Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications

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INTRODUCTION

Metabolic syndrome is a constellation of conditions including abdominal obesity, insulin resistance, dyslipidemia (elevated triglycerides levels and low high-density lipoprotein cholesterol), and hypertension. Patients with metabolic syndrome meeting formal criteria are at increased risk for premature cardiovascular disease, type 2 diabetes mellitus, and early death.

Metabolic syndrome represents a global epidemic. Severe mental illness, unhealthy lifestyles, and the use of antipsychotic medications all play an important role in increasing the risk of metabolic syndrome. Obesity, adipokines dysregulation, and inflammation are all recognized pathophysiologic mechanisms for metabolic syndrome.

This topic describes the diagnosis, epidemiology, pathogenesis, and clinical implications of metabolic syndrome. Modifiable risk factors for cardiovascular disease in patients with severe mental illness, including smoking cessation and individual metabolic abnormalities, are reviewed separately. Lifestyle interventions in patients with severe mental illness are also reviewed separately. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness" and "Lifestyle interventions for obesity and overweight patients with severe mental illness".)

APPROACH TO TREATMENT

Our approach to treating metabolic syndrome in patients with severe mental illness is described separately. (See "Approach to managing increased risk for cardiovascular disease in patients with severe mental illness".)

DEFINITION

Metabolic syndrome, also known as syndrome X, syndrome of chronic cardiovascular disease, or Reaven syndrome [1], is a constellation of conditions including abdominal obesity, insulin resistance, dyslipidemia (elevated triglycerides levels and low high-density lipoprotein cholesterol), and hypertension. Major clinical and research organizations have proposed specific criteria for diagnosing the syndrome. (See 'Diagnosis' below and "Metabolic syndrome (insulin resistance syndrome or syndrome X)".)

EPIDEMIOLOGY

Metabolic syndrome has been recognized as a global problem of increasing prevalence (ie, an emerging epidemic) [2]. Its prevalence depends on the diagnostic criteria used and the ethnicity of the population studied [3].

Prevalence in general population — Using criteria proposed by the American Heart Association [4], studies have estimated prevalence by ethnicity:

- Europeans – 14.4 percent in women; 18.4 percent of men [5].
- South Asian – 31.8 percent in women; 28.8 percent in men [5].
- African Caribbean – 23.4 percent in women; 15.5 percent in men [5].
- Taiwan – 15.7 percent [6].
- United States – 23.4 percent (age-adjusted) in women; 24.0 percent (age-adjusted) in men [7]. However, among some ethnic groups, the difference in prevalence between female and male was greater:
  - African Americans – Women approximately 57 percent, greater than that of men [7].
  - Mexican Americans – Women approximately 26 percent, greater than that of men [7].

- East Asia – 2 to 18 percent in women; 8 to 13 percent in men [8].
- South America – Mean prevalence of 14 to 30 percent [9].
- Australia – 20 to 30 percent [9].

There appear to be variations in metabolic syndrome rates across different psychotic disorders. Patients with schizoaffective disorders may be more prone to higher rates of metabolic abnormalities, such as dyslipidemia, glucose intolerance, diabetes, and obesity, compared with patients with schizophrenia or other nonaffective psychosis [10-12]. More research is needed into possible explanatory factors, including contributions of affective illness (eg, depressive symptoms leading to a sedentary and unhealthy lifestyle) and of various types of medication (antipsychotics, mood stabilizers, and antidepressants).

CONTRIBUTING FACTORS

Multiple factors are believed to contribute to an increased risk of metabolic syndrome in patients with severe mental illness.

Mental disorders — Some evidence of a relationship between severe mental illness and metabolic syndrome predates the era of antipsychotic medications, which began in the 1950s [13]. Antipsychotic medication-naïve patients with schizophrenia or schizoaffective disorders have been shown to present with hepatic insulin resistance compared with matched controls, suggesting a direct link between schizophrenia and insulin resistance independent from the use of antipsychotic medications [14].

With regard to other severe mental illnesses, some reports suggest that metabolic syndrome is present in 8 to 56 percent of patients suffering from bipolar disorder [15]. Depression accelerates cell aging; depressed individuals have a higher incidence of diseases of aging, such as cardiovascular and cerebrovascular diseases, metabolic syndrome, and dementia [16]. Although studies have identified significant linkages between depression and diabetes, findings are not consistent, but contradictory and confusing [17].

