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REVIEW THE CURRENT THERAPEUTIC INTERVENTIONS AND MANAGEMENT STRATEGIES THAT TARGET BOTH MENTAL HEALTH AND METABOLIC ABNORMALITIES IN INDIVIDUALS

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Abstract:

Background: Metabolic syndrome (MS) is characterized by a combination of abdominal obesity, insulin resistance, hypertension, and hyperlipidemia, often accompanied by several associated complications.

Objective: To elucidate the pathophysiological mechanisms linking MS and mental disorders, with a particular emphasis on depression.

Methods: Comprehensive review of literature examining the interplay between metabolic abnormalities and mental health conditions.

Results:
- MS represents a significant health concern due to its association with elevated risks of cardiovascular diseases, type 2 diabetes mellitus, and other prevalent chronic non-communicable diseases, all of which contribute to heightened morbidity and mortality rates.
- Patients with mental disorders, notably depression, exhibit an augmented risk for cardiometabolic diseases. Interestingly, while atypical antipsychotic medications have historically been implicated in exacerbating this risk, evidence suggests that even patients not on these medications display elevated cardiometabolic risks.
- The underlying pathophysiological mechanisms involve intricate neurohumoral alterations. Central to these are dysfunctions in the hypothalamic-pituitary-adrenal axis and dysregulation of the sympathetic nervous system.

Conclusion: The relationship between metabolic syndrome and mental disorders, particularly depression, is multifaceted, with shared underlying mechanisms suggesting the need for integrated care approaches targeting both metabolic and mental health domains.

Keywords: Metabolic syndrome, cardiovascular disease, type 2 diabetes mellitus, mental disorders, depression

INTRODUCTION

The World Health Organization defines metabolic syndrome (MS) as a pathological condition characterized by the coexistence of abdominal obesity, insulin resistance, hypertension, and hyperlipidemia1. Although different health authorities present certain variations in this definition, they tend to be similar and encompass the conglomeration of cardiometabolic risk factors. Additionally, it is accompanied by other components, such as endothelial dysfunction, chronic inflammation, hypercoagulability states, and adenopathies, which increase the risk of cardiovascular disease (CVD), type 2 diabetes mellitus (DM2), and other chronic non-communicable diseases with high morbidity. and mortality2 (Vajdi, Karimi et al. 2023).

This condition dominates the scientific community's attention due to its alarming prevalence figures, which in recent years have increased in parallel to CVD and DM2. Indeed, in Western societies, up to a third of the population could have MS, around 10-12% have DM2, and CVD invariably ranks first in morbidity and mortality. This translates into very high rates of disability due to the complications of these and related disorders, such as cancer, liver disease, and mental disorders (Abramov, Xue et al. 2023).

The last point is the focus of intense research, as it has been shown that patients with mental disorders have a higher risk of cardiometabolic diseases.4, with 60% of mortality in these psychiatric patients being due to CVD5. Other conditions, such as DM2 and each of the components of MetS, tend to be comorbid with different psychiatric illnesses such as depressive disorders6, from the schizophrenia spectrum7, bipolar and related8, and anxiety9, among others. Previously, this problem was prominently attributed to the use of atypical antipsychotics. Although it does not cease to represent an independent and essential risk factor in cardiometabolic diseases10, it has been observed that patients with mental disorders who do not consume these drugs also have a higher risk than the average population. Therefore, in this review, the mechanisms potentially involved in the relationship between mental disorders and the development of MetS are exposed (Endukuru, Gaur et al. 2023).

MENTAL ILLNESS AND METABOLIC SYNDROME

Because MetS are almost ubiquitous among different mental disorders, the presence of some primary pathophysiological component connecting these diseases to MetS has been assumed. Talking about general mechanisms independent of the disease is the first thing that should be addressed. Firstly, the lifestyle habits of the psychiatric patient often involve some unhealthy behaviors.11,12 that are directly related to MetS, such as smoking, excessive alcohol consumption, poor sleep hygiene, a sedentary lifestyle, and inappropriate dietary behaviors13. The problem of establishing the relationship between the lifestyle of psychiatric patients and the development of MetS lies in the fact that the data collection instruments commonly used in this scenario are self-reported. Therefore so, there may be some bias1 (Marycz, Bourebaba et al. 2023)

However, it is undeniable that patients with mental illnesses lead less healthy lifestyles and that lifestyle predisposes them to MS.15. On the other hand, patients with mental health problems could exhibit molecular elements that make them sensitive to the impact of these aspects of lifestyle. It has been documented that patients involving high stress, such as major depressive disorder and posttraumatic stress disorder, may present with variations in peripheral sensitivity to glucocorticoids, with significant dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.16 . Adrenocortical hyperstimulation is related to the activation of lipolytic pathways that lead to an increase in free fatty acids and triacylglycerides, contributing to dyslipidemia.17 . This effect is much more marked in abdominal adiposity due to the broad expression of glucocorticoid receptors in this tissue (Cerrato, Lammi et al. 2023).

In addition, in the last decade, several pleiotropic genes have been identified that seem to link mental disorders with cardiometabolic conditions.19, suggesting a genetic vulnerability to suffering from MetS in patients with mental illnesses. Interestingly, a recent review found that obesity-associated genes such as leptin and serotonin 2C receptor genes could be involved in the pathogenesis of both MetS and schizophrenia.20 . Another aspect to consider is the participation of the intestinal microbiota in this context. It has been determined that this can modulate the production of different signaling molecules related to brain development and its plasticity, resulting in low-grade chronic inflammation, a characteristic shared with MS (Reljic, Frenk et al. 2023).

