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COMPILATION

Multiple Sclerosis and Cholesterol Metabolism

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ABSTRACT

Adult lipid metabolism consists of plasma lipids. Triglycerides are the most important sources of energy reserves, while phospholipids and cholesterol are key components of organelles and cell membranes. Lipids, especially cholesterol, are involved in many cellular functions. Various neurodegenerative cellular processes can develop in metabolism disorders. Neurons have significantly different lipid composition compared to other biological membranes. These differences and the role of these lipids in neuronal pathologies are still poorly understood. Studies on lipid molecules in MS date back four decades. Studies on apolipoprotein alterations, plasma lipoproteins and oxysterols have attracted attention. It is thought that impaired cholesterol metabolism may play a role in both the inflammatory and neurodegenerative pathogenesis of the disease and its correction may favorably affect the progression steps in the clinical course of MS, which is still the most limited point for treatment. In this review, the immunopathogenesis and clinical manifestations of Multiple Sclerosis and alterations in cholesterol metabolism are presented.

Keywords: Lipid Metabolism. Multiple Sclerosis. Immunpathogenesis. Neurodegeneration.

Multipl Skleroz ve Kolesterol Metabolizması

ÖZET

Yetişkin lipid metabolizması plazma lipidlerinden oluşur. Trigliseridler enerji rezervlerinin en önemli kaynağı iken fosfolipidler ve kolesterol organellerin ve hücre zarlarının bileşenleridir. Lipidler, özellikle de kolesterol, birçok hücresel fonksiyonda rol oynar. Metabolizma bozukluklarında çeşitli nörodejeneratif hücresel süreçler gelişebilir. Nöronlar, diğer biyolojik membranlara kıyasla önemli ölçüde farklı lipid bileşimine sahiptir. Bu farklılıklar ve bu lipidlerin nöronal patolojilerdeki rolü hala tam olarak anlaşılamamıştır. Multipl Skleroz'da lipid molekülleri üzerine yapılan çalışmalar kırk yıl öncesine dayanmaktadır. Apolipoprotein değişiklikleri, plazma lipoproteinleri ve oksisteroller üzerine yapılan çalışmalar dikkat çekmiştir. Bozulmuş kolesterol metabolizmasının hastalığın hem inflamatuar hem de nörodejeneratif patogenezinde rol oynayabileceği ve düzeltilmesinin tedavi için hala en kısıtlı nokta olan Multipl Skleroz'un klinik seyrindeki ilerleme basamaklarını olumlu yönde etkileyebileceği düşünülmektedir. Bu derlemede, Multipl Skleroz'un immünopatogenezi ve klinik belirtileri ile kolesterol metabolizmasındaki değişiklikler sunulmuştur.

Anahtar Kelimeler: Lipit Metabolizması. Multipl Skleroz. İmmunpatogenez. Nörodejenerasyon.

Lipid Metabolism

Adult lipid metabolism consists of plasma lipids called neutral lipids (triglycerides, phospholipids, and cholesterol). While triglycerides are the primary source of energy reserves, phospholipids and cholesterol are organelle and cell membrane components. Dietary plasma lipids with low water solubility are transported in lipoproteins. Apolipoproteins with enzyme cofactors and receptor-ligand functions ensure that lipid molecules are transported to the correct sites. The composition of dietary calorie intake varies between societies. In Asian societies, 10-15% of dietary calories are from fat, compared to up to 50% in Western societies. The majority of dietary fat intake is from triglycerides. The source of triglycerides may differ between societies; in Western diets, butter with a relatively high oleate content is the source of triglycerides, whereas in the Mediterranean diet, olive oil rich in palmitate is the source. Regardless of the source, excess calories from the diet are converted to triglycerides and stored in adipose tissue. Adipose tissue has functions other than

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energy storage. The imbalance in fatty acid flux caused by the release of chemokines and cytokines leads to the formation of adipocytes and the accumulation of macrophages, which play an additional role in inflammatory processes. Energy restriction can effectively control inflammation by reducing inflammatory factors and decreasing lipolysis and energy expenditure.[1]

Lipid Metabolism of the Nervous System

Human cells contain thousands of lipids, such as glycerolipids, glycerophospholipids, sterol lipids, sphingolipids, and free fatty acids[2,3] The function of most lipids depends on their molecular structure. The differences in lipid composition in neurons and the role of these lipids in neuronal pathologies are still poorly understood. To understand this, lipid diversity should be considered specific to myelin and neurons and recognized as units with anatomical and functional properties. Lipids make up just over a third of the dry weight of the neuronal soma. Phospholipids, cholesterol, and galactolipids are the most abundant.

