REVIEW ARTICLE

Cholesterol and Dementia: A Long and Complicated Relationship

Oliwia McFarlane[1,*] and Kornelia Kędziora-Kornatowska[2]

[1]*Department of Public Health, Faculty of Health Sciences, Nicolaus Copernicus University Ludwik Rydygier Collegium Medicum, Bydgoszcz, Poland;* [2]*Department of Geriatrics, Faculty of Public Health, Nicolaus Copernicus University Ludwik Rydygier Collegium Medicum, Bydgoszcz, Poland*

Abstract: ***Background***: There is a huge demand for efficient strategies for maintaining cognitive wellbeing with age, especially in the context of population aging. Dementia constitutes the main reason for disability and dependency in the elderly. Identification of potential risk and protective factors, as well as determinants of conversion from MCI to dementia, is therefore crucial. In case of Alzheimer's disease, the most prevalent dementia syndrome amongst the members of modern societies, neurodegenerative processes in the brain can begin many years before first clinical symptoms appear. First functional changes typically mean advanced neuron loss, therefore, the earliest possible diagnosis is critical for implementation of promising early pharmaceutical interventions.

Objective: The study aimed to discuss the relationships between both circulating and brain cholesterol with cognition, and explore its potential role in early diagnosis of cognitive disorders.

Methods: Literature review.

Results: The causal role of high cholesterol levels in AD or MCI has not been confirmed. It has been postulated that plasma levels of 24(S)-OHC can potentially be used as an early biochemical marker of altered cholesterol homeostasis in the CNS. Some studies brought conflicting results, finding normal or lowered levels of 24(S)-OHC in dementia patients compared to controls. In spite of decades of research on the relationship between cholesterol and dementia, so far, no single trusted indicator of an early cognitive deterioration has been identified.

Conclusion: The current state of knowledge makes the use of cholesterol markers of cognitive decline in clinical practice impossible

1. INTRODUCTION

Advanced age is an important risk factor of dementia, which affects about 10% of people aged 65, with the rate reaching about 40% in 90-year olds [1]. According to the World Health Organization, around 50 million people worldwide suffer from dementia, and there are nearly 10 million new cases every year [2]. In the United States, every 65 seconds, an individual develops Alzheimer's disease [1]. In view of the predicted lifespan elongation, neurodegenerative diseases will soon become focal points in the health and social care systems of modern societies [3].

Dementia is a term used to describe different brain conditions with common characteristics of the loss of intellectual and cognitive functions [4, 5]. It refers to a clinical syndrome characterized by a progressive cognitive decline that interferes with the ability to function independently [6, 7]. Symptoms of dementia are gradual, persistent and progressive; individuals experience changes in cognition, function and behavior [8]. The clinical presentation of the syndrome varies greatly among individuals causing impairments such as memory loss, communication and language impairments, agnosia, apraxia and impaired executive function [9].

1.1. Dementia and Mild Cognitive Impairment

The process of neurodegeneration, resulting from the production of degenerated proteins, is at the heart of many neurological conditions and diseases [10]. Due to the fact that neurons cannot reproduce, the process is irreversible. The most prevalent neurodegenerative disease is Alzheimer's Disease (AD), comprising 60% to 80% of cases [11]. Dementia with Lewy Bodies (DLB) accounts for 15% of all dementias [12], and Frontotemporal Dementia (FTD) for 8 - 10% of the cases [13]. Vascular Dementia (VaD), the second most prevalent form (20%) [14] results from cerebrovascular disease, therefore a causal/temporal relationship between a vascular event and cognitive impairment has to be demonstrated [15]. The vascular disease frequently coexists with a cognitive decline in aging individuals, and shares many risk factors with dementia that are considered to be of the "Alzheimer-type," and are observed more frequently than that expected in postmortem material from individuals mani-

*Address correspondence to this author at the Department of Public Health, Faculty of Health Sciences, Nicolaus Copernicus University, Ludwik Rydygier Collegium Medicum in Bydgoszcz, P.O. Box: 85-830, Bydgoszcz, Poland; Tel/Fax: ++48-52-585-5408; E-mail: oliwia.beck@cm.umk.pl

festing disease stigmata such as abundant plaques and tangles [16, 17]. Other dementias, caused by potentially reversible factors [18] may occur in the course of infectious, metabolic, traumatic, toxic, and other diseases (Table **1**) [19]. Patients with cognitive deficits who do not meet the criteria for dementia are considered to have Mild Cognitive Impairment (MCI), an objective cognitive impairment with preserved function (Table **2**) [20].

