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Exploring the Role of Lipid Profile Alterations in Neurodegenerative Disorders: A Narrative Review

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ABSTRACT

Neurodegenerative disorders are characterized by the progressive deterioration of the central nervous system (CNS). Depending on the affected regions, patients may experience a broad spectrum of neurological deficits, such as sensory, motor, cognitive, and psychological symptoms. Notably, cholesterol synthesis in CNS occurs in a *de novo* manner and is distinct from systemic lipid metabolism. However, lipids constitute a large portion of the brain and are involved in crucial brain functions like neurotransmission and synaptic plasticity. Emerging evidence suggests that alterations in lipid metabolism may contribute to the development and progression of different aspects of neurodegeneration, such as neuroinflammation, oxidative stress, and impaired neuronal membrane function.

There are several critical changes in various lipid fractions, like cholesterol and triglycerides (TG), in individuals with neurodegenerative disorders. This narrative review aims to summarize the current understanding of the relationship between lipid profiles and neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). The findings may have important implications for the development of novel diagnostic and therapeutic strategies targeting lipid-related pathways in the management of these debilitating neurological conditions.

Keywords: lipid profile, central nervous system, neurodegenerative disorders.

BACKGROUND

Lipids are chemical elements made mainly from oxygen, carbon, and hydrogen. Due to not dissolving in the water, they can't travel through blood themselves, so they bond to the specific serum proteins known as apolipoproteins and make lipoproteins (1–3). Therefore, the primary function of plasma lipoproteins is lipid transportation (4,5). Some of the main characteristics used for the categorization of the different types of lipoproteins are the source, components, apolipoprotein and fatty acid composition, biological functions, and other structural properties like molecular weight, density, polarity, and diameter (5,6). Some types of particular lipoproteins that circulate in the plasma are chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), intermediate-density lipoproteins (IDL), and high-density lipoproteins (HDL). A lipid profile, also known as a lipid panel or lipid test, is a blood test that measures the levels of different types of fats in the serum and generally measures total cholesterol (TC), LDL, HDL, and TG (5). Cholesterols are necessary for building up the cells and producing hormones, while TGs energy store unused calories and provide the body with energy (7). Although

many body functions depend on the existence of the various types of lipids, it's also crucial to consider their reactivity and potential to harm the body, especially in the case of certain types of lipoproteins like LDL cholesterol (8–10). For instance, the oxidation of LDL cholesterol can lead to the formation of reactive oxygen species (ROS), which can cause further damage to the walls of blood vessels via sticking to them, which could contribute to the inflammatory response and increase the risk of other diseases (11). On the other hand, HDL, due to its anti-thrombotic, anti-inflammatory, and antioxidant effects, is considered a highly beneficial substance (12–14). Thus, understanding the implications of different lipid types and their interactions within the body is essential for maintaining overall health and reducing the risk of diseases.

Noteworthy, cholesterol generation in the central nervous system (CNS) occurs in a *de novo* manner and is distinct from systemic cholesterol (15,16). The existence of the blood-brain barrier as a physiological property impeded the passing of lipids from and into the brain environment (17,18). The unique composition of CNS lipids is in accordance with their specific functions, such as facilitating the rapid transmission of electrical signals along neurons through the myelin sheath and contributing to the fluidity and permeability of cell membranes, which affect synaptic transmission and neural signaling (15,19,20).

Although any disruption in lipids may have primarily a prominent role in disturbances in metabolic processes and developing cardiovascular disorders due to the specific features of CNS cholesterol, lipid profile evaluations may provide helpful and valuable insights into the underlying mechanisms of neurodegenerative disorders (21,22). This narrative review, which examined the available evidence on lipid profiles in some of the most prevalent neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS), highlights the need for further research to elucidate the complex interplay between lipid metabolism and neurodegenerative diseases.

Alzheimer's disease (AD)