Lifestyle factors — Although genetic factors might have a role in the physical health problems of patients with schizophrenia and severe mental illness, they also experience higher rates of comorbid physical health problems compared with the general population due to lifestyle and environmental factors, such as unhealthy diet, smoking, and lack of physical activity [18]. Individuals with severe mental illness usually have a poor diet that, along with cigarette smoking and lack of exercise, is a major contributor to cardiovascular diseases [19].

Schizophrenia patients spend an average of 40 percent longer sitting per day, with a 40 percent reduction in physical activity per week compared with healthy controls [20]. Sedentary lifestyle and unhealthy food consumption patterns, including higher daily intake of calories and cholesterol, are common among individuals with major psychotic and/or affective disorders [21].

Individuals with major psychotic disorders, especially schizophrenia-spectrum disorders, consume more cigarettes per day than do smokers in the general population [22], which partially explains the increased risk of cardiovascular disease in this population. About 25 percent of the general population in the United States are smokers, while up to 75 percent of patients with schizophrenia are smokers [23]. Tobacco users with major psychotic or affective/mood disorders are more likely to consume daily alcohol and caffeine, and less likely to avoid salt and saturated fats [22]. Smokers with schizophrenia reportedly exercise less than nonsmokers [22]. Smoking has been reported to be an independent risk factor for both cardiovascular diseases and diabetes [24].

Antipsychotic drug side effects — Antipsychotic medications, which are first-line treatment for schizophrenia and widely used in other mental disorders [25], have been found to cause weight gain and other metabolic abnormalities. Although second-generation antipsychotics are better tolerated and present with fewer extrapyramidal symptoms compared with first-generation antipsychotics, they are well known to be associated with an increased risk of obesity, impaired glucose tolerance, new-onset diabetes, hyperlipidemia, cardiovascular disease, and metabolic syndrome [26].

The prevalence of antipsychotic-related metabolic syndrome has been reported in varying samples ranging from 23 to 50 percent.

Almost all antipsychotics with prolonged use are associated with weight gain to varying degrees [27-33]:

- High – Clozapine and olanzapine
- Intermediate – Quetiapine, risperidone, paliperidone iloperidone, sertindole, and zotepine
- Low – Aripiprazole, amisulpride, ziprasidone, asenapine, brexpiprazole, lumateperone, olanzapine-samidorphan, lurasidone, and most high- to mid-potency first-generation antipsychotics

A finding that has been consistent with all antipsychotics that have been studied is that weight gain is greater during treatment of antipsychotic-naïve patients compared with patients with a

prior history of antipsychotic use [30].

Prevention and treatment of antipsychotic-induced metabolic syndrome are reviewed separately, including changes to antipsychotic regimens, lifestyle interventions, smoking cessation, and treatments for individual metabolic abnormalities. (See "Approach to managing increased risk for cardiovascular disease in patients with severe mental illness" and "Lifestyle interventions for obesity and overweight patients with severe mental illness".)

PATHOPHYSIOLOGY

Target organ damage occurs through multiple mechanisms in metabolic syndrome.

Obesity, insulin resistance, hyperglycemia, and diabetes — Excess visceral fat is associated with high insulin resistance [34], which plays an important role in the pathophysiology of metabolic syndrome [35]. The larger expanded adipose tissue leads to an increased turnover of free fatty acids, which are released into the portal circulation and shuttled to the liver, where they are stored as triglyceride (the portal theory of metabolic syndrome) [34,36]. Because of the insulin resistance, insulin itself is unable to properly inhibit lipolysis, leading to an increased flux of free fatty acids being liberated into the plasma circulation [35].

The hepatic insulin action has been shown to be impaired by the increased flux of free fatty acids [34]. Hepatic insulin resistance and the abundance of free fatty acids lead to an increase in gluconeogenesis that leads to hyperglycemia [37]. Insulin resistance in muscle tissue also results in decreased glucose disposal peripherally [38]. Over time, the pancreatic beta cell continues to decompensate due to the increased need for insulin to overcome resistance, and the result is type 2 diabetes mellitus.