Alzheimer's disease is clinically manifested by a progressive memory loss and impairment of other cognitive processes lasting over decades [21]. Major neuropathological hallmarks of the disease are the extracellular presence of beta-amyloid (Aβ) peptide, the intracellular accumulation of neurofibrillary tangles composed of hyperphosphorylated tau and the loss of cholinergic neurons in the brain [22, 23]. Tissue changes precede the onset of clinical signs by many years, and neuropathological lesions can be found in individuals who presently do not have symptoms, for they emerge many years after the initiation of the pathological processes in the brain, when neuronal and synaptic loss cannot be compensated anymore by brain plasticity [24]. Genetically, the disease is divided into familial cases and sporadic cases; a vast majority of them manifest as a late-onset sporadic form. Despite many years of research, a full understanding of the etiology of the sporadic form is not yet in reach [25]. The familial form is due to mutations in three major genes (Amyloid Precursor Protein (APP) gene, presenilin1 (PSEN1) gene and presenilin 2 (PSEN2) gene) and is

associated with a series of pathophysiological changes over decades in Cerebrospinal Fluid (CSF) biochemical markers, brain amyloid deposition, and brain metabolism as well as progressive cognitive impairment [26].

Mild cognitive impairment is a relatively new concept with the definition published by the American Neurological Academy in 2001 [27], and updated in 2018 [28]. Initially, the term defined a transitional state between cognitive changes accompanying the physiological aging process, and dementia, whereas currently, it is considered an independent clinical entity [6, 29]. As a group of evident and objective cognitive deficits in patients without dementia diagnosis, MCI is divided into 4 subtypes, of which, the amnestic one could constitute a prodromal stage of AD [30]. MCI is, however, much more heterogeneous than preclinical AD; patients report memory and/or other cognitive function deficits that do not impact the execution of basic everyday activities, but significantly decrease the quality of life through deterioration of complex daily activities [28, 30]. Current knowledge of MCI is limited. Empirical verification is needed specifically for identification of cases that convert into dementia, with cumulative dementia incidence being 14.9% in individuals with MCI older than 65 followed for 2 years, and those with relatively stable - or even improving - cognitive deficits, with reports varying between 14.4% and 55.6% of patients reverting to normal [28]. Due to the higher risk of developing dementia, early diagnosis and monitoring of all people with MCI are recommended. Such conduct forms the basis

Table 1.   Dementia types and characteristics.

DEMENTIA				
Term describing a collection of symptoms caused by disorders affecting the brain with common characteristics of the loss of intellectual and cognitive functions. It refers to a clinical syndrome characterized by progressive cognitive decline that interferes with the ability to function independently. Symptoms of dementia are gradual, persistent and progressive. The clinical presentation of the syndrome varies greatly among individuals causing impairments such as memory loss, communication and language impairments, agnosia, apraxia and impaired executive function.				
Alzheimer's Disease AD	Vascular Dementia VaD	Lewy Body Dementia DLB	Frontotemporal Dementia FTD	Other Dementias
60 - 80% of cases progressive memory loss and impairment of other cognitive processes visual/spatial and language impairment lasting over decades	20% of cases abrupt onset motor dysfunction, aphasia, mood/behavioral changes causal/temporal relationship between a vascular event and cognitive impairment	15% of cases visual hallucinations delusions, falls, fluctuating memory problems with movement and changes in mental abilities	8 - 10% of cases personality and behavior changes difficulties with language executive dysfunction disinhibition impulsivity	1% of cases caused by potentially reversible factors may occur in the course of infectious, metabolic, traumatic, toxic, and other diseases

Table 2.   Mild cognitive impairment types.

