Metabolic syndrome & psychiatric disorders

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The metabolic syndrome, a constellation of symptoms associated with obesity, dyslipidaemia, insulin insensitivity, deranged glucose metabolism and hypertension has been gaining widespread interest due to its immense clinical relevance. We review the metabolic syndrome in terms of its diagnostic criteria and its relationship with severe mental illnesses and psychotropic medications, and the guidelines to manage it.

Key words Metabolic syndrome - psychotropic medication - severe mental illness

Introduction

Psychiatric disorders are among the leading causes of global morbidity. These are often chronic and need treatment with psychopharmacological agents for prolonged periods often extending up to a lifetime. The bulk of the research on metabolic syndrome (MS) shows that the use of the psychopharmacological agents, especially the newer ones, is associated with metabolic side effects such as weight gain, and deranged glucose tolerance and lipid profiles. In contrast, there are studies that show a favourable response of the psychotic disorders to the use of antipsychotic agents to be associated with weight gain and corresponding metabolic derangements. Also, psychiatric disorders have been shown to be associated with MS in a general way even when controlling for the use of the psychopharmacological agents. Thus studying the MS is important heuristically to understand its pathophysiology and practically to determine the appropriate use of the psychopharmacological agents. The latter must be seen in the context of the fact that often patients with psychiatric disorders lack the capacity to get adequately involved in the decision-making regarding their treatment.

A survey on MS in the United States reported the prevalence at 24 per cent in adults and found the cardiovascular mortality and all-cause mortality to be increased in men and risk of coronary disease increased in women. Thus, considering the potential risks of MS its public health importance is immense.

The Metabolic Syndrome

Definition and controversies

First described by Gerald Reaven in 1988 and named as syndrome X, MS is also known as insulin resistance syndrome, and CHAOS (a mnemonic for Coronary artery disease, Hypertension, Adult onset diabetes, Obesity and Stroke). Over the last decade, a number of definitions of MS have been offered.

The World Health Organization defined MS as insulin resistance and/or impaired fasting glucose and/or impaired glucose tolerance and two or more of the following: (i) waist-hip ratio >0.90 (men), >0.85 (women) or body mass index >30 kg/m², (ii) triglyceride level >1.7 mmol/l or high-density lipoprotein <0.9 mmol/l (men), <1.0 mmol/l (women), (iii) blood
pressure >140/90 mm Hg (or treated hypertension), and (iv) microalbuminuria.

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) proposed a definition that was revised in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute (updated ATP III). In the same year, the International Diabetes Federation (IDF) proposed another definition. These definitions lay emphasis on abdominal obesity as measured by abdominal circumference of >102 cm for males and >88 cm for women, with the corresponding values being 90 and 80 cm respectively when people of Asian origin were taken into account. The other criteria being triglyceride levels being elevated beyond 150 mg/dl, decreased high density lipoproteins (HDL) below 40 mg/dl and 50 mg/dl for men and women respectively, elevated blood pressure >130/85 mm of mercury and elevated fasting plasma glucose levels >110 mg/dl. An advantage of the IDF and ATP definitions is that unlike the WHO criteria, these are easily measurable and do not require specialized investigations. A major difference between the ATP and IDF definitions is the necessity of central obesity for making a diagnosis. While the updated ATP III definition requires any three of the five criteria for a diagnosis, the IDF definition needs central obesity plus any other two abnormalities. Despite this difference, updated ATP III and IDF criteria have a great deal of overlap.

The prevalence of MS in populations around the world has ranged among men from 8 per cent in India to 24 per cent in United States and among women from 7 per cent in France to 46 per cent in India. But these definitions may not be ideal for use among the South Asians, especially the populations of Indian origin. In a recent survey in a south Indian population, the prevalence of MS (%) was estimated to be 23.2, 18.3 and 25.8 using the WHO, ATPIII and IDF definitions respectively. The universal application of definitions of MS among populations from different racial backgrounds is still open to question and merits further attention.

To summarize, the MS is a group of disorders comprising mainly of truncal/central obesity, insulin resistance, hypertension, glucose intolerance and dyslipidaemia.