ENDOCRINE-METABOLIC DISTURBANCES IN DEPRESSION

The metabolic impact of mental health and illness appears especially prominent in depression. Almost a century has established the relationship between Major Depressive Disorder (MDD) and cardiovascular mortality22, mainly due to the effect of stress, which can activate the sympathetic nervous system (SNS)23. Specifically, the hypothalamus secretes corticotropin-releasing hormone (CRH) and vasopressin in response to stress. CRH-containing neurons project to noradrenergic centers in the stem and spinal cord. Stimulating the locus coeruleus in the brain stem directly acts on the spinal cord's sympathetic and parasympathetic preganglionic neurons.24, activating sympathetic neurons by stimulating α1 adrenergic receptors and inhibiting parasympathetic neurons by stimulating α2 receptors. This activation of the SNS stimulates the release of CRH in the hypothalamus, creating a two-way positive feedback loop.25. With autonomic dysfunction, a higher heart rate, an indicator of elevated sympathetic activity, has been identified in patients with MDD than in control patients.26 . Narrow heart rate variability (HRV) has also been observed, suggesting decreased parasympathetic activity.27; along with increased QT interval variability28, all related to higher cardiovascular mortality (Raut and Khullar 2023).

Interestingly, reduced HRV has been described as a predictive factor for the development of DM230. These individuals tend to have elevated levels of catecholamines at rest, which translates into greater

activation of lipolysis and, therefore, more excellent FFA circulation. This promotes IR and directly inhibits insulin secretion (Ambroselli, Masciulli et al. 2023).
On the other hand, the elevation of CRH influences the immune system by acting on macrophages and stimulating the production of proinflammatory cytokines.32 that contribute to a state of low-grade inflammation, a characteristic shared with MetS (Reljic, Frenk et al. 2023). This phenomenon is another common point between obesity and MDD (Endukuru, Gaur et al. 2023). It has been observed that patients with MDD have higher levels of acute phase reactants, as well as higher expression of proinflammatory cytokines and their respective receptors in both blood and cerebrospinal fluid. This includes higher levels of IL-1β, IL-10, and TNF-α in patients with MDD and lower levels of IL-8.35. In particular, the elevation of IL-1β and TNF- corticotropin (ACTH) and cortisol (Idres, Tousch et al. 2023, Raut and Khullar 2023)

Additionally, hypercortisolemia is the hallmark of chronic stress, and both correlate with MDD.38 . This hormone stimulates lipolysis and gluconeogenesis, leading to hyperglycemic states in response to acute stress. However, the personification of the effects of cortisol is linked to changes in these effects, mainly at the abdominal visceral fat level, whereby inhibiting the synthesis of the machinery that transports lipids, a surplus of free fatty acids (FAA) is generated. These can interfere with peripheral insulin signaling and induce insulin resistance (Endukuru, Gaur et al.)39. Indeed, the chronic elevation of cortisol interferes with the normal mobilization of lipids, with their subsequent visceral accumulation, resulting in central obesity.40 (Vajdi, Karimi et al. 2023).

Cortisol also interferes with the cytokine secretion pattern of the adipocyte, decreasing adiponectin synthesis. This adipokine is known for its sensitizing effects on insulin activity and regulating oxidative metabolism of glucose and lipids.41 . Due to the establishment of visceral obesity, and leptin production increases substantially in proportion to the amount of fatty tissue. This generates a leptin resistance (LR) state associated with the accumulation of triacylglycerides in muscle, liver, and pancreas, further contributing to the IR state and deficient insulin secretion (Marycz, Bourebaba et al. 2023)
Other pathophysiological aspects of leptin specific to depression have been identified. It has been established that, under physiological conditions, this adipokine could have a basal antidepressant effect.43 . However, these effects are disturbed in the context of an obese patient due to the dyad of hyperleptinemia and LR, with a net impact resulting from abrogation of the antidepressant effect of this hormone44. One study showed that obese mice showed more depressive behaviors compared to those on a controlled diet, a phenomenon that the exogenous administration of leptin did not improve. However, when obese mice were reverted to a controlled diet, reductions in depressive symptomatology were reported, with the apparent restoration of the antidepressant effects of leptin (Raut and Khullar 2023).

Finally, another common characteristic between patients with MDD and MS is that due to the proinflammatory states, the production of reactive oxygen species (Ambroselli, Masciulli et al.) is increased, capable of activating proinflammatory genes such as factor pathways to a greater extent:
nuclear kB (NF-kB) or MAPK pathway46,47. Oxidative stress is involved in direct pancreatic β cell (PBC) injury and neuronal dysfunction. Neurons are susceptible to the effects of ROS due to their high content of polyunsaturated fatty acids and their high rate of oxidative metabolism.48 . For its part, CBP is especially susceptible due to its lower expression of antioxidant enzymes. The damage generated in this cell group contributes to the decrease in pancreatic functional reserves, favoring a deficit in insulin secretion (Vajdi, Karimi et al. 2023).

In the patient with MDD, in addition to the previously mentioned problems, behavioral problems such as poor adherence to treatment are added, with a 1.76 times greater probability of not adhering to treatment than patients without depression50. Similarly, MDD makes it difficult for the patient to generate significant lifestyle changes to prevent MetS, DM2, and CVD. For example, when considering smoking, it has been observed that patients with MDD report more attempts to quit but with much less effectiveness (Abramov, Xue et al. 2023).

CONCLUSION

It has been established that mental illnesses have pathophysiological components that go beyond the central nervous system to the point of being able to establish common mechanisms for entities distant, as has been documented, especially for MetS and depression. Due to the close relationship between these conditions, the health worker must consider mental illness from a comprehensive, holistic perspective, considering its repercussions on general health and quality of life. Given the alarming epidemiological prominence of MetS, CVD, and DM2, endocrine-metabolic evaluation of patients with mental health problems should be a priority aspect of their care (Endukuru, Gaur et al. 2023).

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