Clinical Neuropsychiatry (2023) 20, 2, 100-108

REVIEW PAPER

THE WICKED RELATIONSHIP BETWEEN DEPRESSION AND METABOLIC SYNDROME

Donatella Marazziti, Alessandro Arone, Stefania Palermo, Eric Annuzzi, Gabriele Cappellato, Ilaria Chiarantini, Luca Del Prete, Liliana Dell'Osso

Abstract

Major depressive disorder (MDD) constitutes a challenge in the field of mental disorders, given its high prevalence in the general population and its impact on the quality of life, while representing a major burden of health worldwide. Currently, much interest in the pathophysiology of MMD ìs also directed towards disentangling the possible biological mechanisms shared with that medical condition known as metabolic syndrome (MeS) that is frequent in the general population and often comorbid with MDD.

Therefore, the aim of this paper was to summarize the evidence on the relationships between depression and MeS, and to comment on the common factors and mediators present in these two conditions. For this reason, some of the main databases of scientific literature were accessed, and all the papers fulfilling the goal of this review were selected. The results demonstrated the existence of common pathways between depression and metabolic syndrome involving several mediators, such as inflammation, the hypothalamus-pituitary-adrenal axis, oxidative stress, platelet functions, coronary heart disease and peripheral hormones, thus requiring strict attention from the scientific community. Indeed, such pathways may be targeted in the near future in order to pave the way to new treatment options for these disorders.

Key words: major depressive disorder, metabolic syndrome, inflammation, cytokines, cardiovascular disease, diet

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OPEN ACCESS

Citation: Marazziti, D., Arone, A., Palermo, S., Annuzzi, E., Cappellato, G., Chiarantini, I., Del Prete, L., Dell'Osso, L. (2023). The wicked relationship between depression and metabolic syndrome. *Clinical Neuropsychiatry, 20*(2), 100-108.

doi.org/10.36131/cnfioritieditore20230202

Funding: None.

Competing interests: None.

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Introduction

Ever since its first reports, major depressive disorder (MDD) has been one of the most debated mental conditions among scientists and the general population, given its high prevalence and its heavy impact on both patients and social health systems. Reports from the World Health Organization (WHO) indicate that about 350 million people belonging to all age groups, suffer from MDD that currently represents a major cause of disability (Li et al., 2020; WHO, 2021). Depressed subjects may experience a wide range of symptoms, i.e. depressed mood and/or anhedonia, together with decreased energy, trouble in concentrating, slowing flow of thoughts, feelings of hopelessness or excessive guilt, changes in appetite or body weight, and sleep disturbances (American Psychiatric Association, APA, 2013; Villarroel & Terlizzi, 2019; Li et al., 2021). Such symptoms strongly influence an individual's everyday life and global functioning, and they should be present for at least a two-week period, according to the *Diagnostic and Statistical Manual for Mental Disorders*, 5th edition (DSM5) (APA, 2013). Major depressive disorder is also frequently comorbid with other conditions, particularly, anxiety disorders, obsessive-compulsive disorders and personality disorders (APA, 2013). Its etiology and pathophysiology are with no doubt multifaceted, while resulting from the interplay between genetic, biological and environmental factors (Leff-Gelman et al., 2016; Tayab et al., 2022).

Furthermore, besides the obvious effects on mental wellbeing, depressed patients show a high risk of obesity, cardiovascular and cerebrovascular diseases. Not surprisingly, converging gathered in these latest years highlight a potential bridge to that condition called metabolic syndrome (MeS) (Bot et al., 2020; F Guerreiro Costa et al., 2022). Metabolic syndrome can be conceptualized as a metabolic alteration representing a severe threat to health that needs a rapid identification given its potentially reversible course (Burrage et al., 2018; Kim & Yi, 2018; van der Pal et al., 2018). It can be diagnosed when at least three of the following alterations