**Pathophysiology**

The pathophysiology of MS is not clear, though some clues are available. MS affects various organs in the body, most prominently the vasculature. The changes are influenced by risk factors such as glucose intolerance, dyslipidaemia, and hypertension and finally lead to increased cardiovascular morbidity. Insulin insensitivity/resistance is presumed to be the vital component underlying the development of other abnormalities and leads to increased plasma glucose levels and increased lipolysis that causes an increase in free fatty acid levels (FFA) that are subsequently packaged by the liver into triglycerides and very low density lipoproteins (VLDL). Thus, hyperinsulinaemia, glucose intolerance, type 2 diabetes, hypertriglyceridaemia, and high VLDL levels can be accounted for by resistance to the effects of insulin on carbohydrate and lipid metabolism. The low HDL levels are believed to result from a vicious cycle of lipolysis, increased FFA, and insulin resistance. Insulin resistance would then result in increased triglyceride load in the HDL particle that is acted upon by hepatic lipase which hydrolyses the triglyceride. The loss of triglyceride results in a small HDL particle that is filtered by the kidney resulting in decreased HDL levels. An increase in plasma free fatty acid in normal subjects to levels comparable with that in the obese also results in the induction of oxidative stress, inflammation and insulin resistance. Because resistance to insulin also causes relative non suppression of adipocyte hormone-sensitive lipase, there is further enhancement of lipolysis and increase in levels of FFA. Thus, there occurs a vicious cycle of lipolysis, increased FFA, inflammation and insulin resistance. Inflammation as measured by markers such as elevated C-reactive protein (CRP) levels is a component of MS which is increasingly being recognized. This is probably due to the fact that insulin is also an anti-inflammatory hormone, and that high calorie intake in itself is pro-inflammatory. Insulin resistance would then result in activation of pro-inflammatory factors. Obesity itself is also pro-inflammatory and this state can induce insulin resistance. It has been hypothesized that insulin resistance which leads to the manifestations of MS, comes about as a result of a pro-inflammatory state brought about by obesity and calorie intake. There may be genetic and environmental stimuli such as stress as well that may induce activation of inflammatory mechanisms and these may be particularly relevant in certain racial groups more prone to MS.
Insulin insensitivity has also been shown to be directly associated with increased blood pressure independent of age, gender and degree of obesity\textsuperscript{31,32}. Visceral obesity has been suggested as the primary source of the decreased sensitivity to insulin\textsuperscript{33-35}. Adipocyte derived humoral factors such as free fatty acids, tumour necrosis factor $\alpha$ (TNF-$\alpha$), interleukin-6 (IL-6), resistin are released into the circulation in direct proportion to the visceral fat stores and may lead to decreased insulin sensitivity\textsuperscript{36, 37}.

The glucocorticoid system has also been implicated in MS. Cortisol excess can produce insulin resistance and other symptoms as seen in Cushing’s syndrome. Stress due to psychiatric illness has been implicated in producing activation and subsequent clinically significant hypercortisolaeemia and a deranged hypothalamo-pituitary-adrenal axis (HPA)\textsuperscript{38, 39}. Chronic activation of the HPA axis is well known to cause insulin resistance and development of diabetes. This is an attractive hypothesis to explain the prevalence of MS independent of the psychotropic medication in patients with severe mental illness.

**MS and mental disorders: explanatory hypotheses**

*Insulin resistance and HPA axis derangement*

Though it is not clear as to what extent stress influences onset of diabetes or its course\textsuperscript{40,41}, the association between diabetes and mental illness is undeniable. Though a cause-effect relationship is difficult to establish, it is seen that people with diabetes have a 2-3 times higher prevalence of depression than the general population\textsuperscript{42}. There is some evidence to suggest that depression may precede the manifestation of type 2 diabetes\textsuperscript{43}. In patients with bipolar disorder, the prevalence of type 2 diabetes ranges from 10 to 26 per cent\textsuperscript{44, 45}. Patients with schizophrenia have a 2-4 times greater risk of developing type 2 diabetes than the general population\textsuperscript{46}. Severe mental illnesses like depression, bipolar disorder and schizophrenia are often associated with HPA dysregulation and hypercortisolaeemia\textsuperscript{47-49}. The reasons for increased risk and prevalence of diabetes in people with severe mental illness are unclear but the increased prevalence of MS in these patients may be a reflection of genetic or HPA dysregulation induced insulin resistance.