In contrast to the soma, about one-seventh of the neurites are lipids. They contain a similar proportion of phospholipids and a higher proportion of cholesterol and galactolipids. In addition, the sphingomyelin content is higher in neurites[4] Contrary to the well-known assumption that axonal membrane lipids are synthesized in the soma and then transported anterograde to the axons, recent studies have shown that axons can independently carry out some aspects of lipid metabolism.[5]

Axons are surrounded by a lipid-rich myelin sheath. The primary function of myelin is to insulate the axon and cluster sodium channels in Ranvier junctions, effectively ensuring the conduction of action potentials.[6] Myelin is produced by Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS). Its lipid composition is well known. It is significantly different in neurons compared to other biological membranes. During active myelination, glial cells rapidly produce excessive amounts of lipids for utilization. The most abundant lipids in myelin are cholesterol and galactosylceramide.[7] Cholesterol regulates the fluidity and permeability of the membrane. It gives stability to myelin. It is necessary for the growth and compression of myelin. Among the different lipid classes, sphingolipids are primarily associated with peripheral neurological disorders. 1-deoxy-SL, which is formed in an alternative reaction during de novo synthesis, has a unique role. Pathology in the formation of 1-deoxy-SL may play a role in disorders such as hereditary sensory and autonomic neuropathy type 1 (HSAN1) and diabetic or chemotherapy-induced neuropathies.

Lipid Metabolism of the Central Nervous System

More than one hundred billion cells in the CNS are rich in lipids and are closely associated with fatty tissue. Approximately 50-60% of their weight is made up of lipids. The highest lipid content of all biological membranes is found in the myelin sheath structure. Lipids play an active role in many cellular processes in the CNS, such as synaptogenesis, neurogenesis, signaling, and energy reserves. Disturbances in the steps of lipid metabolism are involved in the pathogenesis of neurodegenerative diseases by causing changes in the lipid composition of intracellular membrane compartments. In Alzheimer's disease, for example, most of the cholesterol in the neuron is catalyzed by the enzyme cytochrome P46A1 (CYP46A1) to 24-hydroxycholesterol (24-OHC), a cholesterol breakdown product called oxysterol. 24-OHC then crosses the blood-brain barrier (BBB) and enters the plasma, while plasma 27-hydroxycholesterol (27-OHC) travels to the brain. 27-OHC promotes the formation of amyloid beta (Aβ), whereas 24-OHC inhibits the production of Aβ protein.[8] Aβ forms a complex with apolipoprotein E Christchurch (ApoE-CH) particles, which are eliminated by endocytosis, secreted into the peripheral system, or degraded by proteases, leading to amyloid deposition. [9, 10] The implications of this theoretical knowledge can also be seen in the results of trials. It has been reported that the disease is associated with increased low-density lipoprotein (LDL) cholesterol and decreased high-density lipoprotein (HDL) cholesterol levels, independently of ApoE; the risk of developing the disease increases up to twofold in people with total cholesterol (TC) levels above 250 mg/dL, and this association is associated with lipid disorders, especially in middle age (40-60).[11-15]

Lipid Metabolism and Neurodegeneration

The relationship between neurodegeneration and lipid metabolism in Parkinson's disease, the second most common neurodegenerative disease, is not clear. Study results are conflicting, and prospective studies with larger numbers of cases are needed.[16,17] However, the demonstration of a decrease in α-synuclein in Lewy bodies after statin treatment suggests that plasma cholesterol may promote α-synuclein aggregation.[18] In addition, in experimental Parkinson's model studies, it was found that a high-fat diet was associated with increased dopamine depletion in the striatum and substantia nigra and oxidative stress in the subthalamic nucleus in rats.[19,20]

