METABOLIC SYNDROME, ACTIVITY OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND INFLAMMATORY MEDIATORS IN DEPRESSIVE DISORDER

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SUMMARY – Depression has been associated with various cardiovascular risk factors such as hypertension, obesity, atherogenic dyslipidemia and hyperglycemia. In depressive disorder, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and changes in the immune system have been observed. On the other hand, somatic diseases such as obesity, hyperlipidemia, hypertension and diabetes mellitus type 2 are now perceived as important comorbid conditions in patients with depression. The pathogenesis of the metabolic syndrome and depression is complex and poorly researched; however, it is considered that the interaction of chronic stress, psychotrauma, hypercortisolism and disturbed immune functions contribute to the development of these disorders. The aim of the study was to investigate the relationship between depression and metabolic syndrome regarding the HPA axis dysfunction and altered inflammatory processes. Literature search in Medline and other databases included articles written in English published between 1985 and 2012. Analysis of the literature was conducted using a systematic approach with the search terms such as depression, metabolic syndrome, inflammation, cytokines, glucocorticoids, cortisol, and HPA axis. In conclusion, the relationship between depression and metabolic syndrome is still a subject of controversy. Further prospective studies are required to clarify the possible causal relationship between depression and metabolic syndrome and its components. Furthermore, it is important to explore the possibility of a common biologic mechanism in the pathogenesis of these two disorders, in which special attention should be paid to the immune system function, especially the possible specific mechanisms by which cytokines can induce and maintain depressive symptoms and metabolic disorders. The data presented here emphasize the importance of recognition and treatment of depressive disorders with consequent reduction in the incidence of metabolic syndrome, but also the need of regular search for metabolic disorders and their treatment to avoid all of these adverse effects and maybe reduce the incidence of depressive disorders.

Key words: Depressive disorder; Metabolic syndrome X; Cytokines; Hypothalamic-hypophysial system

Introduction

Depression is associated with various cardiovascular risk factors such as hypertension, obesity, atherogenic dyslipidemia, hyperglycemia, smoking, and excessive use of alcohol and other psychoactive substances. Sleep disturbances, changes in the autonomic nervous system, hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and changes in the immune system were observed in depressive disorder. On the other hand, somatic diseases such as obesity, hyperlipidemia, hypertension and diabetes mellitus type 2 are ever more perceived as important comorbid conditions in patients with depression. It is still not clear whether these disorders are parts of the pathologic process or the consequences of treatment. How-
ever, ever more data show that severe mental illnesses have an impact on physical health, and only recently researches in the field of psychiatry have begun to observe this situation in the context of the metabolic syndrome. The pathogenesis of the metabolic syndrome and depression is complex and poorly understood, however, it is considered that the interaction of chronic stress, psychotrauma, hypercortisolism and disturbed immune function contributes to the development of these disorders1-7.

**Metabolic Syndrome**

Metabolic syndrome is a complex disorder consisting of several components: abdominal obesity, dyslipidemia, hypertension, and abnormal glucose metabolism8. Although the components of the metabolic syndrome are often pronounced enough to expect overlapping among them, they show clustering more frequently than it could be interpreted just as a coincidence9. Moreover, the syndrome is associated with proinflammatory and prothrombotic states arising from the secretory activity of adipose tissue, and is characterized by elevated levels of proinflammatory cytokines, endothelial dysfunction, hyperfibrinogenemia, increased platelet aggregation, elevated concentrations of plasminogen activation inhibitors, elevated concentrations of uric acid, and microalbuminuria. Metabolic syndrome represents the greatest risk of diabetes and cardiovascular diseases. Metabolic syndrome has been described in patients with polycystic ovary syndrome, non-alcoholic hepatic steatosis, microalbuminuria, and chronic renal failure8-11.

**Pathophysiology**

Metabolic syndrome is a common disorder significantly related with age that is probably due to the increased prevalence of obesity. Central obesity, measured by waist circumference, is considered essential because of the strong evidence linking waist circumference with cardiovascular disorders and other components of metabolic syndrome, and it is likely that central obesity is an initial step in the etiologic cascade that leads to insulin resistance and metabolic syndrome. However, the exact cause remains unknown and probably includes several different factors, many of which are related to lifestyle changes. Certainly, development of the syndrome is boosted by increasing visceral fat, sedentary lifestyle, increased caloric intake and dietary habits. These environmental factors are likely to interact with predisposing genetic factors that are believed to be linked to insulin resistance, obesity and chronic low grade inflammation. Although any of these three situations hypothetically could be the starting point, they are so intertwined that making such a distinction is very difficult or even not possible8,12-16.

Obesity is increasing worldwide and abdominal obesity, according to many authors, is the real cause of the metabolic syndrome. Abdominal obesity is a common finding in people with metabolic syndrome; about 60% of people with metabolic syndrome are obese, while only 10%-20% have elevated morning blood glucose levels. However, metabolic syndrome can occur in people who are not obese; in one study, 5%-10% of the population with body mass index (BMI) of 20-25 kg/m² had metabolic syndrome. Although they were not clearly overweight, they had increased visceral fat deposits. The distribution of body fat, particularly visceral adipose tissue accumulation, which increases with age, was significantly associated with insulin resistance and significantly correlated with many of diabetogenic, atherogenic, prothrombotic and proinflammatory metabolic abnormalities17-21. The results of other studies have shown that visceral fat decreases significantly faster than subcutaneous adipose tissue in response to weight loss. This observation may help explain why even modest weight loss (5%-10%) in the obese can lead to clinically significant improvements in numerous metabolic parameters and blood pressure17.