| MILD COGNITIVE IMPAIRMENT			
Term describing a group of evident and objective cognitive deficits in patients without dementia diagnosis and with preserved function. MCI is classified into two subtypes: amnestic and non-amnestic, based on the involvement of memory, and single domain or multiple domain, based on involvement of the number of cognitive domains affected.			
Single Domain		Multiple Domain	
Amnestic	Non-Amnestic	Amnestic	Non-Amnestic
Only memory affected	Single non-memory domain affected	Memory and other domains affected	Multiple non-memory domains affected
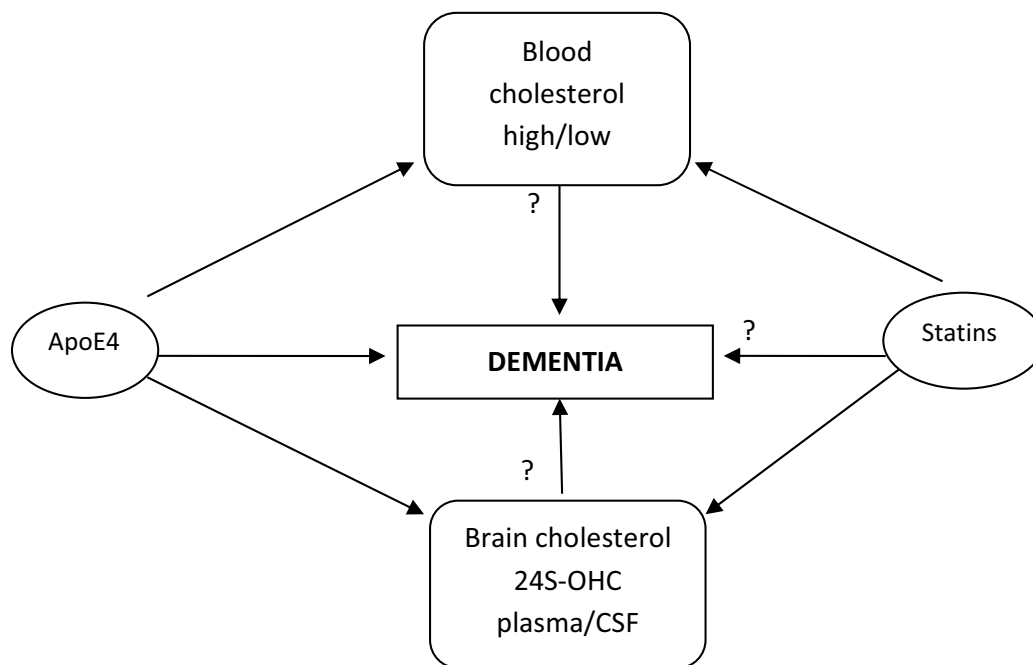
Fig. (1). Diagram comparing and contrasting discussed mechanisms/pathways of relationships between cholesterol and cognition.

Early findings indicated that hypercholesterolemia - expecially high midlife total cholesterol - can be an important risk factor of neurodegenerative diseases and dementia. However, causing role of high cholesterol levels in AD or MCI has not been confirmed and findings concerning circulating cholesterol and dementia are contradictory. The factor that has been suspected of having associations with neurodegeneration is an altered metabolism of brain cholesterol. There are findings suggesting that oxysterols are one of the main factors triggering AD. Because the vast majority of circulating 24(S)-OHC origins in the brain, it is suggested that its concentrations in the CSF and/or plasma can pose peripheral neuronal degeneration markers. It remains to be determined and a challenge to establish if brain cholesterol structure and functions are altered in dementia patients.

Statins, in addition to reducing blood lipids, have potential in regulating cholesterol metabolism in the brain, and supposed role in prevention and treatment of dementia. Their antioxidant and anti-inflammatory effects seem to promote cardiovascular and cerebrovascular health, and might confer neuroprotection through other mechanisms. In spite of a notion suggesting a protective effect of statin use on cognitive decline, it may be attributable to research bias. Initiation of statin use in late life does not seem to prevent cognitive decline and dementia over the subsequent years. The current literature does not address the questions of whether mid-life or long-term statin use have beneficial effects on cognition. In its most recent clinical guideline, the American Academy of Neurology does not address statin use to prevent dementia.

While ApoE is known to be the major mechanism of cholesterol transport within the brain, its direct involvement in AD pathogenesis is unknown and remains an important topic in AD research. Available findings suggest that ApoE status needs to be considered when assessing the relationship between lipid levels and AD risk in population studies and that cholesterol transport may play an important role in the progression of AD.

for deepening the diagnosis, and implementing therapy, and is dictated by obvious advantages to early treatment of dementia. Currently, no high-quality evidence exists to support pharmacologic treatments for MCI, but regular exercise and cognitive training are among the latest major recommendations [28].