Submitted February 2023, accepted April 2023

are present: elevated blood pressure levels (systolic pressure ≥130 mmHg and/or diastolic pressure ≥ 85 mmHg); waist circumference > 40 inches in males and 35 inches in females; hypertriglyceridemia (triglyceride levels ≥150 mg/dL); high-density lipoprotein cholesterol (HDL) < 40 mg/dL in males and < 50 mg/dL in females; fasting glucose levels ≥ l00 mg/dL (Burrage et al., 2018; Kim & Yi, 2018; van der Pal et al., 2018). Metabolic syndrome rates are heterogeneous, although a certain agreement does exist suggesting how around 1 out of 4 people suffer from it, with some gender-differences (Fahed et al., 2022; Swarup et al., 2022). Although the literature on the prevalence of MeS in subjects with MDD is heterogeneous, it is reported that it may reach up to 30% (Vancampfort et al., 2015; Al-Khatib et al., 2022). In the elderly, the co-presence of the two disorders has led to the notion of vascular depression, a peculiar subtype of MDD where metabolic dysregulation would significantly damage blood vessels (Jellinger, 2021). Indeed, symptoms may be more severe and chronic, with more frequent suicidal ideation and impairment of overall social functioning (Penninx & Lange, 2018). As such, it is hypothesized that the treatment of MeS might reduce the rates of depression among the elderly (Jellinger, 2021).

Both MDD and MeS, therefore, represent issues that still remain to be elucidated from the neurobiological point of view. Several hypotheses have been put forward to explain the mechanisms underlying the two conditions when they occur alone, and when they are comorbid. Inflammation, the hypothalamus-pituitary-adrenal (HPA) axis, oxidative processes, platelet endothelial function, coronary heart disease (CHD) and peripheral hormones are among these and, interestingly, may be interconnected (Penninx & Lange, 2018; Zhang et al., 2021; Marazziti et al., 2022) (**figure 1**).

Therefore, the aim of this narrative review was to summarize the main data on the pathophysiology of MeS and MDD, and to further stimulate new research on this relevant topic that might lead to novel and innovative therapeutic perspectives.

Methods

The following databases were accessed in order to research and gather data from articles that were published only in English language from January 1, 1978 to January 31, 2023: PubMed, Scopus, Embase, PsycINFO and Google Scholar. Free text terms and MeSH headings were combined as follows: "(Major Depressive Disorder) AND (Metabolic Syndrome) AND (Inflammation) AND (Cardiovascular Disease)". All the authors agreed to include in the review conference abstracts, posters and case reports if published in indexed journals. All the authors equally contributed in identifying potential information specific to this topic amongst the evaluated titles and abstracts.

Results

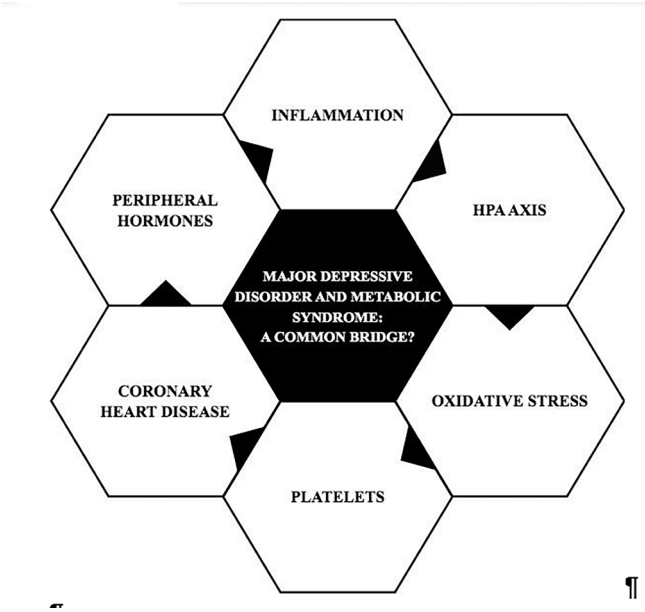
The first selection excluded 1872 titles because: a) duplicates; b) not concerning the scope of the paper; c) not informative enough. The second selection excluded 311 abstracts after being read and reviewed, as the information presented did not fulfil the scope of the paper and/or did not appear to be relevant. Subsequently, 139 more publications were discarded after further reading and evaluation, as they did not provide enough information and/or did not result sufficiently in line with the review. Finally, 74 papers were included in this paper (**figure 2**).