Cholesterol Metabolism and Central Nervous System

Cholesterol in the CNS accounts for a quarter of the total cholesterol in the body and is ten times higher than in the periphery. 70% is found in myelin structures and 30% in cell or organelle membranes (glia 20%, neurons 10%).[21] Clearance of cholesterol metabolism in the CNS is 250-300 times slower.[22] In addition, cholesterol is transported in plasma by several lipoprotein particles because it cannot cross the BBB.[23,24] This suggests that compensation for cholesterol metabolism is more limited in the CNS. Cholesterol synthesis in the CNS is identical to the lanosterol step and is produced de novo. Lanosterol is used for cholesterol synthesis in neurons via the Kandutch-Russel pathway and in astrocytes via the Bloch pathway. The cholesterol produced is highly channeled through ApoE for utilization in cells. Cholesterol, used in glia or neurons, is converted by a cytochromal enzyme, CYP46A1, to 24-OHC, one of the oxysterols oxidized cholesterol forms that can cross the BBB. Increased 24-OHC leads to liver X receptor (LXR) activation, initiating efflux mechanisms from neurons. Thus, toxic accumulation in the cell is prevented. While 1% of 24-OHC circulates in the cerebrospinal fluid, 99% crosses the BBB and enters the peripheral blood circulation. In the liver, it is converted to 27-OHC (the final breakdown product of cholesterol in the whole organism) by a second cytochrome enzyme and excreted in bile acids and feces. However, the formation of 24-OHC as a degradation product far exceeding this clearance rate (e.g., acute demyelinating attack) or the increase in oxysterol resulting from oxidation of LDL with proinflammatory properties after its passage from the circulation to the CNS with impairment of the ENT leads to the accumulation of 24-OHC in neurons. In addition, defects in the synthesis of LXR [e.g., nuclear receptor subfamily 1 group G member 3 (NR1H3) gene mutation], which is involved in maintaining cerebral lipid homeostasis, also accelerate this process.

Consequently, this increased accumulation initiates the process, leading to lipid peroxidation, oligodendrocyte cell death, and neurodegeneration.[25-29] A pre-existing disorder of the lipid profile may facilitate these mechanisms. For example, high LDL levels increase the amount of oxidized LDL in the CNS when the BBB is disrupted, and immune-active cells are more likely to invade the CNS. On the other hand, low HDL and high TC levels accelerate this process by increasing BBB permeability. Studies conducted in this context show a correlation between increased HDL and reduced grey matter volume loss and the number of contrast-enhancing lesions, better BBB integrity, and a reduced risk of developing secondary progressive multiple sclerosis (SPMS). It was found that there was an increase in the number of new or enlarging T2 hyperintense or contrast-enhancing lesions on the Expanded Disability Status Scale (EDSS) with increasing LDL but no change in the frequency of relapse. Therefore, it is suggested that relapse may be associated with disability progression independent of relapse.[14,25,30-39]

Multiple Sclerosis and Lipids

Cholesterol Metabolism and Multiple Sclerosis

Studies of lipid molecules date back forty years. In the early days, studies of apolipoprotein changes in patients with MS were at the forefront. In contrast, studies of plasma lipoproteins and oxysterols have attracted attention in the last two decades. Although the results of many studies on this subject differ, it has been shown that LDL and HDL cholesterol are decreased, and very low-density lipoprotein (VLDL) cholesterol and insulin resistance are increased in MS. Regarding secondary endpoints, the development of new hyperintense or contrasting T2 lesions and cortical atrophy were shown to correlate with decreased HDL or ApoA1 and increased TC/HDL ratio, LDL, 24-OHC, 27-OHC, and ApoB.[31,40,41] In addition, a recent study has shown that dyslipidaemia has a mild negative effect on cognitive performance in people with MS, independent of brain atrophy. [42] It was highlighted that HDL, a mediator of the anti-inflammatory response, has an inhibitory effect on leukocyte migration, has antioxidant properties, and contributes to the improvement of BBB function in MS.[43]

