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Review

The Effects of Metabolic Syndrome on Psychiatric Disorders

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ABSTRACT

The metabolic syndrome (MetS) is characterized by the presence of five parameters including dyslipidemia, abdominal (centripetal) obesity, impaired glucose tolerance, insulin resistance and hypertension. The likelihood of a patient having cardiovascular disease (CVD) is increased by all of these factors. Worldwide, its prevalence is higher among people with severe mental illness, possibly as a result of the harmful lifestyles defined by inactivity, heavy drinking, smoking, unhealthful foods, and psychotropic prescription use. Patients in psychiatric facilities run a higher risk of dying too soon, mostly from CVD. There is some proof that mental illnesses and MetS have a bidirectional longitudinal influence and that there is a dose-response relationship between the intensity and duration of symptoms. In general, associations with dyslipidemia dysregulations and abdominal obesity seem greater than those with hypertension. Unhealthy lifestyle choices and poor adherence to prescribed medications, which are common among people with mental health conditions, are contributing factors. The development of MetS and mental disorders is influenced by pleiotropy in genetic susceptibility and pathophysiological processes, such as those causing greater central and peripheral activation of immuno-metabolic or endocrine systems. Imaging is crucial for assessing abdominal obesity as well as for identifying fatty liver or consequences from MetS. In this article, we aimed to review the link between MetS and psychiatric disorders.

Keywords: Cardiovascular diseases, metabolic syndrome, neurodegenerative disorders, radiology

The metabolic syndrome (MetS), also known as syndrome X, is a collection of five conditions that together raise a patient's risk of cardiovascular disease (CVD). These conditions include dyslipidemia, abdominal obesity, impaired glucose tolerance, insulin resistance, and hypertension.[1,2]

The cardiovascular system, pancreas, and liver are major areas that are vulnerable to injury.[3–5] There are some reported conditions associated with MetS including CVD, neurological disorders (cognitive impairment, vascular dementia, Alzheimer's disease, stroke), endocrinological disorders (polycystic ovary syndrome, nonalcoholic steatohepatitis, type 2 diabetes), psychiatric conditions (major depressive disorder, bipolar disorder, schizophrenia, anxiety disorder, attention-deficit hyperactivity disorder, and posttraumatic stress disorder) and cancer.[6-11]

The purpose of this article was to examine the relationship between MetS and psychiatric disorders.

About 20-25% of people worldwide suffer from metabolic syndrome. In comparison to the general population, it is more prevalent (by about 1.5-2 times) and triples the risk of heart attack or stroke in people with severe mental illness.[12,13]

Studies conducted in developed countries, such as the United States, have shown prevalence rates reaching nearly 35% in adults,[14] while a mean prevalence of approximately 25% has been found in Latin America.[15] According to a recent systematic review, rates for Brazilian adults ranged from 14.9% to 65.3%.[16]

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ETIOLOGY

In order to create preventive and/or therapeutic strategies, it is crucial to comprehend potential shared mechanisms underlying metabolic syndrome and the diseases that it is associated with. Several factors have been mentioned in the literature, including:

Mitochondrial dysfunction: As the disease progresses from insulin resistance to type 2 diabetes and from nonalcoholic fatty liver disease to nonalcoholic steatohepatitis, mitochondrial dysfunction appears to play a role in metabolic syndrome and increases.[17] Insulin resistance has been associated with mitochondrial DNA (mt-DNA) mutations and haplotypes, however, there are differences between ethnic groups that may be explained by varying nuclear genetic origins or environmental variables.[18]

Inflammation: Derived from data of elevated serum levels of several proinflammatory cytokines (e.g., tumor necrosis factor-alpha and interleukin-1 beta) and inflammation biomarkers (e.g., C-reactive protein), metabolic syndrome triggers chronic inflammation at key sites including the liver, the intestine, and adipose tissue. Inflammatory mediators are released, causing broad tissue malfunction and exacerbating chronic inflammation.[19–23]

Microbiome: Due to the fact that meals and calorie intake can modify the gut microbiota, this might result in a faulty barrier function where bacterial metabolites enter the bloodstream and inflame the liver. Normalizing the gut microbiota is possible using prebiotics, probiotics, and fecal transplants. As human cells include receptors that permit cross-talk between the host and the bacterium, microbial metabolites can have an effect on human health. Fecal microbiota and the occurrence of obesity and type 2 diabetes are linked by metagenome-wide association studies.[24,25] The hepatic enzyme flavin mono-oxygenase 3 transforms the trimethylamine (TMA) that intestinal bacteria make into the trimethylamine N-oxide (TMAO). Circulating TMAO is associated with type 2 diabetes, obesity, and atherosclerosis because it improves forward cholesterol transport while lowering reverse cholesterol transport and encouraging atherosclerosis. In mice and people, TMAO has been found to promote atherosclerosis.[26,27]