Discussion

Inflammation

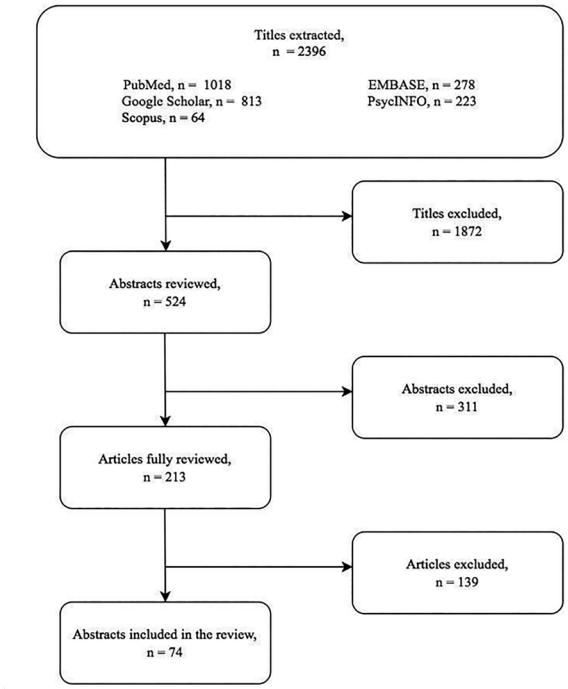
A common concept in the field of mental disorders is that different stressors may favour the onset of MDD (Haroon et al., 2012; Miller & Raison, 2016). A series of data suggests that inflammatory processes and chronic exposure to cytokines may occur in MDD. Following different triggers, cytokines cross

Figure 1. *Mechanisms and mediators involved in major depressive disorder (MDD) and metabolic syndrome (MeS)*



HPA (hypothalamus-pituitary-adrenal axis)

Figure 2. *Flowchart*



the blood-brain barrier, thus leading to the activation of both endothelial and immune cells promoting the release of inflammatory mediators of inflammation (Haroon et al., 2012). In depressed patients, several inflammatory markers have been studied, with most of the evidence supporting the involvement of different interleukins (ILs), mainly IL-1 and IL-6, but also of tumor necrosis factor (TNF) and C reactive protein (CRP). Interestingly, gene polymorphisms of some of these biomarkers seem to be associated with depression (Miller & Raison, 2016). Furthermore, the presence of inflammation may also increase the risk for treatment failure, as a study reported that half of a group of depressed subjects did not respond to antidepressant drugs in presence of CRP levels > 3 mg/L (Arteaga-Henríquez et al., 2019). Antidepressant administration to mice was found to favour neurogenesis in the hippocampus and also a shift in microglia towards the neuroprotective M2 phenotype, thus leading to the production of IL-4 by T-cells in the meningeal space (Maes et al., 1995). Again, IL-4 then stimulated astrocytes to produce brain-derived neurotrophic factor (BDNF), a neurotrophin fundamental the survival and development of neurons (Maes et al., 1995).

The recent identification of a brain lymphatic system has gained much interest given its involvement in the mobility of T-lymphocytes within the brain, particularly within the meningeal spaces. The role of the several subtypes of T-lymphocytes is still an ongoing research, however there is evidence supporting the importance of regulatory T-cells (T-regs), as they may suppress inflammatory mechanisms and contribute to the maintenance of neuronal integrity in stressful situations (Maes et al., 1995; Mucci et al., 2020).