Effects of Anti-Lipids on Multiple Sclerosis

Studies investigating the effect of anti-lipid therapies on MS have been conducted with statin therapies. Initial studies suggested that statins may have a beneficial effect on neurodegenerative processes due to their regulatory effects on cell proliferation, differentiation, migration, and cerebrovascular hemodynamics. With increasing knowledge of the immune pathogenesis of MS, statins have been shown to inhibit major histocompatibility complex (MHC) class II antigen presentation, downregulate T cell activation and proliferation, and induce a switch from a proinflammatory T helper (Th) 1 to a Th2 phenotype in vitro. It was also found to block adhesion molecule expression and inhibit leukocyte migration across the BBB. It was thought to be effective against neurodegeneration and inflammatory processes in MS.[44-50]. Randomized controlled trials of statin therapy date back fifteen years. In patients with clinically isolated syndrome, atorvastatin treatment

did not change the time to definite MS diagnosis or EDSS. However, it had a beneficial effect on radiological activation.[51] Immediately following this study, another multicenter, placebo-controlled, double-blind, randomized, parallel-group, interferon beta-1a (IFNβ-1a, IM) add-on treatment with simvastatin was planned. The patients selected were inflammation-naive (≥ 1 relapse in the previous year). However, the number of relapses, annual relapse rate, relapse-free rate, EDSS scores, radiological activation, no evidence of disease activity (NEDA-3), and no beneficial results on atrophy were not found. In addition, there were no significant results when the in vitro effects of statins were evaluated with serum levels of interleukin 10 (IL10), tumor necrosis factor superfamily member 10 (TNFSF10), MX1, and interferon regulatory factor 7 (IRF7). Simvastatin treatment was found to be ineffective in relapsing-remitting multiple sclerosis (RRMS), with class 1 evidence. However, the inadequate power of this trial (65% instead of 80%) due to the failure to reach the predicted number of relapses, the ineffective results in contrast to in vitro studies on immune markers, and the failure to consider drug tolerance mechanisms have led to criticism.[52] Another small study conducted at a similar time to this trial reported that the use of 80 mg of simvastatin for six months in patients with acute optic neuritis was well tolerated and may have had a beneficial effect on both wave latency and amplitude in visually evoked potential measurements.[53] To evaluate the immunomodulatory and neuroprotective properties of statins, the double-blind, randomized, controlled MS-STAT trial comparing 80 mg of simvastatin with placebo in patients with SPMS with higher disability scores reported a significant 43% reduction in the adjusted mean annual rate of atrophy. This study highlighted that statins may have a neuroprotective effect, and the MS-STAT2 phase 3 trial was initiated (ongoing).[54,55]

Effects of diet on multiple sclerosis

The diet of people with multiple sclerosis (MS) is an important factor that can influence the course of the disease. In particular, foods rich in omega-3 fatty acids, such as fish and flaxseed, can reduce inflammation. In addition, avoiding processed foods, trans fats, and excess sugar can help balance the immune system by maintaining gut health. Drinking enough water and eating a diet rich in fiber can help regulate bowel function and prevent constipation, which is common in people with MS.

There are studies on the amount and variety of dietary fat intake and the development or progression of multiple sclerosis. There is currently no scientifically proven definitive diet for people with MS. However, the Mediterranean diet for MS has been reported to have a preventive effect on the development of the disease. The McDougall diet, a very low-fat, plant-based diet, has been reported to reduce fatigue in people with MS, and the Paleolithic diet, which avoids processed animal foods, wheat products, legumes, refined oils and refined sugars, also has a positive effect on fatigue and improves motor and cognitive function. Calorie restriction and intermittent fasting have been reported to suppress inflammation in experimental models, and a ketogenic diet leads to possible improvements in quality of life and depression. The Swank diet, a diet restricted in saturated fat, has been shown to have a beneficial effect on relapse and progression.[56]

Conclusion

Lipid metabolism is essential for neural function, support structure, signaling, and energy balance. The different lipid composition of the components of the central nervous system results from their different cellular needs. These differences are maintained in a balance that we call lipid homeostasis. Disturbances in homeostasis contribute to neurodegenerative diseases through the formation of cholesterol degradation products, particularly 24- and 27-hydroxycholesterol, lipid peroxidation, oxidative stress, and inflammation.