Insulin resistance and hypertension — The relationship between insulin resistance and hypertension has been well established and it is likely to be multifactorial: partially mediated by endothelial dysfunction caused by free fatty acid-mediated generation of reactive oxygen species, hyperinsulinemia-induced sympathetic nervous system activation and inhibition of nitric oxide synthase, and the effects of adipose tissue-derived cytokines [34,39].

Hyperactivity of the renin-angiotensin-aldosterone system in seen with obesity [40]. Attention has focused on the role of adipocyte-derived resistin and leptin and their contribution to the pathogenesis of hypertension in patients with insulin resistance [41].

Metabolic syndrome and adipokines dysregulation — Adipose tissue is an active endocrine organ [42] that secrets bioactive peptides or proteins called adipokines, fundamental to the

pathogenesis of the metabolic syndrome. Increased adiposity is associated with overproduction of adipokines with pro-inflammatory properties, while other adipokines with anti-inflammatory or insulin-sensitizing properties are decreased [43].

Adipokines dysregulation plays a role in obesity-linked metabolic disorders and cardiovascular disease [43]. Deleterious adipokines overproduced in obesity include tumor necrosis factor-alpha, interleukin 6, monocyte chemoattractant protein 1, plasminogen activating factor 1, angiotensinogen, retinol binding protein 4, and adipocyte fatty acid binding protein [43,44].

Beneficial adipokines dysregulated in obesity include leptin, adiponectin, apelin, resistin, and visfatin [43,45-52].

Metabolic syndrome and inflammation — Several studies have shown a relationship between obesity, chronic inflammation, and metabolic syndrome [3,53-55]. Metabolic syndrome is associated with an elevated inflammatory state [56]. This is evidenced by the presence of elevated concentrations of inflammatory molecules including C-reactive protein, tumor necrosis factor-alpha, plasma resistin, interleukin 6, and interleukin 18 [57], consistent with the increase in adipose tissue mass characteristic of metabolic syndrome.

As seen in obesity, levels of the anti-inflammatory adipokine adiponectin are depressed in metabolic syndrome [58]. As the number of metabolic syndrome components an individual exhibits increases, inflammatory markers, including C-reactive protein [59], tumor necrosis factor-alpha [60], interleukin 18 [61], and plasminogen activator inhibitor-1 activity [62] also increase.

A visceral adipose tissue functions as a paracrine and an endocrine organ, secreting a number of adipokines, some of which are proinflammatory and atherogenic, such as leptin, tumor necrosis factor-alpha, resistin, interleukin 6, and fatty acid-binding protein 4, and others, which have anti-inflammatory, protective effects such as adiponectin [47].

In metabolic syndrome patients, serum adiponectin levels are decreased, while proinflammatory cytokines are elevated [3]. Dysregulation of adipokines as biomarkers of adipose tissue metabolism plays an essential part in all obesity related diseases [47].

Adipokine secretion is disturbed by the increased visceral adipose tissue, leading to a low-grade chronic inflammatory state mediated by the infiltration of macrophages into the adipose tissue itself. Macrophages play an important part as the secretory function of adipose tissue and represent the main source of inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin 6. An increase in circulating levels of these inflammatory macrophage-derived

factors in obesity leads to a chronic low-grade inflammatory state that has been linked to the development of insulin resistance and type 2 diabetes [63].

CLINICAL IMPLICATIONS

Risk of cardiovascular disease — Metabolic syndrome is a cluster of individual cardiometabolic risk factors [64], thus a diagnosis of metabolic syndrome would be expected to predict cardiovascular risk [38].

The vast majority of studies have shown that patients with metabolic syndrome have more cardiovascular disease and are at increased risk for developing cardiovascular disease [65-67]. The presence of metabolic syndrome increases the risk more than is predicted by its component cardiometabolic risk factors when analyzed individually [68].

The absence of metabolic syndrome does not imply safety from cardiovascular disease. In the Cardiovascular Health Study, cardiovascular disease events occurred in 18 percent of those without a metabolic syndrome diagnosis [69]; the chance of a future myocardial infarction was 23 to 42 percent without a metabolic syndrome diagnosis [70].

