

## DEPRESSION AND METABOLIC SYNDROME: TWO SIDES OF THE SAME COIN

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### **Summary**

This aim of this review was to examine the relationship between metabolic syndrome (MetS) and depression, which is complex and multifaceted with many inter-related factors including genetics, lifestyle factors, environmental factors and other psychological factors at play. There is some evidence to suggest that depression may lead to the development of cardiovascular disease through its association with MetS. It has also been suggested that depressive symptoms may be a consequence rather than the cause of the MetS, as obesity and dyslipidemia have been shown as predictive of depressive symptoms. Thus, the relationship between MetS and depression seems to be a two-way street and bi-directional just as the two sides of the same coin.

**Key words:** metabolic syndrome, depression, obesity, development, resistance

### **Introduction**

Metabolic syndrome (MetS) and depression are both considered to be major public health problems worldwide, and both of these conditions are among the diseases with a high disease burden. Some studies have found a strong association between depression and MetS [1-8]. While patients who suffer from depression have been found to have a two-fold increased risk of developing MetS [4, 9-11] one study [12] showed that those who suffered from twelve weeks of 'chronic stress' developed depressive symptoms, which over time became comorbid with insulin resistance. There is general agreement that insulin resistance is one of the principal contributing factors in the development of MetS. However, it has also been found at the same time that the sedentary lifestyle of patients with depression [13] and the use of antipsychotic medication is also closely associated with the MetS [14-16]. As a result, from such findings, it has been recommended that it is essential to screen patients who suffer from depression for features of MetS [17, 18]. Due to the association between MetS and depression, the potential importance of screening patients with MetS for depression is becoming increasingly recognised by psychiatrists and endocrinologists alike.

Further, while the prevalence of MetS has

dramatically increased in the general population in the last few decades and it has also increased in those with mental illnesses [19, 20] studies have revealed a bidirectional association between depression and MetS [19, 21, 22].

At the same time, there are also studies that have shown that depressive symptoms are present in patients with MetS in both childhood and adulthood [21] and that there is a bi-directional relationship between obesity and depression [23]. Obesity continues to be considered as the principal contributing factor in the development of the MetS and the psychosocial factors such as social stigma leading to discrimination further resulting in distress could also lead to depression [24]. Systematic reviews on MetS and depression have found a higher prevalence of depression in patients with MetS than others [21, 22]. Thus, the relationship between the two conditions is starting to generate much research interest because both conditions pose significant public health challenges [22], and this review aimed to elucidate this.

### **What is MetS?**

MetS refers to the clustering of several cardiovascular risk factors, which includes insulin resistance, atherogenic dyslipidemia,

central obesity and systemic hypertension. All these conditions are interrelated and share underlying mediators, mechanisms and pathways [25]. Although the criteria for the definition of MetS vary slightly between the World Health Organisation (WHO) [26], National Cholesterol Education Program and Adult Treatment Panel III (NCEP ATP III) [27], European Group for the Study of Insulin Resistance (EGIR) [28] and the International Diabetes Federation (IDF) [29, 30], there is general agreement that MetS is defined as a clustering of abnormalities that include systemic hypertension, impaired glucose metabolism (impaired fasting glucose or presence of type 2 diabetes), impaired lipid metabolism (low high-density lipoprotein or HDL, and hypertriglyceridemia) as well as central obesity (high waist-to-hip ratio). Out of the various criteria, the NCEP ATP III criteria are the most widely used criteria for the diagnosis of metabolic syndrome. It uses measurements and laboratory results that are readily available to physicians, making it easy to use for clinical and epidemiological purposes [25]. As per updated NCEP ATP III criteria [31] MetS is considered to be present when at least 3 of the five criteria are satisfied (Table 1).

**Table 1.** Updated NCEP ATP III criteria for the diagnosis of metabolic syndrome [30]

Criteria	Definition
Abdominal obesity	Waist circumference over $\geq 102$ cm in men or $\geq 88$ cm in women
Elevated triglycerides	$\geq 150$ mg/dL, or drug treatment for high triglycerides
Low HDL-cholesterol	$< 40$ mg/dL in men or $< 50$ mg/dL in women; or drug treatment for low HDL-C
Elevated Blood Pressure	Systolic $\geq 130$ mmHg and/or diastolic $\geq 85$ mmHg; or drug treatment for hypertension
Elevated fasting plasma glucose	$\geq 100$ mg/dL; or drug treatment for elevated glucose

The practical utility of MetS concept is identifying patients with high risk of developing type 2 diabetes mellitus or cardiovascular disease with a shared pathophysiology, so that these population can be offered lifestyle modifications such as diet control, increasing physical activity, avoidance of smoking and appropriate pharmacological management of the individual components of MetS to reduce their cardiovascular disease risk [24].

### **Mediators of MetS**

Although there is no single contributing factor for MetS, many researchers have recently suggested that visceral obesity is the primary determinant of insulin resistance that leads to MetS [32-35]. However, studies within the last couple of decades have also shown an association between MetS and psychosocial factors. [9, 11, 36-38] It has also been suggested that a tendency for a sedentary lifestyle is also found in both depression and MetS [39] and

that the side effects to medications [40] also contribute to central obesity [41] and insulin resistance [42, 43]. Besides, research has shown that the neuroendocrine effects of depression could increase the accumulation of abdominal fat [41] and interfere with the blood pressure (BP) regulation and glucose metabolism [44].

On the other hand, patients with MetS are found to have a preference for a sedentary lifestyle and their self-perception of low esteem, in turn, can lead to an increased risk of depression [42, 45]. It has further been observed and noted that patients with MetS had increased leptin resistance [46], which could again lead to a depressed mood [47]. Thus, it could be said that both depression and MetS have shared pathophysiology concerning central obesity and insulin resistance.