Pro-inflammatory cytokines were found to activate the enzyme indoleamine 2,3 dioxygenase (IDO) that breaks down tryptophan (TRY) into its catabolites (TRYCATs), including kynurenine (KYN) along the IDO route (Catena-Dell'Osso et al., 2012; 2013; Dell'Osso et al., 2016; Rosenblat & McIntyre, 2017). It was suggested how the finding of decreased serotonin (5-HT) levels in some depressed patients may be caused by the activation of several proinflammatory cytokines that, in turn, leads to IDO activation and lower plasma levels of TRY. Such data may broaden the classical serotonergic hypothesis of TRY and 5-HT depletion in MDD, in favor of a more complex notion encompassing inflammation-induced TRY degradation and TRYCAT synthesis and, as such, a decrease in both TRY and 5-HT (Kessler et al., 2003). Interestingly, TRYCATs can provoke sadness and anxiety behaviors in mice and neurotoxic side effects (Catena-Dell'Osso et al., 2012; 2013; Rosenblat & McIntyre, 2017).

The hypothalamic-pituitary-adrenal (HPA) axis

Different psychosocial stressors, including the loss of a loved one, interpersonal conflicts and social isolation, can lead the hypothalamus to release catecholamines and the stress corticotropin-releasing hormone (CRH), thus promoting the synthesis of cortisol. Catecholamines interact with the adreno-receptors, increasing NF-kB DNA binding and causing the release of different inflammatory mediators (Miller & Raison, 2016; Rosenblat & McIntyre, 2017), whilst cytokines may enter the brain and activate inflammation through specific pathways that involve microglia (Rosenblat & McIntyre, 2017).

In normal conditions, the cytokine-induced activation of CRH and subsequently of the HPA axis leads to the inhibition of different inflammatory signaling pathways. In MDD, the HPA axis loses its inhibitory activity, as glucocorticoids cannot withhold cortisol production and cannot block the activation of several inflammatory pathways, a condition also named "glucocorticoid resistance". Overall, glucocorticoid resistance would result in a continuous state of neuroinflammation, along with an hyperactivation of the HPA axis (Rosenblat & McIntyre, 2017) (**figure 3**).

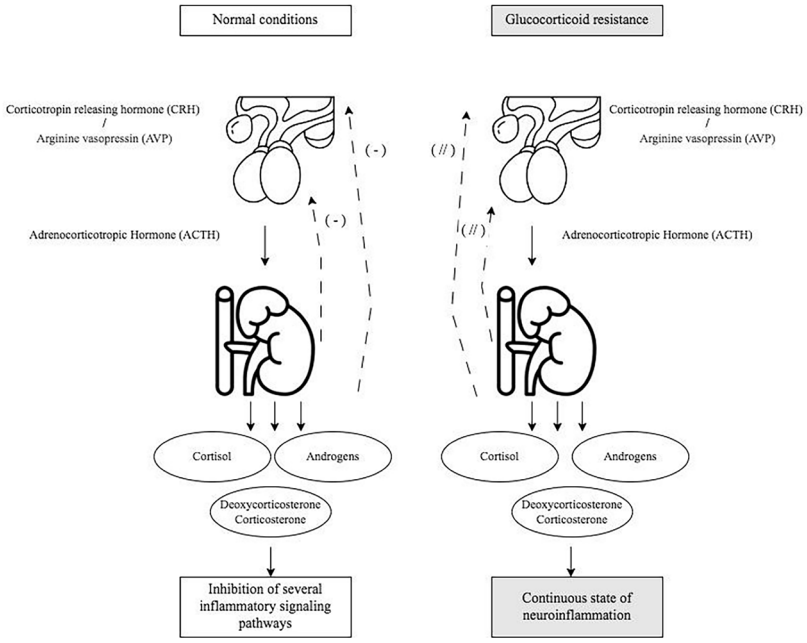
The effects seem in part to be related to activity of cytokines on glucocorticoid receptors (Rosenblat & McIntyre, 2017). As a result, excitotoxicity and changes in the metabolism of monoamines may overall contribute to these brain alterations that underlie and/or can be found in MDD (Catena-Dell'Osso et al., 2013; Dell'Osso et al., 2016; Miller & Raison, 2016). Other common findings include increased cortisol levels in depressed patients' urine, plasma, and saliva that were subsequently linked to enlarged pituitary and adrenal glands (Pariante, 2006).

