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Biological links between Depression and Lipids: A special focus on Serotonin Function, Inflammatory System and Stress Hormones

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Abstract:

In Western populations, the lifetime-documented prevalence of clinical depression (DE) is currently 10%, with a significant burden on general physical health and, most importantly, cardiovascular burden. As for lipid elements, mounting evidence indicates that various exogenous factors, such as unhealthy diet, restricted exercise, and co-occurring anxiety, appear to contribute to the increase in lipid profile abnormalities in depressed patients. To note that in patients with DE, selected biological links are disrupted, resulting in lipid abnormalities, even if the well-established exogenous mediating factors have been controlled. In this review, we explore the possible direct biological links between DE and lipid abnormalities namely serotonin, inflammatory, and stress processes a matter which has not yet been clarified. Serotonin alterations probably play an essential role in lipid and DE association; low lipid levels coexist with decreased serotonergic activity, while low serotonin concentrations have been detected in depressed individuals. Stress - induced lipolysis model may also play an important role; free fatty acids produced by activating lipoprotein lipase derived by stress hormones are available in liver and circulation to elevate lipoproteins. DE appears to be both an internal triggering factor (stressor) but also a consequence of the stress system dysregulation (allostasis), resulting in both emotional burden and dyslipidemia driven in a circular causality. Furthermore, altered immunological profile in depressed subjects is considered to be another factor which probably mediates this connection. Conclusively, although many studies provide reliable data on the presence of the above mechanisms apart from the influences of unhealthy lifestyle attitudes, the presence of a direct biological association between DE and lipid alterations, cannot yet be supported by consistency.

Keywords:

Depression; Lipids; Association; Correlation; Biological Mechanisms; Biological Pathways; Stress; Allostasis;

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Introduction

Depression (DE), a serious illness with a high incidence in the general population **[1]** is associated with an increased risk of suicide, other comorbid emotional and behavioral disorders, development of metabolic abnormalities, and generally with increased all-cause mortality **[2,3].** It is mainly characterized by depressed mood, anhedonia, sleep and appetite disturbances, loss of interest or pleasure in activities once enjoyed and feelings of guilt or worthlessness. Major Depressive Disorder (MDD), the prevalent form of Clinical DE, is now predicted to be a major cause of disability **[1,3]**.

Lipids are structural and functional elements of the cell, derived from food and synthesized de novo [4]. Altered blood lipids concentrations, including polyunsaturated fatty acids (PUFAs), glycerolipids, glycerophospholipids, sphingolipids, Low Density (LDL) & High Density (HDL) lipoproteins, and triglycerides (TG) have been found to be associated with the measures of DE in adult and adolescent populations **[5-14]**, but findings regarding this possible link are contradictory. More specifically, in several studies a link between lower total cholesterol (CHOL) and DE was found **[15-22]**, in other reports DE was associated with higher blood CHOL levels **[11,12,23-25],** while in some studies no association between these variables was shown **[26-29]**. Inconsistent findings have also been obtained with the less extensively assessed LDL- and HDL-cholesterol, and TG **[1,21,22,30].** Finally, it is still unclear if lowered omega-3 PUFAs **[31-33]** or the increase in omega-6/omega-3 PUFAs ratios **[34,35]** might interfere to Clinical DE.

These inconsistent results reflect the complexity of possible associations between DE and lipid biomarkers in which both extrinsic and intrinsic processes are implicated. Among the extrinsic factors, diet habits and high Body Mass Index **[36],** smoking, alcohol **[37,38]**, medication interventions **[6,39,40],** physical illness **[41,42]**, co-occurrence with pathological Anxiety **[43],** education-work status **[44],** fitness **[45]**, etc. are included. The fact that lipid abnormalities are observed even in patients with an adequate control of the above confounders, suggests that the effect of DE on lipids does not appear to be due to extrinsic factors solely **[29,30,46].** So far, the intrinsic pathways including serotonin, inflammation agents, as well as stress hormones have not yet been extensively investigated, while the results of the relative studies are not consistent **[47-51].** Differences in design and inadequate control of confounders in the relative analyses are parameters that probably affect the stability of results **[1,52].**

