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REVIEW ARTICLE

Metabolic syndrome and major depression

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Major depression is associated with a 4-fold increased risk for premature death, largely accounted by cardiovascular disease (CVD). The relationship between depression and CVD is thought to be mediated by the so-called metabolic syndrome (MeS). Epidemiological studies have consistently demonstrated a co-occurrence of depression with MeS components, ie, visceral obesity, dyslipidemia, insulin resistance, and hypertension. Although the exact mechanisms linking MeS to depression are unclear, different hypotheses have been put forward. On the one hand, MeS could be the hallmark of the unhealthy lifestyle habits of depressed patients. On the other, MeS and depression might share common alterations of the stress system, including the hypothalamus–pituitary–adrenal (HPA) axis, the autonomic nervous system, the immune system, and platelet and endothelial function. Both the conditions induce a low grade chronic inflammatory state that, in turn, leads to increased oxidative and nitrosative (O&NS) damage of neurons, pancreatic cells, and endothelium. Recently, neurobiological research revealed that peripheral hormones, such as leptin and ghrelin, which are classically involved in homeostatic energy balance, may play a role in mood regulation. Metabolic risk should be routinely assessed in depressed patients and taken into account in therapeutic decisions. Alternative targets should be considered for innovative antidepressant agents, including cytokines and their receptors, intracellular inflammatory mediators, glucocorticoids receptors, O&NS pathways, and peripheral mediators.

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Clinical Implications

- Major depression is associated with a high risk of different metabolic alterations.
- The association between the 2 conditions seems to be mediated by overlapping pathophysiological mechanisms, involving the hypothalamus–pituitary adrenal axis, the autonomic nervous system, the immune and inflammatory system, the oxidative and nitrosative stress, and peripheral hormones such as leptin and ghrelin.
- These mechanisms may provide targets for innovative prevention and treatment strategies.

Introduction

Depression is a common and disabling disorder that is characterized by emotional, somatic, and cognitive symptoms, each related to behavioral and biological factors affecting physical health, and, therefore, increasing functional impairment, morbidity, and mortality.

Depression affects about 121 million people worldwide. According to the World Health Organization (WHO), it represents the second cause of disability and the fourth leading contributor to the global burden of disease, and it is predicted that by the year 2020, it will be the second after cardiovascular disease (CVD). In addition, depression can be a consequence of medical illness and disability, yet it may also influence morbidity and mortality through different variables. Depressed patients have as much as a 4-fold increase in risk for early death compared to their non-depressed peers.[1] Suicide accounts for a small, albeit important, fraction of the total mortality associated with depression (16–19% of reported mortality in the psychiatric population vs <1% in community samples). After controlling for chronic health conditions and functional limitations at baseline, the depression–mortality association decreases.[2] This indicates that health conditions largely account for the excess of mortality in mood disorders. In particular, mortality studies indicate that

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CVDs are the most common causes of premature death in depressed patients.[3,4] The association between depression and CVD is thought to be mediated by the so-called metabolic syndrome (MeS), which, therefore, represents a major social issue for its increasing prevalence. It is thus important to elucidate the possible underlying mechanisms in terms of prevention, especially in a period of restricted public health budgets.

Based on studies carried out in different countries, a large agreement exists regarding the prevalence of MeS in depression. In Finland, after a 6-year follow-up in a sample of 175 patients, 36% were reported to have MeS (41% men, 33% women), which is significantly higher than those reported in men (41% vs 11–17%) and in women (33% vs 6–20%) in the general population within the same geographic region. The presence of MeS did not differ as a function of age, marital status, education, current smoking, alcohol use, physical exercise, or duration of depressive symptoms.[5] In 170 psychiatric inpatients of a general hospital in Brazil, 48.1% of those with MeS were diagnosed also with major depressive disorder and 38.8% with bipolar disorder.[6] In a German sample of 60 depressed patients, 25% fulfilled the criteria for MeS.[7] A high prevalence of MeS in depressed patients was reported also in Poland.[8] However, a few controversies do exist.[9–11].

The aim of this review is to examine the association between depression and MeS in order to better elucidate the pathophysiological mechanisms underlying their interaction. From a clinical point of view, this could imply the importance of monitoring the metabolic profiles of depressed patients and, vice versa, to pay attention to mood alterations in patients suffering from diabetes, hypertriglyceridemia, obesity, and hypertension. For researchers, the overlap of the pathophysiological patterns of the 2 conditions could offer new targets for innovative treatments.