Effects on the environment and medications: Studies have shown a connection between the chemicals dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and the risk of obesity, type 2 diabetes, and hypertension.[28,29] The risk of metabolic syndrome in adult female babies is increased by DDT exposure during pregnancy, which reduces heat generation and alters lipid and carbohydrate metabolism.[30] Exposure to some medications such as protease inhibitors[31] may exacerbate nonalcoholic fatty liver disease or medications like tamoxifen, irinotecan, and corticosteroids may cause metabolic syndrome.[32]

DIAGNOSTIC CRITERIA

Measures of abdominal obesity, atherogenic dyslipidemia, hypertension, and glucose intolerance are used to diagnose metabolic syndrome clinically. The measurement of fasting insulin or its substitutes and the presence of evidence of insulin resistance are required elements of the World Health Organization's diagnosis of metabolic syndrome. However, a more straightforward definition, created for therapeutic usage and without any calculation of insulin resistance, was put forth by the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP).[33,34]

Metabolic syndrome is defined as meeting the following three requirements[1]:

•High blood pressure (>130/85 mm Hg)

•Low high-density lipoprotein cholesterol (HDL-C) levels (1.04 mmol/l in men and 1.29 mmol/l in women)

•High triglyceride levels (>1.69 mmol/l)

•High fasting plasma glucose levels (>6.1 mmol/l), and abdominal obesity (waist circumference >102 cm in men and >88 cm in women) are all risk factors for heart disease.

The International Diabetes Federation has proposed a new definition with a range of cut-offs for waist circumference for people from different ethnic groups that includes central obesity as a key requirement.

Among the metabolic characteristics of the MetS, abdominal obesity and insulin resistance are particularly important. Incidence of MetS, as well as an elevated risk for additional MetS components and cardiometabolic disease, are all strongly correlated with the duration and severity of obesity. Increased mortality and increased morbidity are both consequences of obesity. An imbalance between adipokines and insulin is recognized to be a primary contributor to visceral obesity, which is also strongly linked to the other four MetS characteristics.[35–37]

Factors Affecting Metabolic Syndrome

Age: MetS is more common as people get older, and as people get older, physiological and environmental changes affect how they eat and how they use their energy, which can contribute to cardiovascular diseases.[38,39]

Gender: There is no discernible difference in the prevalence of MetS between males and females.[15,40]

Ethnicity: Research findings have demonstrated that populations in Asia, China, and Africa have higher rates of MetS and cardiometabolic risk factors than Caucasians. Higher visceral fat, which frequently has nothing to do with high body mass index (BMI) values, is correlated with MetS in these groups. For instance, Asians have a higher body fat index compared to Caucasians.[41–44]

Modalities for Radiological Diagnosis

The evaluation of visceral abdominal adipose tissue (VAT), which is the best predictor of MetS in women and a good predictor in men, using ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) is a useful application of these imaging modalities.[45]

• The use of the US to assess VAT and subcutaneous adipose tissue (SAT) is safe, noninvasive, practical, quick, and reasonably priced.[46] When compared to computed tomography and MRI, VAT measurements in obese people and the elderly taken using the US have better correlations, while SAT has a lesser connection.[47] Independent of body mass index, larger VAT was linked to increased hepatic insulin resistance, triglycerides, and lower levels of HDL-C regardless of ethnic group or gender. These findings imply that the US may be helpful in assessing intra-abdominal adipose tissue. In other words, even after adjusting for clinical risk variables and BMI, there is a substantial link between VAT and cardiovascular disease, although SAT did not.[46,48] However, it has been demonstrated in a study that SAT and VAT assessed by the US are both independently related to MetS.[49]

• Computed tomography and MRI are the guideline procedures for the evaluation of VAT and SAT since they are cross-sectional modalities.[50,51] Although it has the highest temporal and spatial resolution, CT is a quick and efficient diagnostic method that exposes users to radiation.[52] The range of adipose tissue density in CT is between -30 and -190 Hounsfield unit (HU). One slice of a CT scan can be used to quantify VAT at the L4 level, which has a strong correlation with the total abdominal VAT measurement.[53] Compared to waist circumference, CT-measured VAT is more significantly linked with MetS.[54] Although the VAT and SAT measurements rely on a person's race and gender, the values fluctuate depending on the degree of measurement. Total VAT volume was more correctly reflected at L2-3, as opposed to L4-5, in the research of an obese white European population. Nevertheless, several studies used L4 level measurements (in Japanese, Europeans, South Asians, and African Caribbeans)[53,55] and in other studies at L4-L5, where they assert that it is most connected with the overall volume of VAT, and scans at this level best enable VAT and SAT distinction.[56] For the purpose of determining the risk of obesity-related problems, a visceral fat area cut-off value of 100 cm^2 is employed.[53]