Adipose tissue plays an important role in insulin action in humans. Metabolic activity is mainly mediated by enhanced lipolysis and increased concentrations of free fatty acids (FFA). FFA in the muscle directly inhibit glucose transport and glycogen synthesis, increase excretion of glucose and very low density lipoprotein (VLDL) from the liver, and reduce the secretion of insulin from the pancreas22-25. Impaired insulin action in muscle tissue can be increased by FFA activity of the blood vessels, where they reduce the synthesis of nitric oxide and thereby disrupt the action of insulin-mediated vasodilatation26. Metabolic changes associated with increased
total body fat mass and its anatomical distribution are not only caused by lipolysis and FFA secretion, but also are the result of changes in the secretion of numerous factors that affect insulin action, such as leptin, the main function of which is regulation of food intake and energy expenditure in the central nervous system (CNS), resistin that acts antagonistically to the sensitivity to insulin, and adiponectin, the concentration of which was negatively correlated with obesity and glucose tolerance. As the levels of FFA and resistin are higher and the levels of adiponectin lower, insulin resistance is more pronounced. Besides the secretion of FFA, the increased mass of adipose tissue contributes to insulin resistance via the formation of inflammatory conditions in the body. Adipose tissue is a major source of inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6). TNF-α inhibits the tyrosine kinase insulin receptors, while IL-6 enhances hepatic gluconeogenesis, resulting in hyperglycemia and compensatory hyperinsulinemia. According to the results of some studies, elevated concentrations of IL-6 in plasma in combination with low concentrations of adiponectin are associated with an increased risk of developing diabetes.

Insulin exerts strong influence on the regulation of metabolism of very low density (VLDL), high density (HDL) and low density (LDL) lipoprotein. In the states of insulin resistance, the secretion of VLDL in the liver is increased and degradation by lipoprotein lipase (LPL) is reduced, so that hypertriglyceridemia develops as a result of increased hepatic VLDL secretion and abnormal peripheral elimination. Impaired lipolysis of lipoproteins leads to reduced concentrations of HDL, so that a typical atherogenic triad consisting of hypertriglyceridemia, low HDL cholesterol and elevated levels of atherogenic LDL cholesterol is present in insulin resistance. It is considered that hypertriglyceridemia is a central metabolic defect that leads to a cascade of events that ultimately produce the atherogenic lipid profile.

**Diagnosis**

According to the NCEP ATP-III criteria, the diagnosis is based on the simultaneous occurrence of three or more of the following: waist circumference >102 cm in men or >89 cm in women, triglycerides ≥1.7 mmol/L, HDL-cholesterol <1.04 mmol/L in men or <1.3 mmol/L in women, systolic blood pressure ≥130 mm Hg or diastolic pressure ≥85 mm Hg, and morning glucose ≥6.11 mmol/L. The use of antihypertensive drugs or oral hypoglycemic therapy is considered in the criteria for high blood pressure and high morning blood glucose concentration.

**Dysfunction of the Hypothalamic-Pituitary-Adrenal Axis and the Metabolic Syndrome**

Disturbance of the HPA axis is a common finding in patients with metabolic syndrome. Adipose tissue is no longer seen as a passive store of energy but as a highly active endocrine gland that synthesizes and secretes many hormones, cytokines and growth factors. More researches give a key role to cortisol in controlling the physiology of adipose tissue and suggest a reciprocal relationship between HPA axis and adipose tissue. Cortisol plays an important role in regulating the metabolism of glucose, amino acids, fatty acids, distribution of energy, and redistribution of body fat.

Impairment in the synthesis of adrenal hormones has an important effect on changes in food intake, glucose and lipid metabolism, and energy balance. The combination of some genetic variants with environmental factors such as increased food intake, lack of physical activity and chronic stress leads to impairment of the regulatory mechanisms of adrenal cortisol synthesis, secretion, degradation, and conversion of inactive cortisone to cortisol. HPA axis activity and acute reactions to stress are controlled by the inhibitory feedback loop that is executed via glucocorticoid receptors located in the hippocampus, prefrontal cortex and hypothalamus. Acute stress, which is characterized by significant but transient rise in cortisol concentrations, induces mobilization of fatty acids and decreases food intake, and has no adverse consequences for the body. On the other hand, moderate but sustained chronic stress is associated with inappropriate secretion of cortisol, central obesity and endocrine, metabolic and hemodynamic abnormalities. Chronically elevated cortisol levels redistribute fat from the subcutaneous depot in visceral adipose tissue, increase food intake (stress eating), and during prolonged stress induce secretion of leptin as well as leptin resistance leading to decrease in the reduction...
of food intake induced by leptin. Thus, increased cortisol concentrations due to chronic stress favor food intake and visceral fat accumulation, thereby promoting the occurrence of metabolic syndrome.

It has already been pointed out that the secretion of cortisol from the adrenal gland is normally regulated via the HPA axis, but it can be regulated occasionally by the mechanisms independent of the adrenocorticotropic hormone (ACTH). Thus, cortisol can be synthesized locally by converting inactive cortisone to cortisol. Such local production occurs primarily in the visceral adipose tissue. In the presence of insulin, cortisol inhibits lipid mobilization in adipocytes leading to accumulation and retention of triglycerides. As the density of glucocorticoid receptors is higher in the intra-abdominal adipose tissue than in other fat depots, the activity of cortisol leads to accumulation of fat in visceral adipose tissue, development of abdominal obesity, and insulin resistance. Although the metabolic syndrome can mimic Cushing’s syndrome, obese patients generally have normal or subnormal plasma cortisol concentrations. This could be explained by the increased exposure of fat cells to cortisol in adipose tissue, which means that the accumulation of triglycerides in visceral adipose tissue may be caused, at least in part, by the local synthesis of cortisol in the organs sensitive to insulin and cortisol including adipose tissue, liver and skeletal muscles. After initial changes, these disorders induce positive feedback that contributes to the maintenance of these systems in an activated state in the form of an endless spiral: more cortisol in the systemic or local levels leads to accumulation of fat in adipocytes, which leads to insulin resistance. Thus, impaired regulation of adrenal cortisol synthesis in the interaction with HPA axis hyperactivity may be involved in the development of obesity, insulin resistance, metabolic syndrome and its consequences.