Association Between Psychiatric Diseases and MeS

A general agreement exists regarding the association of MeS and different psychiatric disorders. According to epidemiological studies, MeS in bipolar patients is about 37.3% (95% CI = 36.1–39.0), which is 2- to 4-fold higher compared to the general population.[12–14]. In particular, the prevalence of MeS seems to be significantly higher in patients diagnosed as bipolar disorder (BD) I than in BD II patients.[15] It has been observed that BD patients having comorbidity with MeS tend to be older and to have older age of onset, longer duration of untreated illness, greater number of hospitalizations, less favorable response to treatments, adverse course and outcome, and greater risk of suicide.[13] Moreover, they have a greater risk of diabetes, coronary heart disease, and cardiovascular mortality compared to the general population.[13]

A greater prevalence of MeS has emerged also among schizophrenic patients (32.5%; 95% CI = 30.1–35.0) compared to the general population.[16,17] Schizophrenia comorbid with MeS is characterized by a greater severity of depressed symptoms, particularly depressed mood, middle insomnia, and retardation.[18]

The association between MeS and psychiatric diseases does not seem to be mediated by psychopharmacological treatments, as it has been described in drug-naïve patients.[15] Nevertheless, MeS is more prevalent in patients treated with antipsychotics (45.3%; 95% CI = 39.6–50.9) than in drug-naïve patients (32.4%; 95% CI = 27.5–37.4; odds ratio = 1.72; 95% CI = 1.24–2.38).[12] Antipsychotics have a greater impact on metabolic parameters than mood stabilizers.[13]

Association Between Depressive Symptoms and MeS

Epidemiological data and meta-analyses of cross-sectional and cohort studies published up to January 2012 indicate a bidirectional association between depression and MeS. The pooled odds ratio of new depression in subjects with metabolic alterations was 1.27 for cross-sectional studies and 1.49 for cohort studies. Conversely, depressed subjects were at 1.34 (cross-sectional studies) to 1.52 (cohort studies)-fold higher risk to develop MeS than healthy control subjects.[19]

The findings of a study in a cohort of 5232 middle-aged British civil servants demonstrated that MeS, specifically its components involving obesity and dyslipidemia, predicted the emergence of depressive symptoms in a 6-years follow-up period (OR = 1.38).[20] More recently, the study was extended to an elderly population (men and women aged 65–91 years), where MeS determined an approximately 2-fold (OR = 1.73) increased risk for the emergence of depressive symptoms in the age group 65–70 years old, but not in older subjects.[21] Similarly, in a cohort of 12,066 elderly men, an association between MeS, in particular obesity, and new-onset depressive symptoms was found over a 10-years period.[22] It is of special interest to investigate the association of MeS and depression in geriatric populations, because both the conditions increase with age and produce adverse consequences on quality of life. Moreover, it has been proposed that a so-called vascular subtype of depression may exist, which is etiologically linked to metabolic alterations via diseases of blood vessels and circulation. If this association is truly causal, reducing the prevalence of obesity and MeS could potentially lead to a decline in the prevalence and incidence of depression in later life. Furthermore, the results of a 7-year longitudinal study showed that non-depressed subjects with MeS at baseline were twice as likely to suffer from depressive symptoms at follow-up (OR = 2.2) compared with metabolically

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healthy non-depressed subjects.[23] It was concluded that the MeS may be an important predisposing factor for the development of depression, and consequently its effective prevention and treatment could also be important for the prevention of depression. In a population-based study of young adults, women with the MeS in childhood showed higher levels of depressive symptoms in adulthood, and the severity of depressive symptoms increased according to lifetime exposure to the MeS.[24] Of the 5 metabolic components, waist circumference (WC; central obesity) was the strongest predictor of future depressive symptoms.[24]

There is some debate about whether certain components of the MeS are more important than others, and whether it is useful to examine the individual components of the MeS in addition to the MeS as a single construct. Therefore, besides investigations on the MeS as a whole, the association between depression and the individual metabolic factors has been studied. The most consistent finding is the positive association between depression and abdominal obesity (waist circumference)/BMI, hypertriglyceridemia, and low HDL cholesterol. On the other hand, reports about the association of depression with hypertension or hyperglycemia are rare and contradictory.[24-26]

However, depression is more often associated with the construct of MeS rather than with its components. Probably, as proposed by Foley et al,[10] what matters is clustering of metabolic criteria (eg, elevated blood pressure plus abnormal HDL cholesterol plus elevated triglycerides rather than the elevated blood pressure alone).[10] According to this notion, several lines of evidence have shown a positive trend toward the association between the number of MeS components and depression.[27,28] In a longitudinal study of Japanese male employees, the number of metabolic components at baseline significantly correlated with the development of depression in the subsequent year.[29] These findings were replicated and further extended to older people in an Italian cross-sectional study, which showed a linear strong correlation of depressive symptoms with the number of MeS components ($r = 0.663$).[30] It should be noticed that, along with the association of MeS with the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) categorical diagnosis of depression, there is also a link with the severity of depressive symptomatology.[31-36] In a group of 652 women with suspected coronary artery disease, a higher prevalence of MeS and an increased number of MeS risk factors were described in women with more severe depressive symptoms.[33] Interestingly, in a large cohort study, an increased number of MeS components was observed in more severely depressed patients, although an increased prevalence of the MeS *per se* in subjects with major depressive disorder was not reported.[37] Finally, a recent cross-sectional study in Taiwanese older adults (≥54 years) added a further element to the puzzle, ie, functional impairment. Indeed, its findings showed that the presence of any number of metabolic disorders without functional impairment was not associated with depression. Vice versa, the presence of functional impairment regardless of the number of metabolic disorders was associated with a significantly higher risk for depression. In particular, the presence of a basic activity of daily living (ADL) dependency was significantly associated with a 1.45 higher likelihood of depression. It was concluded that perhaps MeS does not necessarily affect a patient's psychological health unless it is accompanied by functional impairment.[38]