**Inflammation**

Recently, much attention has been directed at the inflammatory reaction in patients with severe mental illnesses. Severe mental illnesses like major depression and schizophrenia are commonly associated with altered inflammatory parameters\textsuperscript{50}. MS in these patients may result from insulin resistance arising out of the pro-inflammatory state that mental illnesses represent\textsuperscript{29, 30}. 

**Serotonergic mechanisms**

It has been seen that MS and insulin resistance are associated with blunted central 5-hydroxytryptamine (5-HT) responsiveness\textsuperscript{51}. Reduced central 5-HT responsiveness partially explains the possible relationship between depression and MS as exemplified by better glycaemic control due to improved insulin sensitivity in patients taking selective serotonin reuptake inhibitor (SSRI) class of antidepressants\textsuperscript{51}.

**Lifestyle factors**

Lifestyle factors that can influence MS deleteriously such as physical inactivity, poor dietary habits, smoking and drinking are commonly seen in those with mental illness. These factors may explain some of the increased risks of MS in those with mental illness\textsuperscript{52}.

**Pharmacological factors**

Changes in weight in both positive and negative direction are common side effects of psychopharmacological therapy. Of this, weight gain is particularly problematic and is often responsible for adverse consequences and non compliance\textsuperscript{53}.

**Antipsychotics**

A majority of antipsychotic drugs have been implicated in weight gain, dyslipidaemia and new onset diabetes\textsuperscript{49}. Among conventional antipsychotics, chlorpromazine and thioridazine are known to cause weight gain\textsuperscript{54,55} through the blockage of cholinergic, serotonergic, and histaminergic sites, all of which are related to appetite stimulation\textsuperscript{55}. The newer antipsychotics have better efficacy but also have more troublesome metabolic side effects, clozapine\textsuperscript{56} and olanzapine\textsuperscript{57} being the worst offenders. The weight gain has been seen to progress rapidly at first and then at a slower rate for several years\textsuperscript{58}. The mechanisms are purported to involve the histaminergic, cholinergic, endocrine, and metabolic systems\textsuperscript{57}. Glucose insensitivity via insulin pathways is implied to mediate via the serotonin and histaminergic receptors\textsuperscript{58}. Risperidone\textsuperscript{59} and quetiapine\textsuperscript{60} also lead to modest weight gain.

Weight gain and associated metabolic abnormalities as a result of antipsychotic therapy may be predictive of improvement in psychopathology\textsuperscript{2,3}. This suggests that
an antipsychotic such as clozapine may also act on neurotransmitters which influence weight gain, e.g., 5-HT (2C) and 5-HT (1a) antagonism. This in association with individual variations in these receptors and others molecules, such as peptides and transporters, due to polymorphisms or post-translational editing of mRNAs, may contribute to the improvement in psychopathology.

Mood stabilizers

Long-term lithium therapy frequently leads to weight gain due to carbohydrate craving, oedema and hypothyroidism. Valproate related agents also lead to weight gain of an average of 8-14 kg with an incidence of 8-59 per cent, the mechanisms may involve increased food intake, decreased energy expenditure, and a greater availability of free fatty acids, but the weight gain is difficult to reverse with dietary restriction. Carbamazepine is less commonly associated with weight gain and topiramate may actually induce weight loss through unknown mechanisms.

Antidepressants

Most antidepressants lead to weight gain due to appetite stimulation and craving for carbohydrates as the depression lifts. The tricyclics, notably amitryptiline and imipramine are frequently implicated. The mechanisms for weight gain with mirtazapine are unknown but observed to be dose-dependent weight gain. Bupropion often causes weight loss and may be a good choice in patients where weight loss is important. Selective serotonin reuptake inhibitors (SSRIs) often lead to weight loss in short term however, there are conflicting results with different members of this group.