In multiple sclerosis, abnormalities in lipid metabolism are associated with disease progression and disability. Dysregulation of cholesterol transport and lipid oxidation contributes to blood-brain barrier permeability, neuroinflammation, and neuronal degeneration. The correlation between high LDL cholesterol, low HDL cholesterol, and increased lesion burden highlights the potential of lipid modulation as a therapeutic strategy in the management of MS. Statin therapy, initially investigated for its immunomodulatory and neuroprotective effects, has produced mixed results. While early studies suggested potential benefits in reducing neuroinflammation and brain atrophy, subsequent randomized controlled trials have shown limited efficacy in altering disease progression in relapsing-remitting MS.

Dietary interventions have emerged as a promising avenue for influencing lipid metabolism and modulating disease activity in MS. Although there is no definitive MS-specific diet, research suggests that the Mediterranean diet, which is rich in healthy fats and antioxidants, may have a preventive effect on disease progression.

Given the complex relationship between lipid metabolism, neurodegeneration, and MS pathology, future research should focus on personalized dietary and pharmacological interventions to optimize lipid homeostasis. Understanding how lipid modifications influence neuroinflammation, myelin integrity, and

BBB function may open new therapeutic avenues for neurodegenerative and demyelinating diseases.

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References

1. Kırnap Nazlı, G., *Lipit Biyokimyası ve Metabolizması* in *Geçmişten Geleceğe Endokrinoloji*. 2019, Turkish Endocrinology and Metabolism Society. p. 613-619.
2. Fahy, E., et al., *A comprehensive classification system for lipids.* J Lipid Res, 2005. 46(5): p. 839-61.
3. Fahy, E., et al., *Update of the LIPID MAPS comprehensive classification system for lipids.* J Lipid Res, 2009. 50 Suppl(Suppl): p. S9-14.
4. Calderon, R.O., B. Attema, and G.H. DeVries, *Lipid composition of neuronal cell bodies and neurites from cultured dorsal root ganglia.* J Neurochem, 1995. 64(1): p. 424-9.
5. Vance, J.E., R.B. Campenot, and D.E. Vance, *The synthesis and transport of lipids for axonal growth and nerve regeneration.* Biochim Biophys Acta, 2000. 1486(1): p. 84-96.
6. Simons, M. and J. Trotter, *Wrapping it up: the cell biology of myelination.* Curr Opin Neurobiol, 2007. 17(5): p. 533-40.
7. O'Brien, J.S., *Stability of the Myelin Membrane.* Science, 1965. 147(3662): p. 1099-107.
8. Reed, B., et al., *Associations between serum cholesterol levels and cerebral amyloidosis.* JAMA Neurol, 2014. 71(2): p. 195-200.
9. Kivipelto, M. and A. Solomon, *Cholesterol as a risk factor for Alzheimer's disease - epidemiological evidence.* Acta Neurol Scand Suppl, 2006. 185: p. 50-7.
10. Popp, J., et al., *Cerebral and extracerebral cholesterol metabolism and CSF markers of Alzheimer's disease.* Biochem Pharmacol, 2013. 86(1): p. 37-42.
11. Solomon, A., et al., *Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study.* Neurology, 2007. 68(10): p. 751-6.
12. Kivipelto, M., et al., *Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease.* Arch Neurol, 2005. 62(10): p. 1556-60.
13. Kuo, Y.M., et al., *Elevated low-density lipoprotein in Alzheimer's disease correlates with brain abeta 1-42 levels.* Biochem Biophys Res Commun, 1998. 252(3): p. 711-5.
14. An, Y., et al., *Longitudinal and nonlinear relations of dietary and Serum cholesterol in midlife with cognitive decline: results from EMCOA study.* Mol Neurodegener, 2019. 14(1): p. 51.