The HPA axis hyperactivation, hypercortisolemia, inflammatory patterns, cytokine activation, together with an alteration of several mediators linked to cardiovascular risk (e.g. CRP and platelet reactivity) may all represent key factors involved in the same pathogenetic mechanism of MDD.

Oxidative stress

The overall antioxidant system requires both non-enzymatic and enzymatic antioxidants (Solleiro-Villavicencio & Rivas-Arancibia, 2018). In particular, the former are represented by a wide range of mediators including glutathione, thiol (R-SH), plasma proteins, uric acid (UA), vitamin C, vitamin E, zinc, and coenzyme Q10. All of these display antioxidant activity and play a key role in the neutralization of the free radicals that are produced and are residues of the oxidative metabolism (Solleiro-Villavicencio & Rivas-Arancibia, 2018). On the other hand, enzymatic

Figure 3. *Glucocorticoid resistance*



antioxidants neutralize radical or reactive species (i.e. reductase, catalase and glutathione peroxidase) (Solleiro-Villavicencio & Rivas-Arancibia, 2018). The induction of oxidative stress, along with an immune-inflammatory response, may significantly contribute to the pathogenesis of depression through the impairment of fundamental brain functions (Solleiro-Villavicencio & Rivas-Arancibia, 2018). As a matter of fact, the failure of the HPA axis, in association with changes of both monoaminergic and neurotrophic systems, may impair metabolic and redox statuses in MDD. In parallel, a poor lifestyle or an imbalanced diet may further contribute to the onset of a dysfunctional response to stress that may prolong an antioxidant response, as well as the metabolic and nutritional features of depressed patients (De Melo et al., 2017; Solleiro-Villavicencio & Rivas-Arancibia, 2018). Literature data permit to provide some explanations of the previous assumptions. First, there is evidence in MDD of altered levels of oxidative stress indicators and lower concentrations of some non-enzymatic and enzymatic antioxidants that, can be restored with antidepressants. Second, several antioxidants, such as N-acetylcysteine, zinc and omega-3 free fatty acids, display an antidepressant activity (Siwek et al., 2013). Furthermore, recently a drop in polyunsaturated fatty acids (PUFAs) in red blood cell membranes was demonstrated, suggesting a rise in long-chain peroxide degradation (Guu et al., 2019). The same authors pointed out how an increased oxidation may be found in the most severe forms of depression, along with DNA damage (Guu et al., 2019). Depressed patients, when compared to healthy subjects, also seem to show a different activity of several enzymes, such as catalase and glutathione reductase, as their activities tend to be elevated in MDD and restored by antidepressant drugs (Liu et al., 2015).

Some interesting evidence seems to support the role of UA that is produced from purine nucleotides in MDD (Muti et al., 2015). Uric acid and purines normally exert a key role in the regulation of different processes involved in the sleep-wake cycle, hunger, cognition, memory, seizure threshold, and impulsivity (Muti et al., 2015). According to some authors, the enhancement of the type 1 and type 2 purinergic (P1 and P2) modulators' efficacy may significantly contribute to symptoms of mood disorders. As a result, it is believed that the purinergic system might represent an intriguing target for new therapeutic strategies in the future (Brooks et al., 1978; Ortiz et al., 2015).

Platelets

Adhesion, aggregation and release of inflammatory mediators are classical functions attributed to platelets that represent a great part of body defensive system (Felger, 2019). Indeed, inflammatory processes provoke the increase of the platelet activation factor (PAF) and the release of thrombin inducing the activation of platelets (Chehab, 2000). This process leads to the translocation of P-selectin on the surface of the platelet membranes and the consequent bonding of leukocytes and the expression of IIb3 integrin that in turn binds to fibrinogen. Moreover, platelets produce proteins in response to external signals, including cyclo-oxygenase-2 (COX-2), tissue factor (TF), IL-1, and matrix metalloproteinases, all contributing to the maintenance of an inflammatory state (Ohta et al., 2011; Sinha & Jastreboff, 2013).