MS and psychiatric disorders

MS is quite prevalent in patients with severe mental illnesses. As discussed earlier, many psychotropic medications have deleterious effects on body weight and lipid profile. Also, patients with severe mental illness may have impaired decision making capacity, are more likely to indulge in behaviour such as smoking and poor dietary habits, tend to remain on medications for long periods of time, and often become non-compliant due to the medication side effects. Thus on one hand complications of MS can lead to increased morbidity and mortality, on the other hand outcome of pharmacotherapy of mental illness may be poor.

MS and schizophrenia

Compared to the general population in patients with schizophrenia studies have shown greater prevalence of obesity and visceral fat increase by a factor of 3.4 independent of medication effects. As regards MS in schizophrenic outpatients studies from the USA have reported prevalence rates of 60 per cent by ATP III criteria and 51 per cent in others, and as per the WHO criteria 2-4 times higher than an appropriate control group. Reports from other countries have reported high (but less than those from the USA) prevalence rates ranging from 8-17 per cent, 37 per cent in Finland, 21 per cent in outpatients in Taiwan and 23 per cent in Thailand.

The role of psychotropic medication in the association between MS and schizophrenia remains obscure. Though with differing propensities, all antipsychotics can induce weight gain. As mentioned earlier increase in visceral fat stores is more significant than the increase in fat stores at other regions. The results of studies examining sites of antipsychotic induced weight gain are conflicting.

One study from the United Kingdom reported three times more intra-abdominal fat in treatment naïve as well as antipsychotic treated patients with schizophrenia in comparison to age-matched controls, and that 6 month treatment with olanzapine or risperidone increased total body mass but not visceral fat. In contrast, in a group of Chinese patients with first-episode schizophrenia and matched controls, the visceral fat stores were reported to be similar at intake but significantly different at 10 wk of treatment with risperidone or chlorpromazine.

Other studies have failed to demonstrate significant differences in prevalence of MS across those treated with typical and atypical antipsychotics. Though there are various hypotheses, the definitive mechanisms of metabolic syndrome and psychotropic medications remain elusive.

It has also been hypothesized that the increased fatty acid levels in the plasma are actually responsible for neuronal membrane stabilization and amelioration of schizophrenic symptoms in those suffering from weight gain.

The prevalence of diabetes in people with psychotic disorders has progressively increased from 2.5-4.2 per cent in the pre-antipsychotic era to 17 per cent in the first-generation and 19 per cent in the second-generation antipsychotic era. It has been assumed that the increased prevalence of diabetes type 2 in patients with schizophrenia is a result of treatment with atypical antipsychotics.
However, it has been seen in certain studies that fasting plasma glucose level in drug-naïve patients with schizophrenia does not significantly change with either 10 wk of treatment with risperidone, or 52 wk of treatment with clozapine or chlorpromazine. A genetic association between schizophrenia and diabetes mellitus type 2 has been posited as well as unaffected first-degree relatives of people with schizophrenia have high rates of diabetes mellitus type 2 as compared to controls and over 15 per cent of drug-naïve patients with first episode schizophrenia have impaired glucose tolerance, hyperinsulinaemia and increased levels of cortisol. Though the evidence for an overactive HPA is not universally found, hypercortisolaemia can lead to the features of MS as has been elucidated earlier.

A genetic association between schizophrenia and diabetes mellitus type 2 has also been posited based on the findings that the unaffected first-degree relatives of people with schizophrenia have high rates of diabetes mellitus type 2 as compared to controls and over 15 per cent of drug-naïve patients with first episode schizophrenia have impaired glucose tolerance, hyperinsulinaemia and increased levels of cortisol.

This debate led to the American Diabetes Association’s consensus publication on antipsychotic agents, diabetes and obesity which concluded that clozapine and olanzapine are associated with greater weight gain and higher rates of dyslipidaemia and diabetes than risperidone and quetiapine which are intermediate while aripiprazole and ziprasidone did not appear to be significantly associated with this potential.