Over the past few decades, shortening of sleep has become a very common annoyance in industrialized countries. This trend towards shorter sleep occurs during the same period of a dramatic increase in the prevalence of obesity and diabetes. Current evidence suggests a close link between endocrine, metabolic, cardiovascular and immune functions and sleep disorders. In studies on young healthy persons exposed to recurrent partial sleep restrictions, the increase in hunger and appetite was observed, which led to overeating and weight gain, and was correlated with reduced glucose tolerance and insulin sensitivity and reducing circulating levels of the anorexigenic hormone leptin, while at the same time boosting the levels of the orexigenic hormone ghrelin. On the other hand, chronic sleep loss or disturbances in the periodicity are correlated with altered circadian rhythm of cortisol secretion and secretion of growth hormone associated with sleep, both of which are associated with the temporal pattern of abnormal glucose tolerance with long-term consequences of developing obesity. Chronic stress and sleep disorders are associated with hyperactivity of adrenal glands, resulting in the increased cortisol secretion, induction of food intake and weight gain, which in turn leads to insulin resistance.

Proinflammatory Cytokines and Metabolic Syndrome

Morbid obesity is associated with low-grade systemic inflammation and immune activation. Although low-grade chronic inflammation may be the major pathogenetic factor for the development of metabolic syndrome, the link between inflammation and metabolic syndrome is still unclear. Factors such as increased caloric intake, increased intake of macronutrients, physical inactivity and aging can lead, through expansion of adipose tissue and overproduction of cytokines, to insulin resistance, metabolic syndrome and diabetes in genetically and metabolically predisposed individuals. Macrophage infiltration in adipose tissue can be the first step in maladaptive reaction to prolonged excessive intake of food that leads to a vicious circle with the production of cytokines and other mediators of inflammation. Visceral adipose tissue produces a number of proinflammatory cytokines. Macrophages located in adipose tissue are responsible for the almost complete synthesis of TNF-α and a significant amount of IL-6. Increased synthesis of IL-6, resistin and TNF-α, as a reflection of the expansion of adipose tissue infiltrated by monocytes, results in insulin resistance and lipolysis of triglycerides in circulating FFA. A number of inflammatory genes and genes specific for macrophages are significantly expressed in white adipose tissue in rodents. The fact that this occurs before the development of insulin resistance supports the hy-
A hypothesis that proinflammatory cytokines originating from adipose tissue have a causal relationship with the development of metabolic syndrome.

One of the potentially most important mediators of inflammation is TNF-α, a multifunctional cytokine with numerous roles in the immunomodulatory and inflammatory reactions. TNF-α is a protein, which got its name from the initial identification as a proapoptotic factor in tumor cells, and additionally it has a role in the development of cachexia (alternative name cachectin). The role of TNF-α in obesity was first noticed in 1993 on several models of mice with obesity or type 2 diabetes. A similar increased production of TNF-α in adipose tissue and direct correlation between the increased synthesis of TNF-α, obesity and insulin resistance is found in obese individuals. In humans, TNF-α from adipose tissue is not secreted into the circulation but it acts locally as a paracrine and autocrine factor. There are various mechanisms by which TNF-α affects insulin sensitivity in fat cells: it reduces expression of the genes involved in insulin action, disrupts signaling through insulin receptors, and acts antagonistically on the transcription factors in adipose tissue that regulate insulin sensitivity. TNF-α from adipose tissue also causes diabetogenic effects in obesity indirectly through stimulation of lipolysis in adipocytes, leading to increased secretion of FFA in the circulation, which in turn has adverse effects on insulin sensitivity. The finding that obesity is associated with excessive expression of TNF-α and its negative effects on insulin sensitivity raises the question of why our bodies react in such an unproductive way. Part of the answer could be found through an evolutionary perspective. Over millions of years, our bodies have been adapted to cope with situations where food supply is scarce and unpredictable. There is an evolutionary advantage in gene expression that effectively saves energy (energy sparing gene hypothesi-sis). In such circumstances, it is understandable that TNF-α serves as a regulator of energy homeostasis. In the states of shorter periods of excessive calorie intake, excessive TNF-α expression in adipose tissue reduces the sensitivity to insulin, leading to reduced glucose and fatty acid uptake. Also, by reducing LPL activity, TNF-α inhibits lipid storage in adipose tissue. These mechanisms together foster an increased concentration of circulating fatty acids that are used by muscle tissue in energy expenditure. In the modern lifestyle characterized by constant excessive intake of energy rich food, secretion of TNF-α becomes maladaptive and fosters development of diabetes and atherosclerosis.

C-reactive protein (CRP) is an independent risk factor at all levels of severity of the metabolic syndrome and its level increases with the number of the metabolic syndrome components. Even more, CRP may be predictive for the metabolic syndrome development. Although it is not as predictive for cardiovascular diseases as cholesterol, hypertension or smoking, CRP appears as the most important among the newly discovered risk factors indicating a greater predictive power than other markers of inflammation such as IL-6.