Furthermore, since DE is a non-homogeneous group of psychiatric disorders, with possible variation in expression of subtypes, comprising distinct causes, patho-physiologies and symptomatologies it would be risky to argue that the biological processes through which these disorders are related to changes in lipids are similar **[53-55].**

The purpose of this review is to explore current and past theories that focus on the presence of biological mechanisms involved in the association of DE and lipid changes. Thus, our hypothesis is that depressed patients, via these mechanisms, can develop impaired lipid metabolism, even if they manage to control cardiovascular and exogenous factors (smoking, eating habits, fitness, etc.) that have been established to affect lipids. We specially focus on mechanisms involving serotonin, inflammation and stress system.

Cholesterol, Lipoproteins, Polyunsaturated Fatty Acids and other Lipids.

CHOL is an important part of the plasma cell membrane determining the permeability of membranes to molecules as well as to charged ions **[56-58].** Almost every cell in the body can synthesize CHOL from Acetyl Coenzyme A, while apolipoproteins help the transportation of cholesterol throughout the body, and facilitate the uptake of CHOL by cells. The binding of CHOL to an apolipoprotein (as well as other molecules, such as phospholipids and lipid-surrounding triacylglycerols) forms lipoprotein **[59].** The CHOL molecule differs from total CHOL, as referred in clinical terms, in that it relates to the synthesis of LDL with the potential to build up on the walls of the artery, forming atherosclerotic plaques; HDL can prevent heart disease by removing CHOL from plaques and TG which replenishes total CHOL can also contribute to high total CHOL **[60,61].**

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CHOL is essential for brain development. About 25% of total human CHOL is found in the brain, where it is locally synthesized, because of blood – brain barrier (BBB), by both astrocytes and oligodendroglia. The synthesis of CHOL starts in the embryonal life and continues in the adult brain, albeit at a slower rate **[58].** Almost all brain CHOL is non-esterified, with about 70% of the CHOL to be in myelin and the rest in neuronal and astrocytic cell membranes; CHOL is necessary for the formation of the nerve synapse and important for the smooth signaling of neurons **[62].**

Except for CHOL, PUFAs are also detectable in the circulation, and are considered critical for cell membrane fluidity and subsequently brain function **[63].** PUFAs are made out of a hydrocarbonated chain of variable length with several double bonds; the position of the first double bond (omega) differentiates PUFAs. On the other hand, Phospholipids are a key component of cell membranes and composed of phosphate "heads", glycerol and PUFAs "tails" **[49].** PUFAs are derived from either linolenic acid (omega-6) or alpha-linolenic acid (omega–3). The most basic omega-6 is arachidonic acid, while the most basic omega-3 is docosahexaenoic acid (DHA), followed by the precursor eicosatetraenoic acid (EPA); DHA alone contains 15% –20% of the lipids in the human brain. DHA is the most abundant omega-3 fatty acid in mammalian CNS, especially in the early stages of development **[64].**

Omega-6 PUFAs are generally proinflammatory; their significant detrimental effect is thought to be due to the competitive inhibition of omega-3 PUFAs, as the latter appear to have a protective role **[65].** Both omega-3 and omega-6 PUFAs are basic compounds, which means they can only come from the diet (omega-6s are largely derived from plant oils, while omega-3s are mainly derived from fish oils) **[66].** This fact, combined with the evidence that the differentiation and function of cultured brain cells require alpha-linolenic acid, omega-3 and omega-6 PUFAs, makes the link between brain function and diet clearer **[67].** As reported before, in contrast to high CHOL levels, consumption of omega-3 PUFAs suppresses the production of IL-1β, IL-2, IL-6, and TNF-α **[68,69].**

High CHOL levels and its ingredients have been reported to relate with enhanced levels of proinflammatory cytokines. Particularly, high CHOL concentrations increased the release of IL-6 and TNF-α in hypercholesterolemic rabbits **[70]** as well as in macrophages treated with CHOL in vitro **[71],** while experimental diet with saturated fatty acids in rats increased TNF-α without affecting anti-inflammatory agents **[72].** In addition, oxidized LDL treatment in rabbits has led to increased production of IL-1β **[73].**

Evidence supports that low lipid levels can lead to a reduction in central serotonergic activity **[74];** indicatively, Kaplan et al. **[75]** showed that those adolescent monkeys who consumed a diet low in CHOL showed lower concentrations of 5-Hydroxyindolacetic acid (HIAA) in cerebrospinal fluid (CSF), a metabolite indicative of serotoninergic function, in contrast to those animals that consumed a high CHOL diet.