Several data are also available regarding the risk for developing MeS among depressed patients. Relevant longitudinal studies have suggested a higher incidence of metabolic syndrome and/or its components (high waist circumference, high triglyceride level, low HDL level, high blood pressure, and high glucose level) in depression. In order to clarify the temporal sequence of depression and MeS, prospective studies have assessed the eventual role of depressive symptoms as predisposing factors for the development of MeS. Some of these included women only,[39,40] while others included both genders.[24,26] In the first case, a current or lifetime history of major depression at baseline was significantly associated with the emergence of the MeS during the follow-up (OR ranging between 1.82[40] and 2.5[39,41]). However, when considering both genders, there exist more consistent reports of a positive association between depression and the MeS in women than men.[24,26,41] In a large representative British birth cohort ($N = 3035$), the role of adolescent emotional problems in significantly predicting MeS in adulthood has been recognized for women, but not for men.[26] On the contrary, a few studies have noted an association in men, but not in women.[8,32,42] As a result, the possible importance of gender as a moderating variable is raised. These differences may be due to the fact that depression has a high prevalence in women. Nevertheless it has become evident that health-related risks related to depression may be different in women than in men. An association between affective symptoms and hypertension at age 53 years was observed in men, but not in women.[26] On the other hand, depressed women could be at increased risk for developing the obesity and dyslipidemia components of MeS. It has also been demonstrated that depressed late adolescent girls were more than twice as likely to be obese in adulthood, compared with their nondepressed female peers.[43] This suggests that depressed women could be at increased risk for MeS through effects on adiposity and lipid metabolism. Several possible explanations exist for the gender differences observed in the literature. First, the

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association between MeS and depression in women suggests a role for the gonadal hormone.[44] Second, increased appetite, comorbidity with eating dysregulation and binge eating, and consequent weight gain[45,46] are more common in women than men. Depressed women are more likely to increase their energy balance (eg, hyperphagia), whereas men may be more likely to consume alcohol or illicit substances.[47] Third, epidemiological data have shown physical activity to decrease with age, more deeply in women, probably because of decreasing opportunities for noncompetitive athletic activity, lack of interest or motivation, or changes in family involvement. Depressive symptoms could additionally interfere with a regular physical activity. In summary, MeS could be interpreted as a tracking into adulthood of these unhealthy behaviors in childhood and adolescence.

As already described above, it is important to study not only whether MeS is related with a dichotomous depression classification, but also to take into account separate psychopathological and clinical aspects, namely severity, number of episodes, chronicity, clusters of symptoms, subtypes, and suicidality risk. A dose–response relationship between the number of depressive episodes during adolescence and risk for adult obesity was reported in a sample of patients in New Zealand, and it was postulated that symptom duration may be considered as an independent predictor of obesity severity.[43] A prospective, population-based cohort study of older persons showed that depression associated with MeS has 3-fold greater odds of chronicity (OR = 2.66), with almost every metabolic syndrome component contributing to this association. It has been suggested that depression with metabolic abnormalities, labeled "metabolic depression," may identify a chronic subtype of depression.[48]

Recently, different clinical subtypes of depression were associated with specific clinical or laboratory abnormalities. The results showed that women with atypical and undifferentiated features had more total fat, abdominal fat, and greater waist to hip ratio than control. Consistently, this group had higher LDL, triglycerides, and total cholesterol levels, as well as higher fasting glucose, insulin level, and HOMA-IR (a measure of insulin resistance) compared to control subjects.[49] On the other hand, women with melancholic features did not differ from control in their metabolic profiles.[49] An increased prevalence of MeS was reported among subjects with atypical and undifferentiated depressive symptoms compared to those with melancholic features.[50] These finding are consistent with the hyperphagia that distinguishes atypical depression. On the contrary, in a middle-aged population-based sample, the risk of developing MeS was highest in the subgroups of females with more melancholic symptoms.[41] These last observations may be explained by the fact that, although the marked alteration of appetite is one of the most frequent symptoms of major depression and follows opposite trajectories in the melancholic/atypical subtypes of depression, it occurs mostly during the acute phase. Conversely, the higher prevalence of obesity in depressed patients is related to depressive episodes, and to lifestyle factors, comorbid bulimia, genetic-biological factors, and pharmacotherapy.[51]