Cardiovascular disease is a major contributor of the increased mortality in subjects with schizophrenia and other severe mental illnesses [71]. Compared with the general population, patients with severe mental illness have nearly twice the risk of dying from cardiovascular disease, especially at an early age [72]. Important causal factors are related to lifestyle, including poor diet, lack of physical activity, smoking, substance misuse, and antipsychotic agents.

Risk of type 2 diabetes mellitus — Most patients with type 2 diabetes mellitus have insulin resistance and metabolic syndrome before onset of type 2 diabetes mellitus [73,74]. Insulin resistance, hyperinsulinemia, dyslipidemia, and obesity have been shown to precede the progression to type 2 diabetes mellitus in up to 75 to 85 percent of patients [75].

There is little clinical value in an added diagnosis of metabolic syndrome for risk stratification in patients already diagnosed with type 2 diabetes mellitus [76], confirming other published data that shows that a metabolic syndrome diagnosis does not provide further predictive power for cardiovascular disease events and mortality [77] because type 2 diabetes mellitus is already a cardiovascular disease risk equivalent [78,79].

All components of the metabolic syndrome definition increase risk of new-onset diabetes when analyzed independently [80]. The more metabolic syndrome components, the higher the risk of

type 2 diabetes mellitus [38].

Of all metabolic syndrome criteria, impaired fasting glucose and impaired glucose tolerance are most strongly associated with diabetes [81,82]. Fasting glucose was a superior predictor of incident diabetes than a diagnosis of metabolic syndrome [83].

The prevalence of diabetes mellitus is four to five times higher in schizophrenia than in the general population [72].

Associated conditions

Nonalcoholic fatty liver disease — Metabolic syndrome is associated with nonalcoholic fatty liver disease (NAFLD), which represents the most common cause of chronic liver disease [84]. The prevalence of both metabolic syndrome and NAFLD increases with obesity, excessive intake of simple sugars, and physical inactivity [85].

Both metabolic syndrome and NAFLD predict type 2 diabetes, cardiovascular disease, nonalcoholic steatohepatitis, and hepatocellular carcinoma [85,86]. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

The prevalence of NAFLD increases with the number of metabolic syndrome components present [87]. It has been suggested that 95 percent of obese individuals and up to 70 percent of those with type 2 diabetes mellitus have some form of NAFLD [88]. Although statistical modeling does not support that NAFLD is an independent manifestation that should be added as a component of metabolic syndrome [87], a diagnosis of metabolic syndrome could mean that NAFLD is present; therefore, clinicians should carefully investigate obese patients they suspect might be at risk of developing NAFLD.

A study of 661,266 subjects in a population based database in Taiwan found that patients with schizophrenia had a significantly higher prevalence and incidence of chronic liver disease compared with those in the general population. Younger patients with schizophrenia had a much higher prevalence and incidence compared with those in the general population. Comorbidity with diabetes was the primary risk factor for patients with schizophrenia to develop chronic liver disease [89].

Polycystic ovarian syndrome — Metabolic syndrome is especially common in obese women with polycystic ovarian syndrome (PCOS) [90]. PCOS presents with anovulation, androgen excess, insulin resistance, fertility problems, and consequences of insulin resistance, such as a significant risk for the development of type 2 diabetes mellitus [91] and cardiovascular disease risk factors [92]. There is, therefore, significant overlap between PCOS and metabolic syndrome.

Women with PCOS clearly have a higher prevalence of cardiovascular disease risk factors [93,94]. Although it is not clear whether women with PCOS have a greater risk for cardiovascular disease events, they certainly have evidence of greater risk for subclinical cardiovascular disease [95]. (See "Diagnosis of polycystic ovary syndrome in adults".)

Studies have found that the prevalence of mental health disorders, such as depression, anxiety, bipolar disorder, and binge eating disorder, is higher in women with PCOS compared with the general population [96,97].

Obstructive sleep apnea — Obstructive sleep apnea (OSA) is a potentially serious consequence of obesity and is associated with increasing body mass index, insulin resistance [98,99], and inflammation [100], and with reduced adiponectin concentrations [101,102]. Individuals with OSA are more likely to present with the clinical cluster of metabolic syndrome compared with those without OSA [103-105].