Furthermore, enhanced cortisol activity results in elevated TG concentrations by mobilization of free circulating fatty acids which in turn stimulate the synthesis of very low-density lipoproteins (VLDL) in the liver **[76,77]** and by reduction of apolipoprotein B degradation and decreased TGH expression and activity **[78,79]**. In addition, defects of the glucocorticoid receptor affecting cortisol sensitivity is also involved in lipid metabolism disorder **[80,81].**

Finally, various studies indicate the interrelationship between atherogenic lipids and mobilization of noradrenergic system **[82,83].** In particular, stress-induced mobilization of the noradrenergic system and subsequently catecholamines may trigger lipolysis by activating lipoprotein lipase. Thus, the free fatty acids produced by the above procedure are released to the liver and circulation in order to produce lipoproteins **[84-87].** In addition, both in vivo and in vitro conditions have been shown that noradrenaline stimulate the activity of hepatic 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) in animals, thereby mobilizing CHOL synthesis **[88,89].**

Depression and Lipids, changes in Serotonergic Function

Serotonin is a neurotransmitter that stabilizes the mood and low concentrations have been detected in depressed individuals **[90,91].** On the other hand, as previously reported, low lipid levels are related to a reduction in central serotonergic

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activity **[74].** Lipids appear to possess many neurobiological roles and may affect mood through modulation of neuronal membranes, neuronal survival, dendritic apophyses, myelin, synapse formation, enzyme function, absorption and transfer of fat-soluble vitamins and toxins, and production, re-uptake, or metabolism of neurotransmitters **[62,92-94]**.

Engelberg et al. **[95]** focusing on research in mice, found that lowering serum CHOL may reduce lipid viscosity and CHOL content in brain cell membranes and, serotonin receptors disclosure in surface area of the membrane as well as, leading to reduced serotonin uptake by the blood with consequent decreased entry into the brain cells. Thus, alteration of lipid content in brain cells might affect serotonergic function, which in turn affects mood **[96-98]**,

However, the fact that a large proportion of depressed patients appear not to respond to antidepressants that focus on serotonergic activity **[71,99,100]** and other studies do not support the elevation of lipids after therapy with Selective Serotonin Reuptake Inhibitors **[101],** the explanation of deficient serotonergic function is not sufficient to fully explain the connection between low cholesterol and DE.

Thus, some studies do not confirm the association between lipids and serotonergic function **[38].** In addition, Papakostas et al **[92]** argue that not only low CHOL levels but also high CHOL can contribute to serotonin dysfunction. Furthermore, in contrast to many studies **[102 -105]**, Maes et al. **[106]** did not found lower levels of total CHOL but lower esterified CHOL in depressed patients only compared to healthy controls; thus, they argued that low esterification of CHOL is the one that might play a regulative role in DE through changes in cell membrane viscosity.

Depressive Symptoms and Atheromatogenic Lipid Profile

In contrast to several studies, numerous studies have demonstrated atheromatogenic lipid profiles in subjects with DE. To interpret the above link, studies have focused on the following mechanisms:

Various studies and meta-analyzes have reported increased circulating proinflammatory cytokines, including interleukin IL-6, interleukin IL-1, interleukin IL-12, tumor necrosis factor TNF-α and their soluble receptors, as well as reduced levels of interleukin IL-4, in patients with clinical DE **[107-116]**, postulating the existence of a distinct subtype of DE, called cytokine-related inflammatory DE **[50].** Among all inflammatory cytokines, an increased concentration of IL-6 is probably the most widely and consistently reported in DE **[102,107,109].** Some studies have also measured elevated cytokine concentrations in the cerebrospinal fluid (CSF) of depressed patients compared to controls, while other studies have observed correlations between cytokine in CSF and DE severity **[117-120].** On the other hand, as previously mentioned, atherogenic lipoproteins or diets rich in saturated lipids appear to increase pro-inflammatory cytokines **[69],** which subsequently enhance DE severity, probably through the elimination of brain derived neurotrophic factor (BDNF), a polypeptide that supports the survival and growth of neurons through development and adulthood **[121,122].** Conclusively, the interrelation between these variables have been further corroborated by recent reviews **[123,124],** and data support a possible mediating role of cytokines in the relationship between atheromatogenic lipoprotein concentrations and DE.