An interesting cue is to determine whether a complete mood disorder diagnosis, or rather only specific symptom dimension, is related to the MeS. It is possible that, among the different depressive symptoms, some are "specifically" associated with a distinct MeS component (eg, energy loss, often leading to decreased physical activity, might lead to elevated waist circumference). An alternative for categorical diagnoses is the use of a dimensional approach, in which a patient is described in terms of coexisting different symptom domains or dimensions, rather than in a dichotomous way. Three symptom dimensions were identified by using a dimensional approach: (1) "negative affect" (NA), describing general symptoms of psychological distress (eg, lack of concentration or pessimism) that are seen both in depression and anxiety and could account for their high comorbidity; (2) lack of "positive affect" (PA), targeting anhedonic symptoms, which are mainly specific to depression; and (3) "somatic arousal" (SA), including symptoms of hyperarousal (eg, palpitations, shortness of breath, and dizziness), which are specific for anxiety.[52] Only SA was found to be strongly and independently associated with the majority of MeS components (especially WC, triglycerides, and blood pressure), while showing a graded association with the number of MeS components.[52] These finding are consistent with previous reports, showing that the somatic/affective subdimension, rather than other important dimensions (eg, cognitive/affective and appetitive), correlated with somatic outcomes. Indeed, 416 subjects from the semi-rural community of Lapinlahti in eastern Finland showed an association between MeS and every distinct dimension of the beck depression inventory (BDI-21). In particular, subjects with MeS were significantly worse than subjects without MeS specifically on the items of irritability, work inhibition, fatigability, weight loss, and loss of libido.[53] Findings from a study in Japanese workers identified "psychomotor agitation, restlessness" as the item correlating with a higher proportion of hypertriglyceridemia.[54] It is proposed that the physical symptom dimension could, therefore, be the key feature of the association between depression and somatic outcomes.

Among other depressive symptoms, hopelessness–poor expectations about the future and reaching goals–has emerged to be strongly associated with MeS in

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middle-aged men. Men with the highest levels of hopelessness were 2.1 times more likely to have MeS than those with the lowest levels.[55] As far as the relationship between MeS and suicidality is concerned, in depressed men who had at some time made serious suicidal attempts, serum HDL-C levels are significantly lower than in those with no suicidal behavior.[56]

In conclusion, major depression, when in comorbidity with MeS or its components, shows a more unfavorable course, as it is associated with a more severe presentation of the clinical picture, an increased risk for persistent and recurrent episodes (chronicity), a higher number of depressive episodes and suicidal attempts, and worse social functioning.

Pathophysiology

Although the exact mechanisms linking MeS to depression are unclear, different hypotheses have been put forward. According to one of these, MeS could be a cue of the unhealthy lifestyle habits of depressed patients. This notion is supported by the decrease in the association between adverse lipoprotein patterns (lower HDL level and higher triglyceride level) and major depression after adjustment for lifestyle-related factors, such as education, smoking status, alcohol use, and especially BMI.[37] However, it should be noticed that, after adjusting fully for covariates, lower HDL cholesterol remained independently associated with melancholic features, and so did higher total and LDL cholesterol levels with atypical depression.[37] The latter observation provides instead support to the alternative hypothesis that depression and MeS share common pathophysiologic mechanisms.

Another hypothesis is that these 2 conditions are interrelated in the sense that MeS and depression would share common alterations of the stress system, including the hypothalamus-pituitary-adrenal (HPA) axis, the autonomic nervous system, the immune system, and platelet and endothelial function (Fig. 1).

Hypothalamus–pituitary–adrenal (HPA) axis

Acute stress responses involve activation of the HPA and the sympathomedullary (SM) axis. Moreover, stress activates cell bodies of norepinephrine (NE) neurons in the locus coeruleus. Stress simultaneously triggers the