Increased morbidity and death are consequences of metabolic syndrome. Consequently, the diagnosis, as well as treatment, is crucial. Non-invasive imaging techniques are useful for stratifying risk variables, such as abdominal obesity and insulin resistance, and assessing the damages to the target organs in specific MetS patients. The research has documented the use of imaging techniques like the US or cross-sectional modalities (CT, MRI) in identifying MetS markers like VAT and SAT. Although there are various stated levels of measurement in the literature, a single slice CT scan at the L4 level in late expiration can serve as the standard for measuring SAT and VAT due to its accuracy, reproducibility, repeatability, and convenience. High triglycerides, high ALT, high GGT, and the combination of both VAT and SAT have the highest associations with visceral adipose tissue, and they also have the strongest associations with MetS.[49,53,56]

PSYCHIATRIC CONDITIONS LINKED TO METABOLIC SYNDROME

Cardiovascular diseases increase the risk of premature death in psychiatric patients. Evidence suggests that metabolic syndrome risk factors such as hyperglycemia, dyslipidemia, obesity, and hypertension are more common in those with mental illnesses. Compared to the general population, individuals with psychiatric conditions are more likely to develop MetS. Mental illnesses, such as major depressive disorder[57], anxiety disorder[58], schizophrenia[59], and bipolar disorder, are considerably more likely to have linked to comorbidities such as diabetes, stroke, and obesity.[60] For instance, 47.5% of study participants with bipolar disorder and

39% of participants with major depressive disorder had MetS, and MetS, with a prevalence of 38.4%, was significantly associated with the presence of any anxiety disorder.[8,61,62] Research indicates that those with severe psychiatric problems have life expectancies that are seven to 24 years shorter.[63] Poor adherence to medical therapy and an unhealthy lifestyle are contributing factors.

Major Depressive Disorder

A depressed mood or a loss of interest that lasts more than two weeks are symptoms of major depressive disorder. Depressed mood or irritability, significant changes in weight and appetite, decreased interest in most activities, changes in sleep, feelings of worthlessness, psychomotor agitation or retardation, fatigue, poor concentration, and suicidal thoughts are five of the nine symptoms that must be present almost every day.[64] Numerous investigations have been conducted to determine the connection between depression and metabolic syndrome; the majority of these studies have discovered a favorable correlation.[65-69] Data show a correlation between depression and the beginning of MetS and depression and the onset of MetS.[70] A combination of metabolic dysregulations, according to studies conducted on depressed individuals, is a factor in the persistent chronicity of depression.[71,72] Common molecular processes may contribute to the link between depression and obesity. These illnesses' correlation may result from aberrant neurological or inflammatory networks.[73] The hypothalamic-pituitary-adrenal axis (HPA) abnormalities, hormones and signaling molecules originating from adipose tissue, dysfunctional brain-derived neurotrophic factor signaling, insulin signaling, the activity of inflammatory cytokines, and oxidative stress pathways are some of the hypotheses.[74]

Anxiety

Excessive concern in several areas, together with physical symptoms that have been persistent for at least six months, are signs of generalized anxiety disorder, which can cause clinically substantial discomfort or functional impairment.[75] Unhealthy habits including smoking, binge drinking, being sedentary, and eating poorly have all been linked to anxiety.[76] The cortisol awakening response is less apparent in people who experience high levels of anxiety symptoms, according to research correlating anxiety to altered cortisol activity.[77] Stress and the production of cortisol are two mechanisms through which anxiety may be linked to poor metabolic outcomes. This links metabolic syndrome with anxiety. Additionally, the long-term development of MetS may be influenced by hypothalamic-pituitary-adrenocortical system dysregulation linked to affective disorders, such as anxiety.[67]

Schizophrenia

Schizophrenia is a serious mental illness with high rates of morbidity and permanent impairment. Antipsychotics, prolonged hospitalization, poor lifestyle choices, and eating disorders have all contributed to the development of a metabolic syndrome in schizophrenia patients, which includes obesity, impaired glucose metabolism, dyslipidemia, and hypertension.[59,78,79] In people with schizophrenia, the estimated frequency of metabolic syndrome ranges from 37 to 67%, which represents a 2- to 3-fold greater risk compared to the general population.[80,81] Currently, the mechanism of risk factors for MetS is not well known. According to some research, the pathogenesis of schizophrenia may be influenced by changes in the levels of gene expression as well as alterations in the dopamine and serotonin neurotransmitters and receptors brought on by psychotropic medications or schizophrenia.[82] Additionally, first-episode psychosis patients have changes in their immune system, cardiometabolic system, brain anatomy, neurophysiology, and characteristics related to the HPA. This shows that among those experiencing their first episode of psychosis, malfunction is prevalent throughout several organ systems.[83]