However, it is important to note that deregulation of the cytokine system is not specific to DE and could be an indicator of other major psychiatric disorders, such as schizophrenia and borderline personality disorders, indicating the possibility of common underlying pathogenetic pathways in disorders involved in immune dysfunction **[125,126].** In addition, elevated cytokine levels appear to be found in only a part of patients with DE indicating that this factor does not consist a general component to explain all the phenotypes of DE **[102,127].**

The stress system

As described by Chrousos **[128,129]**, DE is as much an internal stressor, as well as a consequence of the maladaptation of this system resulting in a harmful homeostasis (Allosta-

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sis); allostasis leads to both metabolic disorders and further psychopathological expressions.

Specifically, the network that affects biopsychological responses to stress, is localized in the central nervous system as well as in the periphery of the body. It mainly consists of the system of hypothalamic releasing hormone corticotropin CRH, which regulates the hypothalamic-pituitary-adrenal axis (HPA) axis, and the norepinephrine system in the locus coeruleus of the brainstem which affects both arousal and the autonomic (sympathetic) nervous system.

Therefore, the prolonged chronic stress of a depressed subject, through the allostasis can lead to a further deterioration of his emotional state, through its detrimental effect on brain structures and functions related to fear, anger and remuneration/punishment, while, simultaneously, it can lead to lipidemic abnormalities. In other terms, the pathogenesis of these disorders can be explained by the prolonged, excessive secretion and the effects of both the main hormone mediators of stress as well as the sickness syndrome on the activities of the multiple homeostasis mechanisms.

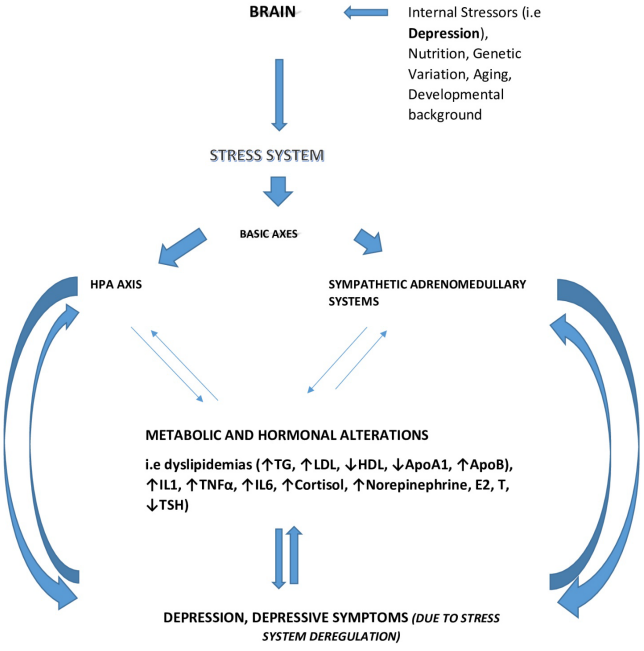
Increased cortisol levels are found in patients with DE **[30,130-135].** As previously reported, abnormal lipid metabolism appears to be associated with increased cortisol; enhanced inflammatory and immune mediators mobilize cortisol in depressed individuals facilitating the deposition of abdominal fat, which is considered to be more sensitive to lipolytic agents **[136-139].** Also, the model of lipolysis induced by stress, as described by McCann et al. **[86]** is likely to play an essential role; chronic stress in depressed patients causes an imbalance except for the HPA axis **[137],** of the noradrenergic system as well **[86,140,141]**, which in turn could cause atherogenic lipoprotein profiles.