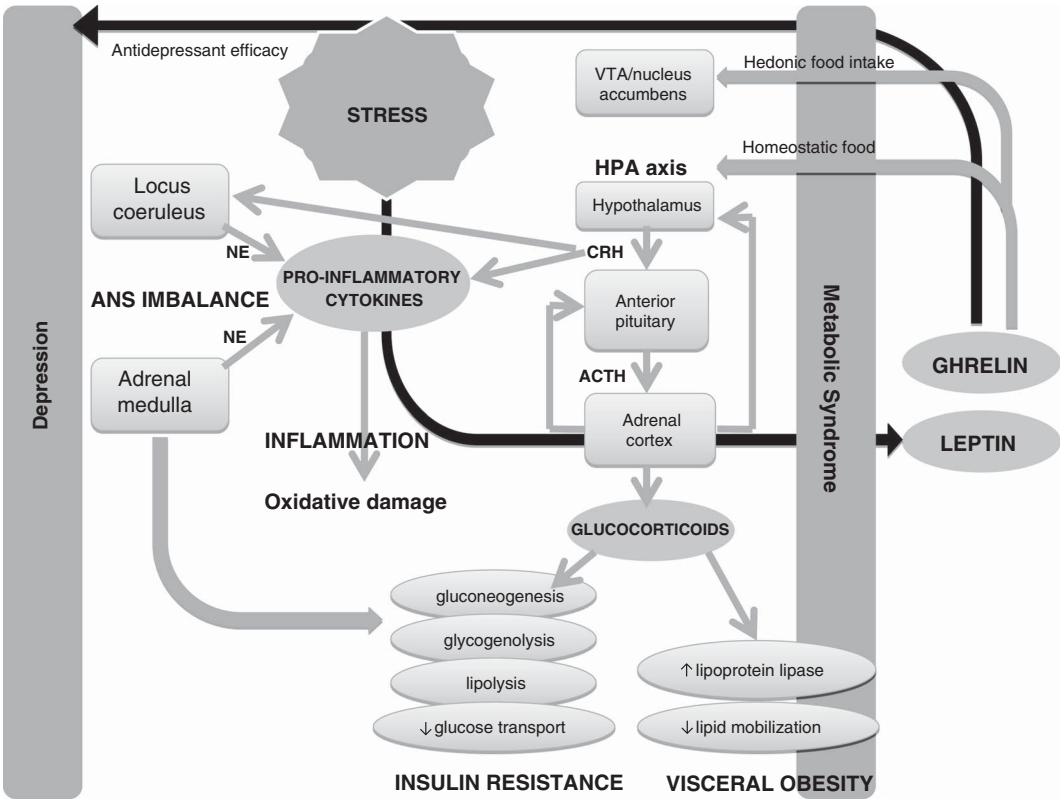


FIGURE 1. Pathophysiological overlap between depression and MeS. Depression and MeS share common pathways in the stress system, involving an abnormal activation of the HPA axis and an imbalance of the autonomic nervous system. In both conditions, there is a low-grade systemic inflammation, which leads to enhanced oxidative and nitrosidative stress. An antidepressant efficacy has been demonstrated for leptin and ghrelin, 2 peripheral hormones that are classically implicated in the homeostatic control of food intake.

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release of the corticotropin-releasing hormone (CRH) from the hypothalamus and cerebral cortex. Hypothalamic CRH activates synthesis and release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which, in turn, triggers release of cortisol and other glucocorticoids from the adrenal cortex. CRH enhances locus coeruleus activity and the synthesis of other stress-reactive gene products, pro-inflammatory cytokines, and anti-inflammatory responses, and decreases synthesis of key neuropeptides such as brain-derived neurotrophic factor (BDNF).[57]

Long-term activation of the stress system, due to exposure to prolonged, inescapable stress, can produce detrimental effects by increasing the risk of depression, but also of obesity and CVD.[58] Interestingly, an interaction between depressed mood and urinary cortisol was found to predict MeS. Further, those depressed patients with urinary cortisol levels in the highest tertile showed an increased prevalence of MeS, which suggests that hypercortisolemic depression constitutes a specific risk factor for MeS.[35]

Evidence of increased HPA activity is present in 20–40% of depressed inpatients. The HPA axis is considered to be the "final common pathway" linking depression to chronic stress. Moreover, elevated HPA activity in depression has been documented via elevated plasma and salivary cortisol and cortisone levels, increased urinary free cortisol excretion, altered dexamethasone suppression test, decreased corticosteroid receptor function, enhanced adrenal response to ACTH, blunted pituitary ACTH response to CRH, and adrenal and pituitary enlargement.[58] Several data underline a central role of hyperactive CRH neurons in the symptomatology of depression. Depressed patients showed an increased number of CRH neurons in the paraventricular nucleus (PVN) and an increased amount of CRH mRNA compared to control subjects. Alternatively, some findings support the glucocorticoids hypothesis of depression. In fact, receptor antagonists and cortisol synthesis inhibitors, such as metyrapone, aminoglutetimide, or ketoconazole, may be effective in the treatment of major depression. Depressive symptoms may be caused by elevated levels of both endogenous and exogenous cortisol. It has been, therefore, proposed that the "melancholic" type of depression would be due to a hyperactivity of CRH neurons (hyperactive HPA axis), while the "atypical" depression would be based on increased levels of corticosteroids and decreased levels of CRH (hypoactive HPA axis).[58,59]

The primary role of glucocorticoids is to initiate and sustain a rise in blood glucose under conditions of acute stress. Elevated cortisol levels promote homeostatic adjustments, such as the mobilization of energy via gluconeogenesis, glycogenolysis, lipolysis, and inhibition of peripheral glucose transport and utilization. However, under conditions of chronic activation of the HPA axis, allostatic effects are observed. Chronically elevated cortisol binds to glucocorticoids receptors, which are highly concentrated in visceral fat depots. Here, particularly when combined with secondary inhibition of sex steroids and growth hormone secretions, it activates lipoprotein lipase and inhibits lipid mobilization, which leads to an accumulation of triglycerides in this area.[60–62] This could explain why especially the combination of depression and high levels of cortisol increases the prevalence of MeS. The visceral fat depot is the preferential site of regeneration of cortisol from cortisone, a process that is facilitated by the enzyme 11-β-hydroxysteroid dehydrogenase type 1, which further amplifies intracellular cortisol levels and visceral adiposity. Substantial evidence exists that shows that circulating cortisol concentrations are higher in individuals with hypertension and glucose intolerance.[63] Glucocorticoids are counter-regulatory hormones that exert an obverse effect on insulin action. Chronically elevated glucocorticoids impede insulin's ability to promote glucose uptake, thereby contributing to insulin resistance and diabetes.

In summary, such alterations in the activity of the HPA axis that are quite common in mood disorders may significantly contribute to the major and most frequent aspects of MeS, including insulin resistance, abdominal obesity, and dyslipidemia.