Another aspect to this issue is the finding that weight gain is directly associated with improvement in psychopathology in patients with psychosis being treated with second generation antipsychotics. For instance, a study found that at 14 wk, the improvement in both positive and negative symptoms correlated with weight gain in patients on olanzapine and clozapine but not risperidone and haloperidol. Another study found that clozapine induced weight gain was associated with antipsychotic efficacy at 6 wk and 6 months as well. The relationship between weight gain and clinical improvement as implied by these studies suggests that weight gain may be essential for antipsychotic efficacy. This area needs further study.

**MS and mood disorders**

The database regarding mood disorders and MS is not as profuse as that for schizophrenia.

**Depression**

Studies in relation to MS and depression have given mixed results. In a 6 yr follow up study, the prevalence of MS in a group of depressive outpatients was 36 per cent, the main predictive factors being current depression and overeating. In another study, it was seen that depression in women was associated with MS at follow up, and MS was associated with anxiety at follow up. Similar results were replicated in women but not in men in another study. However, no association between MS and depression was found in a sample of 5691 men and women in a study by Herva et al. The presence of MS was found to be associated with increased prevalence of depression but not anxiety regardless of confounders like lifestyle factors such as smoking and also body mass index (BMI).

The association between unipolar depression and obesity is unclear. The correlation has been found both positive and inverse while a prospective study reported that the obesity predicted depression but not vice-versa.

**Bipolar disorder**

Studies have examined the association of bipolar disorders with components of MS. Patients with bipolar disorders are reported to have an increased frequency of cardiovascular illness compared with general population. The association of bipolar disorders with obesity, diabetes, dyslipidaemias, and hypertension has been reported as well, though there is no evidence for the opposite direction of causation or association. Medications such as valproate and lithium, and antidepressants with their weight affecting profiles remain a confounding factor.

**MS and post traumatic stress disorder (PTSD)**

Patients with PTSD have been reported to have an increased prevalence of somatic disorders, particularly diabetes mellitus and cardiovascular disorders in comparison with general population. Formal clinical research however, is scarce in this area. PTSD is commonly associated with hyperarousal and sympathetic nervous system hyperactivity, irritability and disturbed circadian rhythms. These may predispose the sufferer to MS.

**Interventions and Management Guidelines**

The primacy of treating a severe mental illness should be firstly acknowledged. To the extent possible, decisions regarding pharmacological agents should be
hypothesis that weight gain is a necessary factor in parts of the world remains to be documented. The comparative prevalence of MS in different mental illnesses have a high prevalence of MS. However, the change in lifestyle or medication, patients with severe antipsychotics109. There are ample data showing that and exercise, or a switch to more neutral the best studied options for weight control include diet and lipid profile in all patients with mental illness to be started on psychotropic medication. This is to be then followed up by monthly weight assessments for the first 3 months and then quarterly, blood pressure, fasting lipid and blood glucose profiles at 3 months and then fasting plasma glucose and blood pressure annually and fasting lipid levels every 5 yr93. For patients with schizophrenia, the best studied options for weight control include diet and exercise, or a switch to more neutral antipsychotics109. There are ample data showing that even modest weight loss results in significant health benefits. A loss of only 2 pounds increases survival by 3-4 months, and a 3 to 5 per cent loss achieves significant improvements in lipid profile and a 5 per cent decrease in diastolic blood pressure; a loss of 10 per cent (15-30 lb) in obese subjects reduces glucose by 29 mg/dl and haemoglobin HbA1c by 1.1 per cent 111-113.

**Conclusion**

Whether as a part of the illness or its consequence (change in lifestyle) or medication, patients with severe mental illnesses have a high prevalence of MS. However, the comparative prevalence of MS in different parts of the world remains to be documented. The hypothesis that weight gain is a necessary factor in improvement of symptoms of schizophrenia is also interesting and raises questions regarding the pathophysiology of schizophrenia and the mode of action of its treatment. The professionals need to be aware of the existence of the MS, be vigilant to its development and take prompt steps to rectify it.

**References**