OSA prevalence may be increased in major depressive disorder and posttraumatic stress disorder [106]. There is insufficient evidence of an association between increased OSA and schizophrenia/psychotic disorders, bipolar and related disorders, or anxiety disorders [106].

Hypogonadism — Men with metabolic syndrome appear to have a greater prevalence of hypogonadism [107,108], which is a risk factor for the development of metabolic syndrome and type 2 diabetes mellitus [109]. (See "Clinical features and diagnosis of male hypogonadism".)

Microvascular disease — Metabolic syndrome has also been shown to be associated with an increased risk of chronic kidney disease [110], microalbuminuria [111], and neuropathy [112].

Cancer — Other metabolic syndrome-associated diseases can be considered in relation to the component of obesity [113]. Data support the relationship between obesity and the increased risk of colon, pancreas, kidney, prostate, endometrial, and breast cancer [114]. Each individual risk factor for metabolic syndrome also has an association with cancer [74].

Studies have had conflicting results on whether there is an association between overall cancer incidence/mortality in psychiatric patients compared with the general population [115]. Some have reported an increased risk, other studies no risk, while others have found a lower than expected cancer incidence or mortality; results have varied based on sample, psychiatric diagnosis, cancer site, and methodology [115].

Patients with psychiatric disorders do not appear more likely to develop cancer compared with the general population, but are more likely to die because of cancer [115]. One reason might be a disparity of care existing among patients with severe mental illness [116]. Cancer care

disparities are likely the result of patient-, provider-, and systems-level factors and are influenced by the pervasive stigma of mental illness [117].

DIAGNOSIS

Subsequent to the development of multiple, differing criteria for the diagnosis of metabolic syndrome [4,118-120], major clinical and research organizations proposed harmonized criteria defining the syndrome. Diagnosis is based on the presence of any three of the following abnormal findings [121]:

- Fasting glucose – ≥100 mg/dL (or receiving drug therapy for hyperglycemia).
- Blood pressure – ≥130/85 mmHg (or receiving drug therapy for hypertension).
- Triglycerides – ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia).
- High-density lipoprotein cholesterol – <40 mg/dL in men or <50 mg/dL in women (or receiving drug therapy for reduced high-density lipoprotein cholesterol).
- Waist circumference – ≥102 cm (40 in) in men or ≥88 cm (35 in) in women; if Asian American, ≥90 cm (35 in) in men or ≥80 cm (32 in) in women. (The International Diabetes Federation criteria allow the use of a body mass index >30 kg/m^2 in lieu of the waist circumference criterion.)

SUMMARY

- **Metabolic syndrome** – Metabolic syndrome is a constellation of risk factors for cardiovascular disease including abdominal obesity, insulin resistance, dyslipidemia (elevated triglycerides levels and low high-density lipoproteins), and hypertension. (See 'Definition' above.)
- **Epidemiology** – The prevalence of metabolic syndrome in the general population ranges between 14 to 18 percent in Europeans and 29 to 32 percent in South Asians. (See 'Epidemiology' above.)
- **Contributing factors** – Compared with the general population, the prevalence of metabolic syndrome is greater in patients with severe mental illness. Contributing factors include higher rates of a sedentary lifestyle and cigarette smoking, side effects of many

antipsychotic medications, and, possibly, the presence of severe mental disorders independent of medication. (See 'Contributing factors' above.)

- **Clinical implications –** The prevalence of metabolic syndrome is associated with a twofold increase in cardiovascular disease over 5 to 10 years, a fivefold increase in development of diabetes, and an increased risk of mortality. (See 'Clinical implications' above.)

- **Associated conditions** – The diagnosis of metabolic syndrome is associated with other health problems, including fatty liver and chronic liver disease, polycystic ovarian syndrome, hypogonadism, obstructive sleep apnea, microvascular disease, and cancer. (See 'Associated conditions' above.)

- **Diagnosis** – Major clinical and research organizations have developed consensus-based criteria for the diagnosis of metabolic syndrome based on the presence of at least three abnormalities using specified threshold: fasting glucose, blood pressure, triglycerides, high-density lipoprotein cholesterol, and waist circumference (or body mass index). (See 'Diagnosis' above.)

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