Autonomic nervous system

Abnormalities in autonomic nervous system activity are common findings in depression, insulin resistance, and MeS. Depressed patients commonly have higher resting heart rates than healthy controls (a global marker of poor autonomic nervous system modulation), diminished heart rate variability (HRV; a marker of decreased parasympathetic input), baroreflex dysfunction, and increased QT variability, all of which have been linked to increased cardiac mortality, including sudden death.[64] Heightened sympathetic activity is also suggested by increased norepinephrine metabolites and by nonsuppression of the dexamethasone suppression test.[65]

A disturbance in the sympathetic/parasympathetic equilibrium is likewise found in MeS and has been proposed to result in elevated concentrations of serum insulin and decreased insulin sensitivity (markers of insulin resistance), independent from glucose levels.[66–68] In a communities study, subjects who had reduced HRV in the low-frequency range and high resting heart rate were at increased risk for developing type 2 diabetes mellitus.[69] Subjects with low HRV presumably have considerable resting sympathetic input. Increased sympathetic activation leads to enhanced catecholamine release and consequent increases in circulating free fatty acids

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and thus increased insulin resistance.[70] It has been postulated that in MeS, the sympathetic branch is prevalent on the functions of the heart, large vessels, and skeletal muscles, while leading to high blood pressure and impaired glucose uptake by the muscles (ie, insulin resistance). In the intra-abdominal compartment, however, the autonomic nervous system balance is shifted in favor of the parasympathetic branch, resulting in increased insulin secretion and growth of intra-abdominal fat tissue.[71]

Inflammation

It has been proposed that inflammatory pathways play a relevant role in the pathophysiology of depression, because in this condition there is evidence of a chronic, systemic, low-grade inflammatory process and cell-mediated immune activation characterized by a T-helper (Th1)-like response with activation of IFN-γ–related pathways. Recent publications showed increased levels of pro-inflammatory cytokines, particularly interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), and cell-mediated activation, as evidenced by higher levels of neopterin (a marker of increased IFN-γ macrophage activation) and soluble IL-2 receptors. Levels of inflammatory biomarkers are significantly correlated with depressive symptom severity.[72] On the other hand, acute and chronic administration of cytokines or cytokine inducers was found to trigger depressive symptoms.[73] According to the cytokine hypothesis, depression would be due to a stress-related increased production of pro-inflammatory cytokines that, in turn, would lead to indoleamine-2,3-dioxygenase (IDO) induction, with production of tryptophan (TRP) catabolites along the IDO pathway (TRYCATs) and consequent reduced availability of TRP and serotonin (5-HT). Cytokines would also play a role in the onset of the glucocorticoid resistance, underlying the overdrive of the HPA axis.[74]

MeS is also strongly associated with inflammatory markers. Intriguingly, obesity is now considered to be a pro-inflammatory state. Adipose tissue functions as an endocrine organ, as it secretes cytokines and hormones with paracrine functions, such as TNF-α, resistin, IL-6, and C-reactive protein. The systemic concentrations of IL-6 increase with adiposity, and it has been estimated that almost 30% of total circulating concentrations of IL-6 originate from adipose tissue in healthy subjects.[75] TNF-α induces production of IL-6, which is the major determinant of the acute phase response. Among the metabolic effects of TNF-α and IL-6 are inhibition of the action of lipoprotein lipase and stimulation of lipolysis, which induce dyslipidemia (low level of HDL and high level of triglycerides). Furthermore, TNF-α impairs the function of the insulin signaling pathway by effects on phosphorylation of both the insulin receptor and its substrate, IRS-1. Elevated levels of CRP and of cytokines were also associated with a series of indicators of endothelial dysfunction, such as plasma levels of von Willebrand factor, tissue plasminogen activator, and cellular fibronectin. Both TNF-α and IL-6, through endothelial expression of chemokines and adhesion molecules, may cause impairment of vasodilatation of resistance vessels, predisposing one to hypertension.[76]

Recent data demonstrated that depressed men with higher levels of C-reactive protein were more likely (OR = 4.28) to develop abdominal obesity and MeS over an 11-year follow-up than men with lower levels of C-reactive protein.[77] Thus, the presence of systemic low-grade inflammation together with depressive symptoms seems to put men at a particularly high risk for developing abdominal obesity.

In summary, both depression and obesity may be considered as "low-grade inflammatory states," with cytokines playing a major role that needs to be more thoroughly clarified.