IL-6 is generally considered as a proinflammatory cytokine and its concentration increases in response to inflammation. However, some recent researches suggest that one of the major functions of IL-6 is to decrease the inflammatory response primarily by inhibiting secretion of TNF-α and IL-1β. IL-6 is also the subject of sleep-wake cycles with increased output during the night. In humans, 35% of the basal concentration of IL-6 originates from adipose tissue, it is secreted directly into the circulation, and besides the inflammatory and immune reaction, IL-6 is involved in many biologic processes such as maintenance of normal glucose homeostasis and body metabolism, brain function and fatigue. During different metabolic requirements, the contribution of individual tissues in the secretion of IL-6 is also changing, such as skeletal muscles that become a major source of IL-6 synthesis after exercise. While the levels of IL-6 increase 18 times during exercise, the level in the cerebrospinal fluid remains stable, suggesting that cerebrospinal IL-6 is separated from serum IL-6. It is possible that the increased secretion of IL-6 during exercise acts as a mediator of improved muscle metabolism and insulin sensitivity throughout the body. In healthy subjects, acute IL-6 secretion stimulated by exercise plays an important role in maintaining normoglycemia and helps deliver adequate nutrients for working muscles. In this context, IL-6 may be part of a mechanism of improving insulin sensitivity induced by exercise. Several studies report positive correlation between IL-6, obesity and insulin resistance as well as with
BMI, but the levels of IL-6 tend to increase with age, as well as in insulin resistance and type 2 diabetes, which may partly explain the observed correlations. However, studies show that chronic elevation of IL-6 may promote insulin resistance in the liver and fat cells. Increasing obesity in overweight and sedentary individuals may be the result of chronic excessive secretion of IL-6. IL-6 increases lipolysis in obesity and contributes to increased serum levels of FFA and hypertriglyceridemia. These negative effects of IL-6 will continue to be strengthened by inactive lifestyle. Results of previous studies suggest an important but still not fully comprehended role of IL-6 in the regulation of glucose and lipid metabolism in the body\(^{38,51,55}\).

**Dysfunction of the Hypothalamic–Pituitary–Adrenal Axis in Depression**

Different impairments of neuroendocrine regulation have been reported in mood disorders, and correlation between increased secretion of cortisol and depression is one of the oldest observations in biological psychiatry. In about 50% of patients with depression, elevated cortisol levels can be found. Furthermore, elevated concentrations of the corticotrophin-releasing hormone (CRH), which is frequently found in the cerebrospinal fluid, may be the result of CRH receptor desensitization in corticotroph cells. Because of the elevated basal cortisol concentration, secretory response of ACTH to CRH is limited, but also because of the constant hyperactivity of HPA axis gradually comes to adrenocortical hyperplasia making adrenal gland hypersensitive to ACTH. Other mechanisms unrelated to ACTH, such as neural sympathetic factors or humoral immune system factors, may also contribute to dissociation between ACTH and cortisol in depression\(^{56-58}\).

Although genetic predisposition may be necessary for the development of affective disorders, stressful life events often serve as a trigger for the onset of illness. Long-term exposure to stress and high levels of cortisol induce atrophy and loss of cells that contain corticosteroid receptors in the hippocampus, which are responsible for cortisol-induced suppression of CRH-secreting neurons in the paraventricular nucleus. Elevated levels of cortisol affect glucose transport in the hippocampal pyramidal neurons, foster cytosolic calcium elevation, and may contribute to the accumulation of free radicals by reducing the maximum capacity of antioxidant enzymes. Besides, elevated levels of cortisol reduce proliferation of glial cells and lead to changes in glial glutamate metabolism and may promote vulnerability of neurons via excitotoxic processes through upregulation of the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-4-isoxasolepropionic acid (AMPA) glutamate receptors. To avoid these adverse consequences, the cascade of biochemical changes that constitutes an adaptive response to stress must be effectively stopped. Numerous afferent fibers from different regions of the brain are involved in the regulation of HPA axis activities in stress conditions, as well as the negative feedback mechanism mediated by cortisol from adrenal gland, acting on corticosteroid receptors located in different regions of the brain (pituitary, hypothalamus and limbic areas)\(^{56-63}\). Negative feedback mechanisms that stop the stress caused by HPA axis hyperactivity are impaired in depressed patients; however, there is no proper answer yet to explain the mentioned endocrine abnormalities. The possible causes are malfunction of the glucocorticoid receptors in depression and impaired functioning of the systems involved in the regulation of gene expression of corticosteroid receptors\(^{64,65}\).

The role of the brain serotonin (5HT) in regulating the HPA activity was investigated greatly, but there is no consensus of opinions except that it represents an important regulatory component of HPA axis activity in response to stress. Increased activity of HPA axis actually coincides with changes in the 5HT system including enhanced transmission, upregulation of postsynaptic 5HT2 receptors, and down-regulation of 5HT1A receptors. The same changes were observed in depression. Perhaps the most important aspect of the 5HT system is related to the negative feedback action of cortisol. The negative feedback mechanism of cortisol is done via receptor sites localized in hypothalamic neurons, septum, amygdala and reticular formation. Innervation of these areas is enabled by efferent noradrenergic fibers from locus ceruleus and serotonergic fibers from raphe nuclei. Cortisol increases the concentration of 5HT synthesis and alters the dynamics of secretion and reuptake of 5HT\(^{57,58}\).
Proinflammatory Cytokines in Depressive Disorder