### ***Psychosocial factors as mediators for MetS***

While there is no single cause for MetS [31] all available evidence in literature seem to suggest that psychosocial factors including personality characteristics and stressful life events are predictive of notable changes and abnormalities in metabolic parameters as well as a risk for cardiovascular disease and related morbidity and mortality [11, 36, 48]. Several psychosocial mechanisms come into play in determining this association between the psychosocial factors and characteristics of MetS. And in that regard, symptoms of depression, together with frequent feelings of anger and irritability, has been shown to be predictive of an increased risk for MetS over an average of 7.4 years, while marital dissatisfaction, divorce and widowhood has also been shown to be predictive of an increased risk, over an 11.5-year period. The same group of investigators in a subsequent [11] evaluated a cohort of women who did not have MetS to start with, to see if psychosocial factors that are related to cardiovascular disease and type 2 diabetes can prospectively predict the risk for MetS in them. Also, they found that the risk of MetS in the group that was studied varied between 1.21 to 2.12-fold increase, in those with more severe depressive symptoms and or very stressful life events. The researchers further found that in those at the baseline and were symptomless to start with, reported feeling frequently and more

intensely angry, tense or stressed and they too had an increased risk of developing MetS. However, another study [49] observed that MetS, while associated with depression, was not associated with psychological distress or anxiety.

### ***Overlapping pathophysiology***

Both drug treatment for depression and a sedentary lifestyle that is commonly associated with depression, can lead to weight gain and eventually to MetS. Further, there is a growing interest in the co-morbidity in mental and physical illnesses and the effects on each other as well as the associated physiological, emotional and hormonal factors that mediate their inter-relationships [2, 50-54]. As patients with MetS are at increased risk of developing mood disorders, common pathways for depression, abdominal obesity and glucose metabolism have been proposed with overlapping genetic, environmental and lifestyle factors. For example, psychosocial antecedents that are commonly associated with adverse health choices such smoking and noncompliance with treatment are more common among those from lower socioeconomic and disadvantaged backgrounds who are also likely to succumb to increased life stresses.

Furthermore, stress and psychosocial factors related to it, have been shown to be associated with the physiological changes attributable to the onset and development of MetS. These physiological changes include changes in the functioning of the autonomic nervous system characterised by sympathetic arousal, elevated heart rate and BP and a dysregulation of the hypothalamic-pituitary-adrenocortical system. These changes lead to elevated cortisol and glucocorticoid levels, resulting in central obesity and hyperinsulinism, as well as altered inflammatory and haemopoietic processes such as heightened platelet aggregation, fibrinogen, pro-inflammatory cytokines and white blood cell count [55]. Also, some of these physiological changes have been linked to changes in the neurotransmitter system such as serotonin that is involved in mediating depressive and other negative emotions, which in turn has been associated with MetS. It is possible that although the activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to behavioural as well

as peripheral changes with beneficial effects in adjusting the homeostasis and thus improving the chances of survival, it is the arousal of the corticotrophin-releasing hormone (CRH) and the locus coeruleus-norepinephrine autonomic (LC/NE) system along with it that leads to the other complex metabolic changes [56].

Another interesting possibility is that both psychological attributes (such as anxiety and depression) and the risk factors for MetS share a common genetic underpinning with environmental and external factors determining the course and eventual outcome of both conditions. In connection with this, the role of innate and genetic versus external and lifestyle factors was investigated in an Omani population [57]. They estimated the chances of inheriting the determinants of MetS versus the environmental factors and found that while aspects such as body weight, body mass index (BMI) and HDL levels had significant genetic influences, other aspects such as insulin resistance, abdominal obesity, diastolic BP and triglyceride levels, had significant environmental influences. From the results of this single study, it would seem that genetic and lifestyle, as well as environmental factors, act in concert in the development of MetS.

### ***Depression and MetS: cause or effect?***

It could be said that the relationship between depression and MetS, is a bi-directional one which cannot be fully explained by lifestyle and external risk factors alone, as it has been shown to persist even after controlling for these external factors [21, 22, 42, 58, 59]. Further, both cross-sectional and cohort studies have shown a higher incidence of depression in those with MetS compared to those without MetS [3, 21, 60]. Concerning this, it is also worth noting that childhood overweight and obesity that continues into adulthood has a significant impact on both the physical and psychological health of the individual. Further, those with a major depressive illness have been shown to have an increased risk of developing obesity and vice versa. Studies that have examined the phenomenology, co-morbidity, family history, biological and hormonal factors implicated in mood disorders and obesity have shown that both conditions share many similarities. Given the

role of an unhealthy lifestyle (including smoking, poor dietary choices and an inactive lifestyle) in the aetiology, the role of the overlapping pathophysiological mechanisms in the course of both conditions are important considerations. The negative impact of poor compliance to treatment programs on the prognosis is also to be considered in the context of psychosocial factors and mood disorders such as depression that may co-exist with MetS because these factors have a special place in the comprehensive management of these patients.

### **Conclusions**

Cardio-metabolic health concerns in patients with both MetS and depression are expected to increase in the coming years. Available evidence from the literature suggests that a two-way relationship exists between MetS and depression in terms of the pathogenetic processes in so far as each of these two conditions may be contributing to the other. Identifying the determinants of both depression and MetS is therefore critical because both can predict chronic health problems in the future. Thus routine screening of all patients with MetS for depression and those with depression for MetS is vital for early detection and intervention that can lead to a better outcome.

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