Oxidative stress

Inflammatory and nitrosidative (O&NS) pathways are linked in a vicious cycle, wherein immune-inflammatory responses deplete the storage of endogenous antioxidants and reactive oxygen species (ROS) activate pro-inflammatory promoter genes through intracellular signaling cascades such as mitogen-activated protein kinases (MAPKs) and NF-kB. O&NS are responsible for both neuronal endangerment and β-cell toxicity. The central nervous system (CNS) is vulnerable to the effects of oxidative stress due to its high oxidative metabolic activity, polyunsaturated fatty acid content, and relatively low endogenous antioxidant capacity. In depressed patients, pro-inflammatory cytokines lead to increased O&NS brain damage through both reduced neurogenesis and increased neurodegeneration.[74]

Pancreatic β-cells are also more susceptible to the toxic effects of O&NS, because of their low expression of antioxidant enzymes. ROS penetrate into and cause damage to β-cells. Moreover, O&NS alters intracellular signaling systems, such as mitochondria, uncoupling proteins, endoplasmic reticulum, and ultimately protein kinase B (Akt). Akt has a central function to hepatic glucose output, triglyceride release, and insulin sensitivity. Perturbations in Akt kinase activity are accompanied by impairment in insulin-stimulated glucose transport in muscle and adipocytes. Akt is also a central modulator to prevent apoptotic cell injury during O&NS.[78] Through these mechanisms, O&NS injures insulin-producing cells within the pancreas thus inducing insulin resistance.

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Peripheral hormones (leptin and ghrelin)

Leptin is secreted by the adipocytes and acts at the hypothalamic level as an anorexigenic peptide. Recently, animal models of chronic stress demonstrated that leptin is involved in mood regulation, with an antidepressant-like efficacy.[79,80] Obese people, although with high circulating levels of leptin in proportion to their greater fat mass, are resistant to its effects. Similarly, in obesity-associated depression, leptin resistance could underlie depressive symptoms. In this case, leptin resistance should be seen as a feature of comorbidity of obesity and depression. In support to this hypothesis, diet-induced obese (DIO) mice fed a high-fat diet showed more depressive behaviors compared to mice fed a control diet (CD), which were not reverted by leptin administration. Foremost, diet substitution from high-fat diet to CD in DIO mice ameliorated the depressive behavior and restored leptin-induced antidepressive action.[81]

The new leptin hypothesis of depression is complementary to previous hypotheses, eg, the monoamine, the HPA, and the neurotrophin hypotheses. Since a high percentage of 5-HT and dopamine neurons in the raphe nuclei and in the ventral tegmental area (VTA), respectively, express leptin receptors, leptin could modulate synaptic availability of the 2 monoamines. There is consistent evidence that shows that leptin may modulate the HPA function: Leptin administration reverses hypercorticosteronemia and decreases the secretion of ACTH and corticosterone in response to stressful events. Finally, reduced brain weight and cortical volume and decreased expression of total neuronal and glial proteins have been observed in association with leptin deficiency in *ob/ob* mice. The neurodegenerative changes in *ob/ob* mice can be rescued by leptin replacement. These findings support the notion that leptin has neurotrophic effects.[82]

The presence of leptin receptors in VTA neurons has pointed out a role for this hormone in modulating the dopaminergic mesolimbic systems regulating the reward process. Direct administration of leptin to the VTA decreased the firing of dopaminergic neurons, and consequently food intake. In addition, leptin receptor knockdown led to increased food intake, and foremost, sensitivity to highly palatable food.[83]

Another peripheral hormone with a prominent role in the regulation of homeostatic feeding is ghrelin. Ghrelin is a gut-derived orexigenic hormone, which, in response to energy insufficiency, induces a potent feeding response through the stimulation of its central nervous system receptors (GHSR) in the hypothalamic circuits. As already reported for leptin, recently ghrelin has been involved in stress-induced changes in feeding and behavior. In animal models of depression, major behavioral deficits were concomitant with elevated levels of ghrelin. Peripheral administration of ghrelin to wild-type mice produced antidepressant-like responses, whereas Ghrs-null mice exhibited more depressive-like symptoms than wild-type littermates. Interestingly, wild-type mice, but not Ghrs-/- mice, showed hyperphagia in response to social stress.[84] These findings suggest that activation of ghrelin signaling pathways in response to chronic stress may be a homeostatic adaptation that helps an individual cope with stress, but at the expense of increased caloric intake. Catecholamines secreted in response to stress seem to directly stimulate ghrelin cells. Like leptin, ghrelin has emerged as a potent modulator of the mesolimbic dopaminergic circuits.[85]

It may be concluded that the role of the peripheral hormones, leptin and ghrelin, can be extended from the regulation of energy balance in the hypothalamic circuits to the processing of reward for natural reinforcers, such as palatable sweet food in the mesolimbic dopaminergic pathways. Given the recently discovered alterations of the peripheral hormones leptin and ghrelin in mood disturbances, depressed people may be more susceptible to a dysregulation of the central mechanism of food reward, leading to what has been called "stress-eating." The hedonic value of palatable high-fat and/or high-sugar food can override homeostatic signals, leading to overconsumption despite a state of satiety, and hence, obesity.

Diet and Depression

Although the primary scope of the present paper does not include diet and depression, a few general considerations on this topic should be added.