From the psychoneuroimmunologic perspective, brain is no longer considered a privileged organ completely separated from the circulating immune cells by the blood-brain barrier, which has a reduced or altered immunoreactivity. It is now clear that many interactions occur between the neurologic, immune and neuroendocrine system\textsuperscript{66}. Since most cytokines are relatively large hydrophilic molecules, they do not pass the blood-brain barrier under physiological conditions. Yet, there are places where there is no barrier, such as the circumventricular area, or where it is less restrictive, such as the organum vasculosum of laminae terminals and median eminence, in which areas the passive transport of cytokines from the blood into the brain parenchyma is possible. Furthermore, the blood–brain barrier integrity may be damaged by trauma or pathologic conditions that can lead to increased influx of various inflammatory cells and molecules, including cytokines. Moreover, cytokines themselves can contribute to damage to the blood–brain barrier, which is especially true for TNF-\(\alpha\). Furthermore, the mechanism of active transport with cytokine-specific transport molecules may be involved in the transfer of cytokines through the barrier. After entering the brain parenchyma, peripheral cytokines bind to the assumed receptors on the surface of different cells, including microglia, astrocytes and neurons. In addition to passing through the blood–brain barrier, cytokines can bind to receptors on vascular endothelial cells and thus induce the activation of second messengers such as nitric oxide (NO) and prostaglandins, which can provide an indirect mechanism of signaling in the CNS. Another possible indirect route for cytokine-mediated communication between the immune system and the brain is signaling through the vagus. Activation of different vagal fibers transmits signals from cytokines to specific brain nuclei, such as nucleus tractus solitarius, which is located in the medulla oblongata, which then serve as a relay station to the other brain nuclei including the paraventricular nucleus in the hypothalamus. In addition to infiltration or indirect signaling from the periphery, cytokines and their receptors are synthesized in the brain under the influence of elevated cortisol levels, mainly in astrocytes and microglia. Furthermore, the synthesis of cytokines in glial cells can be triggered by antigenic stimuli such as viral infections, local and peripheral inflammatory responses, and brain injuries. It is also assumed that under certain circumstances, neurons are able to secrete cytokines. The synthesis of cytokines was found in several brain regions, including the circumventricular area, hypothalamus, hippocampus, cerebellum, basal ganglia, and nuclei in medulla oblongata. Although the exact role of the central synthesis of cytokines is not yet understood, it is thought that proinflammatory cytokines, including IL-6 and TNF-\(\alpha\), contribute to neurodevelopmental and neuroplastic processes, synaptogenesis and recovery of tissues\textsuperscript{58,60-68}. Numerous studies have shown that cytokines, including TNF-\(\alpha\), modulate glutamate-dependent synaptic plasticity and may be important in brain development and in regulating synaptic plasticity. The secretion of TNF-\(\alpha\) in glial cells in response to reduced neuronal activity increases the number of synaptic glutamate AMPA receptors, and thus synaptic strength, while the removal of TNF-\(\alpha\) leads to weakening of synapses. It is possible that a delicate balance between physiological and pathophysiological levels of TNF-\(\alpha\) is important in these processes, so that in physiological conditions low levels of TNF-\(\alpha\) serve as a modulator of synaptic plasticity, and in pathological conditions, when the central TNF-\(\alpha\) levels become elevated, there are harmful apoptotic effects\textsuperscript{58}.

The concept of two-way communication between the immune system and the CNS has led to the questions whether the immune system except for immune processes is involved in the neuropathologic processes such as depression\textsuperscript{66}. In 1991, Smith proposed the macrophage theory of depression, according to which an increased secretion of cytokines from macrophages may explain the majority of depressive symptoms and endocrine changes during depression\textsuperscript{67,71}. In 1999, Maes proposed a model of depression in which depression is associated with activation of the inflammatory response. According to this model, depression can be considered as a psychoneuroimmune disease in which the peripheral immune activation is responsible for a number of behavioral, neuroendocrine and neurochemical changes associated with depression\textsuperscript{72}. 

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This assumption is also described as a cytokine hypothesis of depression\(^73\). Characteristics of immune system activation in a depressive disorder include increase in the number of circulating lymphocytes and phagocytes, elevated serum concentrations of positive acute phase proteins such as haptoglobin and CRP, as well as increased secretion of proinflammatory cytokines. Proinflammatory cytokines such as IL-6 and TNF-\(\alpha\), which are secreted during the immune response and inflammation, activate the central stress system components, lead to changes in the activity of neurotransmitter network, and induce weakness, drowsiness, fatigue, loss of appetite, and decreased libido, suggesting a potential link between depression and activation of inflammatory responses\(^58,67,68,74-78\).

Psychological stress is a common risk factor for developing depressive disorders and most of the first episodes of depression are preceded by a recognizable stressor. In chronic stress, constantly elevated CRH and consequently higher levels of cortisol and proinflammatory cytokines induce resistance to cortisol action in the CNS and on the immune cells in the periphery interrupting the negative feedback mechanism of cortisol – CRH – proinflammatory cytokines. HPA axis tends to uncontrolled activation and the immune system to the proinflammatory state\(^68\). Chronic stress increases the level of proinflammatory cytokines such as IL-6 and TNF-\(\alpha\) and their signaling pathways centrally and peripherally, while simultaneously reducing the level of normal neuroprotective and growth factors. This action starts a cascade of molecular events that favor the inflammatory and apoptotic mechanisms that can damage cellular plasticity, or even survival of neurons, and lead to consequent changes in the functioning of the monoaminergic system. Elevated circulating concentrations of proinflammatory cytokines can disrupt synaptic plasticity and cognitive processes; patients with depression showed prominent deficits in explicit memory and cognitive capacities that depend on the hippocampus and medial temporal lobes. In addition, findings that centrally present TNF-\(\alpha\) and IL-1 play an important role in the regulation of synaptic plasticity enhance the possibility that maintaining the intricate balance between the physiologic and pathologic levels of these cytokines plays an important role in the complex pathophysiology of depressive disorders\(^58,74,79-84\).