15. Anstey, K.J., K. Ashby-Mitchell, and R. Peters, *Updating the Evidence on the Association between Serum Cholesterol and Risk of Late-Life Dementia: Review and Meta-Analysis.* J Alzheimers Dis, 2017. 56(1): p. 215-228.
16. de Lau, L.M., et al., *Serum cholesterol levels and the risk of Parkinson's disease.* Am J Epidemiol, 2006. 164(10): p. 998-1002.
17. Jeong, S.M., W. Jang, and D.W. Shin, *Association of statin use with Parkinson's disease: Dose-response relationship.* Mov Disord, 2019. 34(7): p. 1014-1021.
18. Emamzadeh, F.N. and D. Allsop, *alpha-Synuclein Interacts with Lipoproteins in Plasma.* J Mol Neurosci, 2017. 63(2): p. 165-172.
19. de Oliveira, J., et al., *Diphenyl diselenide prevents cortico-cerebral mitochondrial dysfunction and oxidative stress induced by hypercholesterolemia in LDL receptor knockout mice.* Neurochem Res, 2013. 38(10): p. 2028-36.
20. Morris, J.K., et al., *Neurodegeneration in an animal model of Parkinson's disease is exacerbated by a high-fat diet.* Am J Physiol Regul Integr Comp Physiol, 2010. 299(4): p. R1082-90.
21. Lutjohann, D., et al., *Cholesterol homeostasis in human brain: evidence for an age-dependent flux of 24S-hydroxycholesterol from the brain into the circulation.* Proc Natl Acad Sci U S A, 1996. 93(18): p. 9799-804.
22. Wang, Y., E. Yutuc, and W.J. Griffiths, *Neuro-oxysterols and neuro-sterols as ligands to nuclear receptors, GPCRs, ligand-gated ion channels and other protein receptors.* Br J Pharmacol, 2021. 178(16): p. 3176-3193.
23. Saeed, A.A., et al., *Effects of a disrupted blood-brain barrier on cholesterol homeostasis in the brain.* J Biol Chem, 2014. 289(34): p. 23712-22.
24. Minagar, A. and J.S. Alexander, *Blood-brain barrier disruption in multiple sclerosis.* Mult Scler, 2003. 9(6): p. 540-9.
25. Lorincz, B., et al., *The role of cholesterol metabolism in multiple sclerosis: From molecular pathophysiology to radiological and clinical disease activity.* Autoimmun Rev, 2022. 21(6): p. 103088.
26. Glaria, E., N.A. Letelier, and A.F. Valledor, *Integrating the roles of liver X receptors in inflammation and infection: mechanisms and outcomes.* Curr Opin Pharmacol, 2020. 53: p. 55-65.
27. Wang, Z., et al., *Nuclear Receptor NR1H3 in Familial Multiple Sclerosis.* Neuron, 2016. 90(5): p. 948-54.
28. Berghoff, S.A., et al., *Microglia facilitate repair of demyelinated lesions via post-squalene sterol synthesis.* Nat Neurosci, 2021. 24(1): p. 47-60.
29. Fukumoto, H., et al., *Induction of the cholesterol transporter ABCA1 in central nervous system cells by liver X receptor agonists increases secreted Abeta levels.* J Biol Chem, 2002. 277(50): p. 48508-13.
30. McComb, M., et al., *Apolipoproteins AI and E are associated with neuroaxonal injury to gray matter in multiple sclerosis.* Mult Scler Relat Disord, 2020. 45: p. 102389.
31. Murali, N., et al., *Cholesterol and neurodegeneration: longitudinal changes in serum cholesterol biomarkers are associated with new lesions and gray matter atrophy in multiple sclerosis over 5 years of follow-up.* Eur J Neurol, 2020. 27(1): p. 188-e4.
32. Jakimovski, D., et al., *High density lipoprotein cholesterol and apolipoprotein A-I are associated with greater cerebral perfusion in multiple sclerosis.* J Neurol Sci, 2020. 418: p. 117120.
33. Tettey, P., et al., *Adverse lipid profile is not associated with relapse risk in MS: results from an observational cohort study.* J Neurol Sci, 2014. 340(1-2): p. 230-2.
34. Tettey, P., et al., *An adverse lipid profile and increased levels of adiposity significantly predict clinical course after a first demyelinating event.* J Neurol Neurosurg Psychiatry, 2017. 88(5): p. 395-401.
35. Weinstock-Guttman, B., et al., *Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis.* J Neuroinflammation, 2011. 8: p. 127.