Consequently, lipid metabolism disorders as well as DE represent chronic, maladaptive effects of the above two intrinsic processes; hormone mediators, under normal conditions, are produced in defined time and quantitative contexts, but in the case of prolonged stress, these processes are dysregulated **[128,129,142,143].** Extending the rationale of Papakostas et al **[92],** allostasis caused by DE could be associated not only with the atherogenic lipid profile but also with low CHOL levels (figure 1).

Other mechanisms

Other metabolic and biochemical changes occurring in patients with DE have also been implicated in the link between lipids and DE, including genetic alterations in lipoprotein coding **[14]**, the rate of melatonin secretion in relation to cortisol secretion **[144]**, the effect of IL-2 on melatonin reduction [145], the induction of oxidative stress and lipid peroxidation **[146-149].** In addition, a connection of DE with the endocannabinoid system has been subject to research **[150,151]** while according to older theories an atheromatogenic lipid profile is likely to be associated with DE through the defective oxygenation of red blood cells leading to partial brain hypoxia **[152].** As is expected, these theories are beyond the scope of this review while there is a smaller pool of evidence supporting their role in the connection between lipids and DE.

FIGURE 1



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Conclusions

in addition to the effects of unhealthy behaviors, many studies provide reliable data on the presence of direct biological mechanisms linking lipid metabolism to depressive disorders; lipid profile abnormality appears to have a direct relation with depressive syndromes possibly through an endocrine imbalance. Furthermore, presence of these mechanisms explains why a depressed patient may develop lipid abnormalities without exhibiting other lifestyle factors that might affect the lipid profile (eg obesity, smoking, malnutrition, drug use). The significance of this conclusion lies in the fact that it might be useful in patients with chronic DE to perform routine blood tests to monitor lipid levels, easily accessible, low cost biological markers for the cardiovascular burden independently of the presence of other external cardiovascular risk factors **[153].**

Based on the stress system described by Chrousos, as well as by compiling the findings of previous studies, it appears that DE disrupts homeostasis by deregulating behavioral and biochemical mechanisms in a bidirectional (circular) correlation. The central and peripheral factors of the stress system affect various body systems (gastrointestinal, cardiopulmonary, immune), including the metabolic pathways. Thus, malfunction of this system may affect growth, development, behavior, and metabolism, resulting in deregulation of the lipid profile.

Future Directions

Findings so far could justify the need for lipid levels to be investigated in patients with DE, not only in routine examinations, but also in a different philosophy of health care prevention and care policy for this patient category.

On the basis of the above, it might be necessary to systematically monitor lipidemic factors, as well as to implement prevention programs for the development of atherosclerosis and its complications in patients with DE. In addition, the study of the efficacy of evidence-based psychotherapies to regulate lipid levels in patients with DE would be of great clinical interest.

Further future research, including prospective studies, could evaluate with greater validity the correlation of lipid changes with the intensity or severity of depressive symptoms. In addition, it would be interesting for researchers to focus more on the relationship of lipid metabolism with selected subgroups of depressive symptoms, for example, the relationship of autonomic hyperarousal with lipids in DE, while each specific subgroup of symptoms may have different biomarkers.

Finally, more studies in animals in laboratory conditions could highlight the possible biological pathways that link DE to lipid metabolism with even greater consistency.

Abbreviations:

CHOL: Cholesterol; LDL: Low density Lipoprotein; HDL: High density Lipoprotein; TG: Triglycerides; PUFAs: Polyunsaturated Fatty Acids; TGH: triacylglycerol hydrolase; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; IL-8: Interleukin 8; IL-6: Interleukin 6; IL-1α: Interleukin 1α; TNF-α: Tumor Necrosis Factor-α; BBB, blood–brain barrier; BDNF: brain-derived neurotrophic factor; CNS: central nervous system; CRH: corticotropin-releasing hormone; CSF: cerebrospinal fluid; GRs: glucocorticoid receptors; HPA: hypothalamic–pituitary–adrenal; LPS: lipopolysaccharide; MDD: major depressive disorder; DE: clinical Depression; HIAA: 5-Hydroxyindolacetic acid; BDNF: brain derived neurotrophic factor;

Conflicts of Interest

The author state that there are no conflicts of interest regarding the publication of this paper.

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