Platelets are strictly linked to the serotonergic system. In particular, the metabolism, storage, reuptake of 5-HT, platelets share significant biochemical similarities with that present in presynaptic serotonergic neurons (Stahl, 1985), and they are uses as a reliable peripheral model of neuronal activity in biological psychiatry. Patients suffering from MDD may present an altered platelet structure, reuptake velocity and 5HT transporter (SERT) proteins, changes in intracellular

calcium levels, and an increased response to pro-activating stimuli (Marazziti et al., 2022; Carbone et al., 2021). Moreover, since platelets are the primary source of amyloid-(A) in plasma, it is conceivable that depressed patients may present alterations of the amyloid-precurson protein (APP) metabolism and amyloid-(A) generation, as a result of changes in platelet responsiveness to specific pro-activating stimuli. Therefore, a link an be hypothesized between depression and MeS, cardiovascular problems and strokes due to changes in APP metabolism and amyloid-(A) formation that cause platelets hyperactivation.

Finally, it is worth pointing out that selective 5-HT reuptake inhibitors (SSRIs) can reduce mortality in depressed individuals by preventing cardiovascular events due to their antiplatelet effects in vivo (Marazziti et al., 2022; Tagliarini et al., 2022).

Cordiovascular disease

Coronary heart disease, stroke, heart failure, and other heart and blood vessel dysfunctions are part in the so-called cardiovascular disease (CVD), also known as heart disease that nowadays is still a major cause of global death. Coronary heart disease and MDD appear to be strictly related (Almeida et al., 2019; Graham et al., 2019; Jee et al., 2019; Xue et al., 2020). Depression can double or triple the risk of CVD, as well as the risk of cardiac morbidity and mortality (Carney & Freedland, 2017; Amadio et al., 2020).

In spite of all the epidemiologic data on this issue, the knowledge on its pathophysiology remains weak and limited. In any case, it is believed that inflammatory processes might play a significant role. Therefore, the maintenance of a mild inflammatory state in depressed individuals, as a result of cortisol hyperproduction would facilitate heart diseases (Chávez-Castillo et al., 2020). Another potential mechanism might be related to the evidence that high cortisol levels may also directly harm blood vessels, favour the formation of plaques and, as such, lead to CVD (Shao et al., 2020).

Peripheral hormones

The interest in peripheral hormones, such as ghrelin, an endogenous peptide involved in the brain-gut axis, has increased over the years, for their possible pathogenetic impact on several diseases. Ghrelin, produced by gastric parietal cells, enters the blood system, crosses the blood-brain barrier, and it may exert its actions in several brain regions (Bouillon-Minois et al., 2021; Harmatz et al., 2017). In spite of being considered as mainly involved in the regulation of appetite, ghrelin was also found to play a role in different processes, including inflammation, cardiovascular function, anxiety and depression. As the latter is concerned, higher levels of ghrelin were found to decrease depressive symptoms by favoring appetite (Harmatz et al., 2017). On the other hand, in both MDD and obesity, a ghrelin dysregulation was demonstrated in several brain areas, such as the the hypothalamus, the hippocampus and the dentate gyrus (Esteban-Cornejo et al., 2021; Huang et al., 2019; 2021; Jiao & Luo, 2022; Pierre et al., 2019). Leptin is another appetite-regulating hormone. After being released from adipocytes, leptin reaches the brain through the bloodstream, where it promotes weight loss through a reduction of appetite (Field, 2014). It is worth mentioning that these two hormones display opposite effects on food intake (**figure 4**), as well as on stress response, with leptin inhibiting CRH mRNA expression and glucocorticoid levels, and ghrelin basically showing opposite actions.