36. Palavra, F., et al., *New markers of early cardiovascular risk in multiple sclerosis patients: oxidized-LDL correlates with clinical staging.* Dis Markers, 2013. 34(5): p. 341-8.
37. Gafson, A.R., et al., *Lipoprotein markers associated with disability from multiple sclerosis.* Sci Rep, 2018. 8(1): p. 17026.
38. Weinstock-Guttman, B., et al., *Lipid profiles are associated with lesion formation over 24 months in interferon-beta treated patients following the first demyelinating event.* J Neurol Neurosurg Psychiatry, 2013. 84(11): p. 1186-91.
39. Fellows, K., et al., *Protective associations of HDL with blood-brain barrier injury in multiple sclerosis patients.* J Lipid Res, 2015. 56(10): p. 2010-8.
40. Jende, J.M.E., et al., *Peripheral nerve involvement in multiple sclerosis: Demonstration by magnetic resonance neurography.* Ann Neurol, 2017. 82(5): p. 676-685.
41. van de Kraats, C., et al., *Oxysterols and cholesterol precursors correlate to magnetic resonance imaging measures of neurodegeneration in multiple sclerosis.* Mult Scler, 2014. 20(4): p. 412-7.
42. Lorincz, B., et al., *Lipid measures are associated with cognitive functioning in multiple sclerosis patients.* Mult Scler Relat Disord, 2024. 91: p. 105879.
43. Damiza-Detmer, A., M. Pawelczyk, and A. Glabinski, *Protective Role of High-Density Lipoprotein in Multiple Sclerosis.* Antioxidants (Basel), 2024. 13(11).
44. Greenwood, J., L. Steinman, and S.S. Zamvil, *Statin therapy and autoimmune disease: from protein prenylation to immunomodulation.* Nat Rev Immunol, 2006. 6(5): p. 358-70.
45. Greenwood, J., et al., *Lovastatin inhibits brain endothelial cell Rho-mediated lymphocyte migration and attenuates experimental autoimmune encephalomyelitis.* FASEB J, 2003. 17(8): p. 905-7.
46. Weber, M.S., et al., *Statins in the treatment of central nervous system autoimmune disease.* J Neuroimmunol, 2006. 178(1-2): p. 140-8.
47. Zamvil, S.S. and L. Steinman, *Cholesterol-lowering statins possess anti-inflammatory activity that might be useful for treatment of MS.* Neurology, 2002. 59(7): p. 970-1.
48. van der Most, P.J., et al., *Statins: mechanisms of neuroprotection.* Prog Neurobiol, 2009. 88(1): p. 64-75.
49. Giannopoulos, S., et al., *Statins and cerebral hemodynamics.* J Cereb Blood Flow Metab, 2012. 32(11): p. 1973-6.
50. Greenwood, J. and J.C. Mason, *Statins and the vascular endothelial inflammatory response.* Trends Immunol, 2007. 28(2): p. 88-98.
51. Waubant, E., et al., *Randomized controlled trial of atorvastatin in clinically isolated syndrome: the STAyCIS study.* Neurology, 2012. 78(15): p. 1171-8.
52. Sorensen, P.S., et al., *Simvastatin as add-on therapy to interferon beta-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN study): a placebo-controlled randomised phase 4 trial.* Lancet Neurol, 2011. 10(8): p. 691-701.
53. Tsakiri, A., et al., *Simvastatin improves final visual outcome in acute optic neuritis: a randomized study.* Mult Scler, 2012. 18(1): p. 72-81.
54. Chataway, J., et al., *Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial.* Lancet, 2014. 383(9936): p. 2213-21.
55. Blackstone, J., et al., *Evaluating the effectiveness of simvastatin in slowing the progression of disability in secondary progressive multiple sclerosis (MS-STAT2): protocol for a multicentre, randomised controlled, double-blind, phase 3 clinical trial in the UK.* BMJ Open, 2024. 14(9): p. e086414.
56. Zielinska, M. and I. Michonska, *Effectiveness of various diet patterns among patients with multiple sclerosis.* Postep Psychiatr Neurol, 2023. 32(1): p. 49-58.