MANAGEMENT AND TREATMENT

Reducing the risk for clinical cardiovascular events such as atherosclerotic disease is the main objective of clinical care in people with metabolic syndrome. First-line treatment is focused on addressing the main risk factors such as high low-density lipoprotein cholesterol (LDL-C), hypertension, and preventing type 2 diabetes mellitus, even in those with metabolic syndrome. The main goal of managing metabolic syndrome is to minimize all of the metabolic risk factors (obesity, physical inactivity, and atherogenic diet) by modifying the modifiable underlying risk factors through lifestyle modifications. Drug therapy can be administered when the absolute risk is great. Additionally, efforts should be made to help cigarette smokers stop smoking. The presence of additional metabolic syndrome risk factors in diabetics indicates a higher likelihood of developing atherosclerotic cardiovascular disease (ASCVD) in the future.[84,85]

Physical exercise: Increasing physical activity helps people lose weight, has positive impacts on metabolic risk factors, and, most significantly, lowers their risk of developing ASCVD overall. A moderate-intensity workout lasting more than 30 minutes, like brisk walking, provides greater advantages.[86,87]

Diet: Saturated and trans fats, cholesterol, salt, and simple carbohydrates should all be consumed in moderation. fruits, veggies, whole grains, and fish should all be consumed in sufficient amounts. Diets high in protein and low in carbohydrates will help you lose weight.[88–91] After achieving the LDL-C goal in patients with atherogenic dyslipidemia whose serum triglyceride levels are 200 mg/dL, non-HDL-C is the next treatment goal. While non-HDL-C targets are similar to LDL-C targets, the former is 30 mg/dL higher. Triglyceride-lowering medications ought to be taken into consideration to stop the onset of acute pancreatitis when blood levels are below 500 mg/dL. Fibrinolytic acid and fibrates both increase HDL-C and lower triglycerides and small LDL particles. Fenofibrate can be chosen if a statin is being used to lower LDL-C.[34,85,92]

Controlling high blood pressure: According to the Dietary Approaches to Stop Hypertension (DASH) diet, it can be successfully managed with lifestyle therapies like weight management, increased physical activity, moderate alcohol consumption, sodium reduction, and increased consumption of fresh produce and low-fat dairy products. Medications like angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may be used if blood pressure is not controlled by lifestyle changes. First-line treatment for hypertension in metabolic syndrome should include ACE inhibitors, particularly in cases of type 2 diabetes or chronic renal disease. ARBs may be used in patients with left ventricular dysfunction or in those who cannot tolerate ACE inhibitors.[88,93,94]

Control of high fasting blood sugar: Impaired fasting glucose and type 2 diabetes mellitus are both considered to have high fasting glucose (100 mg/dL). To reduce the risk of type 2 diabetes mellitus in persons with impaired fasting glucose or impaired glucose intolerance, drugs including metformin, thiazolidinediones, and acarbose can be used if lifestyle treatments are unsuccessful. Metformin reduces the risk of metabolic syndrome in individuals with increased fasting plasma glucose levels, however, lifestyle changes were more effective and altered the intestinal flora.[95–98]

Antipsychotics are used in the long-term therapeutic strategy for the treatment of schizophrenia, which has the potential side effect of increasing the risk of metabolic syndrome and cardiovascular events.[99] Hyperprolactinemia is most frequently caused by antipsychotics.[100] Antipsychotics can all result in hyperprolactinemia since they all block D2 receptors, which also eliminates dopamine's inhibitory influence on prolactin release.[101] Tricyclic antidepressants, regardless of how they affect weight, can increase blood lipids and produce insulin resistance. With regard to weight gain, second-generation antipsychotics clozapine and olanzapine pose the biggest risk. Risperidone, paliperidone, and quetiapine have a moderate risk of making patients gain weight. Asenapine, amisulpride, ziprasidone, and aripiprazole have less of an impact on body weight. A total mean weight gain of 12.1 kg was recorded three years following the start of treatment in a cohort trial involving 170 patients with psychosis.[102]

Antipsychotics and other psychiatric medications are linked to weight gain. A reduction in basal metabolic rate, as well as an increase in hunger and a yearning for carbohydrates, are possible side effects of treatment. The use of antidepressants was linked to high levels of fasting plasma glucose, low HDL cholesterol, and hypertension.[103]

In conclusion, although metabolic syndrome poses a high risk, especially in terms of cardiovascular system diseases, it can also accompany psychiatric disorders such as major depressive disorder, anxiety disorder, schizophrenia, and bipolar disorder. Therefore, metabolic diseases should be considered in the differential diagnosis of psychiatric disorders in the evaluation and especially in the treatment phase of high-risk patients.

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