Depression is significantly associated with unhealthy behaviors. In particular, the diet of depressed patients is often characterized by an excessive cholesterol, carbohydrate, and caloric intake, and a low consumption of fish, vegetables, and cereals.[45,46,86,87] Reciprocally, it has emerged that adherence to the Mediterranean dietary pattern (MDP; high in fruits, nuts, vegetables, legumes, cereals, olive oil, and fish, and low in meat and dairy products, with a moderate alcohol intake), exerts a protective effect against depressive disorders, maybe because it ensures the adequate intake of vitamins, specifically B vitamins such as B1, B2, B6, and B12 vitamins and folic acids, ω3-polyunsaturated fatty acids (ω3-PUFA), and monounsaturated fatty acids (MUFA). Folate and vitamins B6 and B12 are involved in the homocysteine cycle, which is needed for the synthesis of catecholamines, serotonin, and other monoamine neurotransmitters. On the one hand, their deficiency may impair the synthesis of biogenic amines; on the other, it results in the accumulation of homocysteine

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and its metabolites, which exert an excitotoxic effect on the N-methyl-D-aspartate glutamate receptors in the central nervous system.[88–91]

The increase of fish consumption, rich in ω3-PUFA, has been noted to correlate with decreased annual prevalence of depression worldwide.[92] ω3-PUFA seems to inhibit the synthesis of pro-inflammatory cytokines, especially TNF-α and interleukin 1β (IL-β). Even olive oil, a good source of MUFAs (oleic acid), has been shown to reduce the risk of depression.[93] MUFAs have antioxidant properties; increase the δ-9 desaturase enzyme activity, which is crucial for the physiochemical properties of neuronal membranes; and improve the binding of serotonin to its receptor.

The synergistic combination of nutrient components may be more important than their individual effects. Indeed, the MDP has been noted to exert effects on the overlapping mechanisms between MeS and depression. In particular, the MDP improves endothelial function, decreases pro-inflammatory cytokines, reduces plasma homocysteine levels, and induces favorable changes in insulin/glucose homeostasis.

In summary, a bidirectional relationship exists between depression and diet habits. Depressed people are more prone to unhealthy diets that are mainly based on highly palatable food, with a content rich in sugar and fat. On the other hand, healthy diets exert a protective role against depression, through favorable changes in vascular, inflammatory, metabolic pathophysiologic mechanisms.

Conclusion

Given the crucial role of alterations in the metabolic networks in depression, depressive syndromes could be conceptualized as "metabolic syndrome of type II."[63] From a clinical perspective, defining the overlapping pathophysiological mechanisms that underlie both depression and MeS provides an opportunity for us to develop prevention and treatment strategies. MeS components are modifiable risk factors that negatively impact on the prognosis of depression. Individuals with mood disorders should receive care from a multidisciplinary coordinated team. Management of depressed patients should include screening for risk factors related to MeS (eating patterns, exercise habits, comorbid binge eating disorder, bulimia nervosa, caffeine dependence, smoking, and thyroid dysfunction), baseline and systematic surveillance of anthropometrics (weight, BMI, waist-to-hip ratio), fasting blood glucose, and lipid fractioning. The modification of risk factors should be considered a primary therapeutic target. Existing metabolic conditions in depressed patients need to be targeted, such as psychopathological syndromes. In the presence of a metabolic comorbidity, the "metabolic profile" (ie, effect on glucose lipid homeostasis) of antidepressant treatment should be taken into account in therapeutic decisions.[94,95] Several psychotropic drugs are associated with adverse metabolic effects.[96] Tricyclic antidepressant (TCA) users show a distinct metabolic pattern, mainly due to the antihistaminergic side-effects, which induce weight gain and dyslipidemia.[97–99] TCA use is also associated with hypertension through peripheral α1 adrenergic receptor agonism.[100,101] It has been demonstrated that TCA-induced weight gain positively correlates with dosage and duration of treatment. On the contrary, selective serotonin reuptake inhibitors (SSRI) seem to transiently decrease body weight during the first few weeks of treatment and then increase it.[102] The notion of depression as "metabolic syndrome of type II" gives support to the research about novel and innovative "metabolic treatments" for depressive symptoms. In obese children, a dietary intervention led to a significant decrease in anxiety and depression scores.[88,103] Exercise interventions as single strategies or in combination with other antidepressant options have been demonstrated to reduce affective symptom burden.[104] Moreover, other targets, possibly within the O&NS pathways, should be considered for the future treatment of depression: cytokines and their receptors, intracellular inflammatory mediators, IDO, TRYCATs, glucocorticoid receptors, and neurotrophic factors may all represent possible therapeutic targets for novel antidepressants. In addition, the role of the existing anti-inflammatory drugs in the treatment of depression should be also clarified, and those compounds with anti-inflammatory and antioxidative properties should be examined either as monotherapy or adjunctive therapy.[74] Preliminary clinical trials indicate that antidiabetic agents (eg, insulin and insulin sensitizers) exert neuroprotective, neurotrophic, anti-inflammatory, and glucocorticoid effects.[105,106] The thiazolidinedione class of antidiabetic drugs, in particular pioglitazone, may be capable of improving mood when prescribed for depression augmentation.[107,108] Clinical research currently is testing the safety and efficacy of different "metabolic" strategies for the management of mood disorders, notably for neurocognitive deficits.

Disclosures

The authors do not have anything to disclose.

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