Depression is characterized by disturbances in noradrenergic and serotonergic neurotransmission. Hypothetical activation of the immune system may be causally associated with impairments in these signaling processes. Proinflammatory cytokines may lead to changes in noradrenergic and serotonergic neurotransmission in brain regions that are thought to be involved in the pathogenesis of depression, such as the hypothalamus, hippocampus, amygdala, nucleus accumbens and prefrontal cortex. The effect of cytokines on the serotonergic system is reflected in reduced activity of presynaptic 5HT neurons as a reflection of reduced 5HT synthesis, changes in 5HT reuptake in the synaptic cleft, and in changes of postsynaptic 5HT receptors. The synthesis of 5HT in the highest degree depends on the availability of precursor tryptophan in the brain. Cytokines reduce the availability of tryptophan by activation of indoleamine-2,3-dioxygenase (IDO), an enzyme that metabolizes tryptophan into kynurenine. Thus, excessive stimulation of IDO may lead to a decrease in tryptophan serum levels, which is accompanied by a significant reduction of 5HT synthesis. Low availability of tryptophan in the brain may represent a major cause of serotonin deficits which accompany depressive disorder. The development and severity of depressive symptoms, especially depressed mood, anorexia and loss of concentration in patients on immunotherapy was positively correlated with the decrease in plasma tryptophan concentrations during treatment. Furthermore, proinflammatory cytokines enhance 5HT transmission, which can lead to rapid depletion of reserves in conditions when the presynaptic 5HT availability is low due to reduced synthesis of 5HT\(^\text{TM}\). Peripheral immune activation can also result in positive regulation of serotonin transporters leading to the depletion of extracellular 5HT and change in the number and sensitivity of postsynaptic receptors. These changes may affect the 5HT transmission and may thus represent a possible cause of serotonergic impoverishment in depressive disorder\(^66,74,75\).

It was observed that the occurrence of depressive and anxiety symptoms after cytokine induced stimulation of IDO, which converts tryptophan to kynurenine, except for the consequence of reduced availability of tryptophan in the brain and decreased 5HT synthesis, can be caused by increased synthesis of IDO metabolites mediated by kynurenine way, such
as 3-hydroxy-kynurenine (3OH-KYN) and quinolinic acid (QUIN), which are neurotoxic substances that are present in several neurodegenerative conditions such as Parkinson's disease. An increased synthesis of these kynurenine metabolites was also observed in psychiatric disorders such as anxiety and depression. 3OH-KYN can lead to overproduction of free oxygen radicals as well as to the increased activity of monoamine oxidase (MAO). Overproduction of oxygen radicals may adversely affect the function and density of serotonergic and catecholaminergic receptors by inducing changes in membrane viscosity. Increased MAO activity results in a lower concentration of 5HT and catecholamines. Therefore, apart from the direct reduction of 5HT availability, IDO may contribute to the monoaminergic disturbances that are observed in depression in an indirect manner. Thus, it appears that exogenous administration of proinflammatory cytokines may induce depressive symptoms at least in part through the modulation of monoaminergic transmissions. Moreover, kynurenine metabolites by stimulating of hippocampal NMDA receptors can promote tissue damage contributing in this way to the pathogenesis of depressive disorders.

Researches in the past 30 years and more suggest an association between depressive disorders and vulnerability to various diseases. Conditions such as acute and chronic infections are accompanied by depression. The immune system is activated in response to infection, and if such activation is systemic, the body typically shows symptoms common to depressive episodes such as weakness and a variety of behavioral responses including decreased appetite, weight loss, fatigue, sleep disturbances, psychomotor retardation, reduced interest in physical and social environment, loss of libido, impairment of cognitive abilities, dysphoria, irritability, depressed mood, and anhedonia. Depressive symptomatology, which is associated with other diseases such as multiple sclerosis, Alzheimer's disease, Huntington's disease, Parkinson's disease and other neurodegenerative diseases, may not be solely a psychological reaction to pain, distress and disability associated with a somatic disease, but may be caused by direct activation of the immune system and secretion of cytokines from microglia (IL-1, IL-6, IL-8, TNF-α and IFN-β), which may affect neurodegenerative processes through the synthesis of free radicals and toxic kynurenine metabolites that are present in many neurodegenerative diseases. In addition to central mechanisms, inflammatory condition can be activated by peripheral mechanisms such as atopic dermatitis. Women with allergic symptoms are at an increased risk of depression, furthermore, the presence of atopy doubles their risk of developing depression later in life. A higher incidence of depression or depressive symptoms was observed in rheumatoid arthritis, cancer, lupus (systemic lupus erythematosus), and cardiovascular diseases.

However, these symptoms are not observed only during infection or other somatic diseases, but also occur after systemic or central administration of cytokines. Treatment of patients with oncologic, autoimmune and infectious diseases, which often involves treatment with proinflammatory and antiviral cytokines (IL, TNF-α, IFN-α), is associated with depressive symptoms and flu-like symptoms and cognitive disorders. The most common side effects of cytokine therapy, those which occur early in the course of treatment, usually within two weeks, include flu-like symptoms such as fever, malaise, headache and myalgia. Psychiatric side effects typically occur later in treatment, within 1-3 months, involving dysphoria, depressed mood, irritability, anhedonia, anxiety, fatigue, anorexia, weight loss, changes in sleep, psychomotor retardation, loss of social interaction and libido, and abnormal cognitive capabilities. While the symptoms which are flu-like retreat with continued treatment, psychiatric side effects can only disappear after discontinuation of therapy or with the administration of antidepressants. The fact that cytokine therapy is often accompanied by negative psychiatric symptoms that disappear after cessation of therapy or after antidepressant administration suggests a potential causal role of cytokines in the etiology and pathophysiology of various behavioral, psychological and cognitive symptoms of depression. In a research of interferon use in infectious diseases and cancer, the prevalence of the major depressive disorder development ranged from 30% to 50%, depending on the dose.

Proinflammatory state may be responsible for depressive symptoms but may play a broader role of a common denominator among various psychiatric and somatic disorders. Identification of a common denominator among the nosologic entities that have not
been pathophysiologically linked, such as depression, schizophrenia, Alzheimer’s disease, atopic dermatitis, rheumatoid arthritis, Crohn’s disease, psoriasis and myocardial infarction, may have epistemologic and therapeutic implications. The division to somatic and mental diseases is perhaps a mistake that needs to be reconsidered. The possibility that different chronic diseases may be manifestations of a common individual proinflammatory predisposition emphasizes the importance of the holistic approach that brings a new challenge for pharmacological research to find strategies for recovery of neuro-endocrine-immune homeostasis.