Alzheimer's disease is a growing global health concern, with an estimated 81 million individuals expected to be affected by 2040 (23). There is a growing focus on lipidomic studies to understand the role of lipids in the pathogenesis of AD better and to develop a lipid-based diagnostic test (23–25). Although different studies show a controversial relationship between lipid profiles and AD pathogenesis, some of them have highlighted the pivotal role of lipids and their potential as biomarkers of diagnosis and progression of this disease (26–28). One of the most prominent pieces of evidence regarding this issue is the maintenance of lipid hemostasis balance, which is typically a tightly regulated process (26,28). In a way, any lipid dysregulation, including alterations in the optimal level of saturated and unsaturated fatty acids, phospholipids, and cholesterol, may contribute to the accumulation of amyloid-beta proteins, a hallmark of AD pathology (28). Alterations in lipid composition, particularly in fatty acids and cerebral lipid peroxidation, have been observed in early-stage AD (29,30). There is a conflicting relationship between AD and plasma cholesterol levels. Some studies mentioned that plasma cholesterol in AD patients is higher than the normal range (31). Another study mentioned that the cholesterol levels of AD patients were not different from those of the control group (32). HDL could reduce the formation of beta-amyloid plaques and, consequently, lower inflammation. In contrast, an increase in LDL cholesterol in AD patients can accelerate the build-up of amyloid and disrupt the cell cycle (33). However, various lipids, including cholesterol, fatty acids, and phospholipids, have been identified as potential biomarkers for AD diagnosis and progression. Higher levels of TC, LDL cholesterol, and non-HDL cholesterol have been associated with the presence of neuritic plaques, even in the early stages of AD pathology (29). Noteworthy, advanced lipidomic analysis of a broad panel of lipid molecules has revealed promising lipid signatures that can classify AD patients with high accuracy and predict disease progression and brain atrophy (34). These findings suggest that blood lipids may serve as valuable AD

biomarkers and could lead to new therapeutic strategies.

Parkinson's disease (PD)

Parkinson's disease, the second most common neurodegenerative disorder after AD, is defined by the death of dopaminergic neurons in the substantia nigra and basal ganglia that is manifested by tremors, bradykinesia, stiffness, and instability in the posture (35). In this disease, lipid peroxidation happens following phospholipase activation in the substantia nigra (36). A study revealed that although the serum levels of TG and LDL were remarkably lower in patients with PD compared with healthy subjects, there was no meaningful statistical difference in the concentrations of HDL between these groups (37). Generally, several studies have shown that PD patients exhibit lower serum lipid levels compared to healthy controls. Specifically, TC, LDL, HDL, and TG were found to be significantly reduced in PD patients (37). Brain-derived neurotrophic factor has been identified as a predictor of various lipid parameters in PD patients, suggesting its importance in lipid metabolism (38). However, the metabolism of brain cholesterol has been described as altered in PD patients, and plasma 24-OH-cholesterol has been considered as a possible biomarker for PD (39). Additionally, oxysterols, which are oxidized cholesterol products, may contribute to PD pathophysiology through mechanisms such as α-synuclein accumulation, oxidation, inflammation, and cell death (40). Conclusively, lipids play a central role in the pathogenesis of PD, but the results are inconsistent and vary based on patient characteristics, making it difficult to draw firm conclusions (41,42). These findings highlight the need for further investigation into their use as potential biomarkers or therapeutic targets in PD.

Huntington's disease (HD)

Huntington's disease is an autosomal dominant neurodegenerative disease that causes a massive degeneration of several brain areas, including the striatum and cortex, along with severe diffuse atrophy at magnetic resonance imaging (43,44). Behavioral abnormalities, cognitive impairments, and involuntary motor functions are some of the most common features of HD (45). Interestingly, a considerable number of studies have dealt with lipid metabolism in the CNS regarding HD patients (43,44,46). Phospholipid disturbances in HD primarily occur in the white matter of the dorsomedial prefrontal cortex and the putamen but not in the caudate nucleus (46,47). This evidence suggests that susceptibility to phospholipid disturbance may be more dependent on specific brain regions and cellular response to pathology rather than just cell type (47). In HD patients, markers of cholesterol synthesis and metabolism (24OHC, lanosterol, lathosterol, and 27-hydroxycholesterol) were decreased, and this correlated with disease progression and brain atrophy (44). In a study on HD, plasma levels of TC were significantly higher than those of the healthy controls (48). Another study showed a significant change in all lipoprotein subfractions and components. Their results revealed that plasma levels of TC, apolipoproteins, components of LDL, and HDL were lower in HD patients compared to the healthy controls. In contrast, the components of VLDL were higher in individuals with HD than in the controls (49). The key conclusion is that the mutant Huntingtin protein in HD disrupts the normal regulation of cholesterol metabolism, leading to reduced cholesterol synthesis and transport in the brain and body. These lipid abnormalities may be related to the underlying genetic mutation responsible for HD, which can lead to disruptions in lipid metabolism (43). These findings underscore the involvement of lipids in HD pathogenesis and their potential as diagnostic and prognostic markers.

Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis is a fatal idiopathic CNS neurodegenerative disorder that affects the motor system, including upper and lower motor neuron involvement (50). However, there is a remarked phenotypic heterogeneity among individuals with ALS, and despite massive research, the current management of this disease from the diagnosis to prognosis stages is suboptimal (50,51). Studies that have investigated lipid profiles in ALS patients yielded mixed results. A meta-analysis found

that Asian ALS patients had lower TC levels than controls, but lipid levels were not associated with ALS mortality (52). Another study reported no significant effect of lipid profiles on ALS prognosis when adjusted for prognostic covariates (53). However, a Chinese study suggested that higher TG levels might be protective and associated with more prolonged survival in ALS patients (54). A study indicated that higher TC levels were associated with an increased risk of ALS. Still, higher HDL and LDL cholesterol levels were associated with a poorer prognosis, while higher TG levels were associated with a better prognosis in ALS patients (55). The inconsistent findings across studies highlight the need for further research to clarify the relationship between lipid profiles and ALS progression and prognosis.

Multiple sclerosis (MS)

Multiple sclerosis is an autoimmune disorder of the CNS characterized by the demyelination of neurites (56,57). The damage or loss of myelin sheath impairs neurological function, leading to the diverse array of symptoms experienced by patients with MS, including vision problems, muscle weakness, numbness, and cognitive impairment (58,59). Several studies have investigated the disturbance of lipid metabolism in the brains of MS patients (60–62). Changes in lipid metabolism may contribute to the inflammation and demyelination of the CNS, which are hallmarks of MS (63). However, studies have yielded controversial findings regarding the serum lipid profile. A study revealed that the lipid levels in these patients' blood serum stay within the normal range (64). Another study showed that more worsening in the score of MS individuals was associated with higher baseline LDL and TC levels and with trends for higher TG. In contrast, lower levels of acute neuroinflammation accompanied a higher HDL level (65). In line with this study, another research indicated that TC was independently associated with a worsened functional score (66). In another study on MS patients, there was a significant increase in the level of TC and HDL but a decreased level of TG compared to the control group (67). It is noteworthy that reaching the borderline levels of TG, LDL, and cholesterol was associated with a decrease in cognitive performance in MS patients (68). Multiple studies suggest that optimizing and balancing serum lipid levels may provide beneficial effects for individuals with MS, potentially leading to improved clinical outcomes. This indicates that managing serum lipid profiles could be a valuable therapeutic approach for MS patients.

CONCLUSION

The present study aimed to evaluate the serum lipid profile in some neurodegenerative diseases such as AD, PD, and MS. However, any disruption in the lipid profile, such as LDL and HDL levels that have been observed in some neurodegenerative diseases, may reflect the underlying metabolic disturbances associated with the disease. On the other hand, these lipid abnormalities could potentially impact mitochondrial dysfunction, oxidative stress, and neuroinflammation, which are known to be involved in the development of neurodegenerative disorders. Finally, these lipid abnormalities could potentially disrupt neuronal function.

The findings suggest that alterations in serum lipid levels may be associated with the pathogenesis and progression of these neurological disorders and highlight the importance of evaluating the serum lipid profile in patients with neurodegenerative diseases. The observed associations between lipid abnormalities and the pathogenesis of these disorders suggest that targeted interventions aimed at managing lipid levels may have the potential to positively impact the course and outcomes of these debilitating neurological conditions. These findings highlight the importance of monitoring and managing lipid levels in patients affected by neurodegenerative disorders and further emphasize the need for comprehensive lipid management in these patients. One of the most important findings was the controversial results regarding each neurodegenerative disease that may reflect their heterogeneous nature and the urgent need for individualized therapeutic strategies. However, further research is warranted to elucidate the

underlying mechanisms and explore the clinical implications of these lipid-related findings.

ETHICAL CONSIDERATIONS

Compliance with ethical guidelines

This study is a narrative review with no involvement of humans or experimental animals.

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AUTHORS' CONTRIBUTION LIST

Conceptualization: Ameneh Omidi; **Original draft:** Amin Zolfaghari, Masoumeh Khosravi; **Research:** Ameneh Omidi, Amin Zolfaghari, Masoumeh Khosravi; **Writing and Editing:** Ameneh Omidi, Amin Zolfaghari, Masoumeh Khosravi.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ABBREVIATIONS

AD: Alzheimer’s disease; CNS: central nervous system; HD: Huntington's disease; MS: multiple sclerosis; PD: Parkinson’s disease; VLDL: very-low-density lipoprotein; LDL: low-density lipoprotein; IDL: intermediate-density lipoprotein; HDL: high-density lipoprotein; ALS: Amyotrophic Lateral Sclerosis; TC: total cholesterol; TG: triglycerides.

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