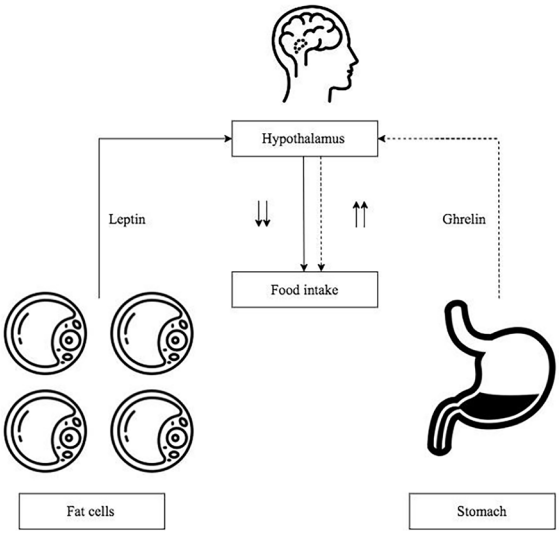
In a similar fashion, regardless of its effects on mood, 5-HT was suggested to control satiety and feeding behaviour through different receptors, specifically 5-HT_{2C} and 5-HT_{6} in the ventromedial hypothalamus and lateral nuclei. The mechanisms involved are different, as 5-HT interacts with both orexin and melanocortin-stimulating hormone (MSH) in the nucleus of the solitary tract (Voigt & Fink, 2015), and it is also intertwined with ghrelin and leptin (Marazziti et al., 2022). Specifically, leptin inhibits appetite by decreasing the 5-HT synthesis or release by neurons of the brainstem, targeting arcuate nucleus $5HT_{1A}$ and 5-HT_{2B} receptors, but it may also increase appetite, depending on the subtype of receptor involved. Consequently, it appears clear how the overall functioning of the 5-HT network is complex and, as such, several factors contribute to it, such as its biosynthesis rate from TRY, its release and catabolism (Höglund et al., 2019), the rates of occupation/sensitivity of the different 5-HT receptors and the activity of its reuptake system through its 5-HT transporter (SERT) (Marazziti et al., 2022). In a study of our group, the density of the SERT (B_{max}) was shown to be progressively reduced by increasing body mass indexe (BMI) in obese subjects, to be negatively correlated with BMI, waist/hip circumferences, triglycerides, glucose, insulin, and positively with HDL. The velocity of the 5-HT uptake rate was negatively correlated with leptin, and positively with glycemia. The insulin levels resulted to be negatively related to B_{max} independently from BMI. Taken together, these findings suggest the presence of a possible alteration of insulin/5-HT/leptin axis in obesity that might constitute a vulnerability actor towards the onset of MDD (Rajan & Menon, 2017; Marazziti et al., 2022), whose prevalence of depression is around 20% (Milaneschi et al., 2017). Interestingly, peripheral 5-HT seems to be strictly linked to adipose tissue formation (El-Merahbi et al., 2015).

The impact of diet on depression

Although not representing the main topic of our review, it is still worth discussing the importance of dietary habits and their effects amongst individuals suffering from MDD. It is a common notion that the diet of these subjects frequently includes the consumption of hypercaloric foods, and it is rich in carbohydrates and cholesterol, while there is usually a poorer intake of fish, vegetables and cereals that are fundamental for a variety of biochemical pathways. For instance, the consumption of specific food groups like seafood or fish was found to be associated with lower rates of depression (Molendijk et al., 2018; Quirk et al., 2013). A possible explanation is that these foods ensure an adequate intake of vitamins, particularly of the B group, such as B1, B2, and B6, along with folic acid, v3-PUFA and monounsaturated fatty acids (MUFA) that are essential for the homocysteine cycle. The latter is fundamental for the synthesis of catecholamines, 5-HT and other monoamine neurotransmitters (Parletta et al., 2019). Furthermore, their absence might affect the production of biogenic amines by rising homocysteine and of its metabolites that may have neurotoxic effects through the interaction with glutamatergic N-methyl-D-aspartate (NMDA) receptors.