Relationship between the Immune and Neuroendocrine Factors in Depression

The proinflammatory cytokines TNF-α, IL-1 and IL-6 are the primary stimulators of HPA axis and have a key role in activating HPA axis in depression. They activate cortisol secretion acting directly at three levels of HPA axis: hypothalamic, pituitary and adrenergic. At the central level, they stimulate the secretion of CRH in the hypothalamic paraventricular nuclei. IL-6 is a potent stimulator of CRH synthesis, which leads to increased HPA axis activity characterized by increasing levels of cortisol. Since IL-6 stimulates the secretion of ACTH and cortisol to the levels above the maximal stimulation achieved by CRH, it is thought that IL-6 also stimulates the parvicellular arginine-vasopressin (AVP) and other ACTH secretagogues. CRH is transported to the pituitary, where in synergy with vasopressin it stimulates the secretion of ACTH, which in turn stimulates the adrenal cortex to secrete cortisol. An elevated level of cortisol in normal conditions establishes control by the negative feedback mechanism and inhibits the secretion of TNF-α, IL-1 and IL-6 in immune cells, ACTH in the pituitary, and CRH in the hypothalamus. However, it seems that there is impairment in the regulation of this inhibitory feedback mechanism that normally reduces hyperactivity of the HPA axis in depressive disorder. During chronic stress and depression, the concentration of proinflammatory cytokines grows despite the hypersecretion of cortisol. This suggests that the glucocorticoid receptors on immune cells are hypofunctional in patients with depression and cortisol cannot suppress many components of cellular immunity. Studies in patients with depression have shown that these glucocorticoid receptors are less sensitive but return to normal after effective treatment.

Elevated levels of cytokines further interfere with the negative feedback mechanism to increasing the resistance of corticosteroid receptors in the hypothalamus and pituitary. Furthermore, activation of IDO induced by cytokines may also be involved in the attenuation mechanism of negative feedback through the production of kynurenine metabolites (QUIN), which by acting on NMDA receptors may cause hippocampal atrophy and loss of corticosteroid receptors. Thus, elevated levels of QUIN may represent an additional mechanism by which cytokines can disrupt the negative feedback mechanism causing hyperactivity of HPA axis. However, it should be noted that 30%-50% of depressed patients do not show signs of HPA axis hyperactivity. On the other hand, changes in the synthesis of cytokines in the periphery can be caused by neuroendocrine influence on the immune system. In this sense, most important are the effects of cortisol, which is synthesized in the adrenal cortex as the final product of HPA axis. Cortisol is involved in the regulation of immune responses, and through it in the synthesis of cytokines. While low concentrations of cortisol stimulate the synthesis of cytokines, high concentrations are immunosuppressive.

Depression and the Metabolic Syndrome

Depression is a complex disease associated with changes in sleep, appetite, body weight and level of physical activity, which can be risk factors for the development of metabolic disorders. Depression can contribute to the pathogenesis of the metabolic syndrome in the physiological (HPA axis, noradrenergic deregulation) and behavioral (smoking, diet, inactivity, sleep) mechanisms. It is possible that metabolic syndrome is a link between depression and both cardiovascular disease and diabetes on the other side. It is believed that chronic stress causes depression and consequential bad lifestyle that can lead to metabolic syndrome and subsequent development of cardiovascular disease. HPA axis dysregulation is typically linked to chronic stress, and numerous studies have described such an association between depression and high cortisol levels. On the other hand, elevated levels of cortisol are associated with components of metabolic syndrome such as abdominal obesity and...
glucose intolerance, thus depression may indirectly affect glucose metabolism and the risk of developing diabetes. Moreover, psychosocial variables such as depressed mood can lead to changes in the levels of proinflammatory cytokines that are also important components in the development of metabolic syndrome. There is ample evidence that depression is accompanied by changes in the immune system, particularly in terms of imbalance between proinflammatory and anti-inflammatory cytokines. CRP is an acute phase protein and a nonspecific marker of systemic inflammation that is elevated in depression and metabolic syndrome. IL-6 is elevated in depression and positively correlated with obesity and hypertension. TNF-α reflects the clinical course of depression, and its expression is increased in adipose tissue of the obese.

Based on previous researches, we can say that depressed patients, who are in a high percentage overweight, have a higher incidence of cardiovascular disease, hypertension and diabetes than other psychiatric patients and the general population. Depressive symptoms were associated with individual components of metabolic syndrome in male twins aged 63. Among middle-aged women, depressive symptoms were associated with an increased risk of developing metabolic syndrome 7 years later. Women with a history of depression are at a twofold risk of developing metabolic syndrome when compared with others. There was no association found between depression and metabolic syndrome in young Finnish subjects, while it was found in younger women but not in men in the United States. The results of two longitudinal studies of middle-aged women show predictability of depressive symptoms for the development of metabolic syndrome. In a recent review from 2007, Jakovljević et al. report that 24.6% to 50% of bipolar patients and 12%-36% of patients with depression have metabolic syndrome.

Symptoms of depressive disorders are common in patients with metabolic syndrome, and fatigue is a common symptom in conditions of chronic activation of nonspecific immunity, such as metabolic syndrome. A number of components of metabolic syndrome and individual components such as obesity, diabetes, hyperglycemia, hypertriglyceridemia and hypertension were correlated with depressive symptoms and with the likelihood of depression development. The mechanisms responsible for the development of depressive symptoms in patients with metabolic syndrome are not yet understood; however, the results of some studies suggest that chronically activated inflammatory processes in metabolic syndrome may participate in the changes of mood. There is evidence of low tryptophan serum levels in the obese. The obese have increased tryptophan degradation caused by chronic immune activation, which further results in a reduced synthesis of serotonin. Serotonin is an important biochemical regulator of the balance between hunger and satiety and regulates the intake of carbohydrates and fats. Carbohydrates raise serotonin levels in the brain in patients with mood disorders, and excessive carbohydrate intake improves mood and state of well being. This quantitative deficiency of serotonin caused by chronic immune stimulation in the obese can lead to a reward deficiency syndrome and the consequent pathologic eating as a compensatory mechanism for reduced levels of neurotransmitters, enabling support for a functional link with obesity. Depressive symptomatology in patients with metabolic syndrome is primarily associated with neurovegetative features such as fatigue, loss of energy and anhedonia, and to a lesser extent with mood and cognitive symptoms.

