studies comparing CS patients (both cured and uncured) with the general population, the standardized mortality ratio (SMR) ranged from 1 to 4 [31, 33–36] with very large confidence intervals (CI), the highest SMR of 4 (95% CI 2.5–17) being found in the study with the lowest immediate postoperative cure rate (32% of the patients) [34], while the lowest SMR of 1 (95% CI 0.44–2.2) was found in the study with the highest cure rate (85% of the patients) [36].

#### *Intermediary Markers*

One year after Cushing's disease cure the mean IMT in a group of 25 patients was lower than before treatment but remained abnormal compared to sex- and age-matched controls, and similar to that of BMI-matched controls. Systolic lumen diameter and the distensibility coefficient both improved but remained abnormal. Atheromatous plaques remained visible in the 8 patients (32%) in whom they were present before treatment [8]. Five years after the cure the results were very similar: all the intermediary markers (IMT, distensibility coefficient, etc.) remained abnormal compared with sex- and age-matched or BMI-matched controls. Atheromatous plaques remained visible in four patients (27%) but in none of the age- and sex-matched controls [30]. As shown in another study [37], despite long-term cure, patients who have suffered CS exhibit persistent accumulation of central fat, as in active hypercortisolemia, with the consequent unfavorable adipokine profile, leading to a state of low-grade inflammation.

Thus, whether they are cured or only improved, all patients with CS remain at risk for complications such as MetS, diabetes and cardiovascular disease.

### **Does Growth Hormone Deficiency Contribute to Metabolic Syndrome in Patients with Cushing's Syndrome?**

Growth hormone secretion is impaired in Cushing's disease, not only in patients with active disease but also in about half of all the patients in remission [38–41]. Elsewhere, MetS is highly prevalent in patients with GHD (42% in total, 52% in the USA and 28% in Europe) [42]. Although we and others have shown that GH therapy in patients with GHD does not affect the prevalence of MetS [42, 43], it was tempting to use GH to treat patients with GHD and a history of Cushing's disease. In the HypoCCS



cohort of adult-onset GHD patients, a total of 160 patients with a history of Cushing's disease were treated with GH and were compared with 879 GH-treated patients whose GHD was related to treatment of a nonfunctioning pituitary adenoma [44]. The prevalence of MetS was very similar in the two groups at baseline. After 3 years of follow-up it was 20% in the patients with GHD and a history of Cushing's disease, compared to 10% in the patients with a history of non functioning pituitary adenoma. Moreover, the prevalence of MetS after 3 years of GH treatment remained the same as at baseline. The frequency of diabetes increased more strongly in patients with a history of Cushing's disease than in patients with a history of nonfunctioning pituitary adenoma [44]. This was also true of cardiovascular and cerebrovascular disease. This led the authors to conclude that previous hypercortisolism may predispose GH-treated, GH-deficient subjects with a history of Cushing's disease to an increased risk of MetS, diabetes, cardiovascular and cerebrovascular disease.

In conclusion, MetS is highly prevalent in patients with CS, with visceral obesity playing a central role. Remission of Cushing's disease improves MetS, lowers the risk of diabetes and improves intermediary markers of cardiovascular risk, but some abnormalities persist. Thus, treatment of CS is not sufficient to eliminate MetS, and active management of comorbidities (high BP, dyslipidemia, IGT and diabetes) is therefore strongly recommended.

### Disclosure Statement

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