Moreover, hyperhomocysteinemia has long been considered a risk factor for a depressed mood, and it is a common finding in depressed patients (Zaric et al., 2019;

Figure 4. *The effects of ghrelin and leptin on food intake*



Young et al., 2019). Again, hyperhomocysteinemia may have several detrimental consequences, including oxidative stress, inflammation and DNA damage that may all alter neurological functioning (Moradi et al., 2021).

Specific eating habits may have a protective role towards MDD, such as those typical of the mediterranean diet (MD) (**figure 5**) and of the so-called "anti-inflammatory" diets (low in meat and dairy products, high in fruits, nuts, vegetables, legumes, grains, olive oil, and fish, moderate alcohol consumption), that are associated with lower rates of depression (Lassale et al., 2019; Tolkien et al., 2019).

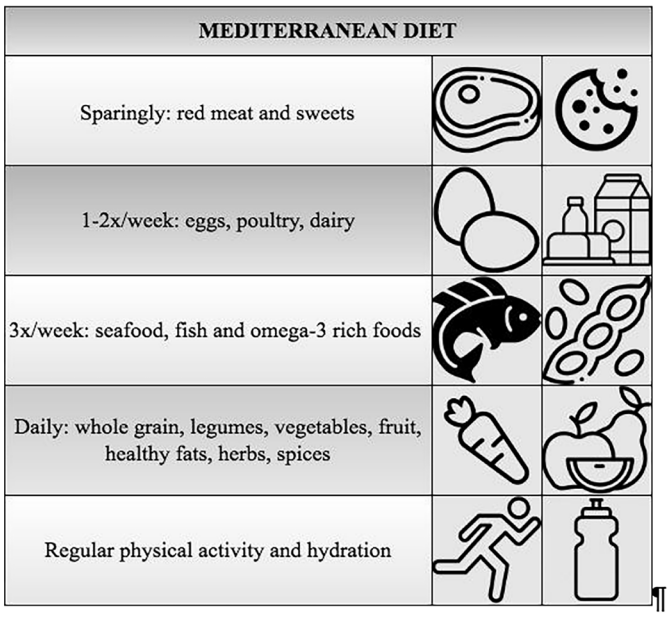
Interestingly, MD was found to have a positive impact on the shared mechanisms between MeS and depression as it specifically promotes a correct insulin/glucose balance, decreases pro-inflammatory cytokines and plasma homocysteine levels, and enhances endothelial function. Moreover, it has been linked to significant improvements in fasting blood glucose, glycated hemoglobin (HbA1c) and insulin levels (Beyer & Payne, 2016; Mirabelli et al., 2020).

To summarize, although a large part of depressed individuals are more likely to follow poor diets that mostly focus on delicious foods with high sugar and fat contents, evidence would indicate that healthy eating habits in MDD might induce beneficial vascular, inflammatory and metabolic pathways.

Conclusions

Given the crucial role that alterations of metabolic networks play in MDD, it is plausible that depressive syndromes could be considered as part of MeS and vice versa. A better understanding of the common pathophysiological mechanisms is expected to lead to new therapeutic options for the management of both conditions in the future. Indeed, patients with MDD

Figure 5. *The Mediterranean Diet*



should receive a multidisciplinary treatment coordinated by several experts that also consider MeS risk factors, such as eating habits, exercise routines, eating disorders, caffeine and tobacco abuse, and dysthyroidism. Several anthropometric and metabolic factors should also receive the right attention, as in the case of BMI and waist-to-hip ratio, but also of glycolipid metabolism. The intervention on such factors should be a priority in the treatment of these patients. Furthermore, the effects of common antidepressant drugs on both glucose and lipid homeostasis should be taken into account, since common antidepressants cause adverse metabolic effects. Future treatments for MDD should also take into account other targets, like cytokines, their receptors, other markers of inflammation, glucocorticoid receptors and neurotrophic factors, whose role in the pathogenesis of MDD and MeS cannot be denied any longer.

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