However, the relationship between depression and metabolic syndrome, with respect to the question of whether depression is a cause, consequence or simple marker of the metabolic syndrome, is still a subject of controversy. Further prospective studies are needed to clarify the possible causal relationship between depression and metabolic syndrome and its individual components, or whether the metabolic syndrome precedes depression or depression precedes metabolic syndrome. Moreover, it is important to explore the possibility of the existence of a common biologic mechanism in the pathogenesis of these two disorders, in which special attention should be paid to disorders of the immune system, especially the possible specific mechanisms by which cytokines can induce and maintain depressive symptoms and metabolic disorders. As stated earlier, depression plays an important role in the pathogenesis of cardiovascular disease, a large number of depressive patients meet the criteria for metabolic syndrome, and somatic consequences of
The metabolic syndrome are numerous with the possible fatal outcome. The World Health Organization predicts that depression will be the second cause of disability by 2020. The data presented here emphasize the importance of timely recognition and treatment of depressive disorders with consequent reduction in the incidence of metabolic syndrome, but also the need to regularly search for metabolic disorders and their treatment to avoid all of these adverse effects and possibly reduce the incidence of depressive disorders.

References

15. DESPRES JP. Our passive lifestyle, our toxic diet, and the atherogenic/diabetogenic metabolic syndrome: can we afford to be sedentary and unfit. Circulation 2005;112:453-5.


M. Martinac et al.  
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60. SAPOLSKY RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925-35.


68. ADLER UC, MARQUES AH, CALIL HM. Inflammatory aspects of depression. Inflamm Allergy Drug Targets 2008;7:19-23.


77. KARLOVIĆ D, SERRETTI A, VRKIĆ N, MARTINAC M, MARČINKO D. Serum concentrations of CRP, IL-6, TNF-α and cortisol in major depressive disorder with melancholic or atypical features. Psychiatry Res 2012;198:74-80.


83. MILLER AH, RAISON CL. Cytokines, p38 MAP kinase and the pathophysiology of depression. Neuropsychopharmacology 2006;31:2089-90.


105. MAES M, BOSMANS E, DE JONGH R, KENIS G, VANDOOLAEGHTE E, NEELS H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9:853-8.

106. FERNANDEZ S, KNOPF MA, BJORK SK, McGIL-LIS JP. Bone marrow-derived macrophages express functional CGRP receptors and respond to CGRP by increasing transcription of c-fos and IL-6 mRNA. Cell Immunol 2001;209:140-8.


120. WHOOLEY MA. Depression and cardiovascular disease: healing the broken-hearted. JAMA 2006;295:2874-81.


Metabolic syndrome, HPA axis and inflammatory mediators in depressive disorder

Sažetak

METABOLIČKI SINDROM, AKTIVNOST OSI HIPOTALAMUS-HIPOFIZA-NADBUBREŽNA ŽLJEZDA I MEDIJATORI UPALE U DEPRESIVNOM POREMEĆAJU

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Depresija je povezana s različitim kardiovaskularnim rizičnim čimbenicima kao što su hipertenzija, pretilost, aterogeni dislipidemija i hiperglikemija. U depresivnom poremećaju su uočeni hiperaktivnost osi hipotalamus-hipofiza-nadbubrežna žlijezda (HHN) i promjene u imunom sustavu. S druge strane, somatske bolesti kao što su pretilost, hiperlipidemija, hipertenzija i dijabetes melitus tipa 2 sada se shvaćaju kao važna komorbidna stanja u bolesnika s depresijom. Patogeneza metaboličkog sindroma i depresije je složena i nedovoljno istražena. Smatra se da interakcija kroničnog stresa, psihotraume, hiperkortizolizma i poremećene funkcije imunog sustava može doprinijeti razvoju ove bolesti. Cilj ovoga istraživanja bio je ispitati odnos između depresije i metaboličkog sindroma u odnosu na disfunkciju osi HHN i promjene u upalnim procesima. Pretraživanje literature na Medlineu i drugim bazama podataka obuhvaćalo je radove na engleskom jeziku objavljene između 1985. i 2012. godine. Analiza literature je provedena pomoću sustavnog pristupa s terminima pretraživanja kao što su depresija, metabolički sindrom, upala, citokini, glukokortikoidi, kortizol i os HHN. Zaključno, odnos između depresije i metaboličkog sindroma je još uvijek predmet proturiječja. Potrebne su daljnje prospektivne studije u svrhu utvrđivanja moguće uzročnost-poštledične veze između depresije i metaboličkog sindroma i njegovih sastavnica. Nadalje je važno istražiti mogućnost zajedničkog biološkog mehanizma u patogenezi ovih dviju bolesti, pri čemu pozornost treba naročito posvetiti funkcioniranju imunog sustava, a osobito mogućim specifičnim mehanizmima kojima citokini mogu inducirati i održavati depresivne simptome i metaboličke poremećaje. Podaci izneseni ovdje naglašavaju važnost prepoznavanja i liječenja depresivnog poremećaja s posljedičnim smanjenjem učestalosti metaboličkog sindroma, ali potrebu redovitog traganja za metaboličkim poremećajima i njihovim liječenjem kako bi se izbjegli svi njihovi negativni učinci i tako možda smanjila učestalost depresivnog poremećaja.

Ključne riječi: Depresivni poremećaj; Metabolički sindrom X; Citokini; Hipotalamo-hipofiziarni sustav