1.2. Cholesterol

Cholesterol is a compound synthesized exclusively in animal organisms. About 60% of endogenous cholesterol in humans is produced in the liver, 15% in bowels, and the remainder in the skin. Cholesterol is an important structural component of nerve cells, and the brain is the most cholesterol-rich organ, containing about 20% of the total body's cholesterol [18]. Brain cholesterol exists in two pools: the plasma membranes of neurons and glial cells and the myelin membranes [31], with the majority (70%) located in the myelin [32]. Cholesterol is the main constituent of cell membranes [33]. In many neurons, it constitutes the myelin

sheath providing insulation for the conduction of nerve impulses; therefore, its loss greatly contributes to neurological problems. Cholesterol affects the functioning of brain synapses, and is crucial in production, and secretion of neurotransmitters. Cholesterol and lipid homeostasis are critical for normal brain function, including neuronal repair, membrane remodeling, and plasticity [34]. A link between cholesterol metabolism defects and neurodegenerative disorders is now recognized (Fig. **1**) [31].

Classical research on cholesterol and cognition was initiated decades ago by an interesting observation by Sparks *et al.*, who noticed senile plaques, resembling the ones in AD, in brains of patients with advanced Coronary Heart Disease (CHD) [35]. A subsequent research claimed that feeding rabbits with high cholesterol diet caused occurrences of plaques in the brain tissue [36]. Those initial studies sparked numerous research works on cholesterol and cognitive impairment, from searching for relationship between cholesterol and Aβ, to associating statins with AD, in both animals

and humans. Findings indicated that hypercholesterolemia – especially high midlife Total Cholesterol (TC) - increases the risk of late-life AD, and may correlate with the onset of AD pathology [37], suggesting that it can be an important risk factor for neurodegenerative diseases [38]. Some reports, mostly from retrospective epidemiological studies, mentioned lower AD prevalence among patients on 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly known as statins [39-44].

1.3. Cholesterol, Statins, and Dementia

Statins have been widely used clinically. They comprise the first-line drug therapy for the treatment of hyperlipidemia and prevention of CHD [45]. In addition to reducing blood lipids, their potential in regulating cholesterol metabolism in the brain, [46] and the supposed role in the prevention and treatment of dementia, have been eagerly discussed [47, 48]. Their antioxidant and anti-inflammatory effects seem to promote cardiovascular and cerebrovascular health [49, 50], and might confer neuroprotection through other mechanisms, *i.e.* lipophilic statins might cross the blood-brain barrier and exert antioxidant and anti-inflammatory effects within the CNS [49, 51]. Given the potential role of dyslipidemia in the development of dementia, statins have been proposed as potential therapeutic options to inhibit or prevent the disease [52]. Experiments in animal and cell models of AD also suggest that statins modulate both Aβ and brain tau metabolism [53, 54]; however, little evidence currently supports a similar effect in humans [49].

Statins have become a cornerstone of treatment for dyslipidemia mainly due to their marked lowering of Low-Density Lipoprotein Cholesterol (LDL-C). Findings suggest that statin treatment typically reduces the relative risk of cardiovascular disease by 24-37%, regardless of age, sex, prior history of CHD, or other co-morbid conditions [55]. Also, evidence that more intensive lipid-lowering regimens could provide additional clinical benefits, has been found [55]. A recent meta-analysis of 31 studies involving a total of 3332.706 participants with 184.666 incident cases found that statin use was associated with a reduction in AD and other forms of dementia risk in both women and men [48]. Although statin use potentially may be able to prevent cognitive impairment [56], growing concerns, partly due to the conflicting results of the associations between their use and dementia, have emerged [48].

In the United States, nearly 30% of adults aged 40 years and older are on statin [57]. It is the first choice cholesterol-lowering medication for 93% of them, with increasing use [58]. Its widespread use highlights the importance of careful consideration of its varied effects on the body. According to Power *et al*, previously discussed protective effect of decreasing the risk of dementia and improving cognitive impairment, reported from observational studies that considered statin use at or near the time of dementia diagnosis, could be attributable to reverse causation [59]. Moreover, statins have also been shown to have the ability to cause reversible cognitive impairment in some patients. However, well-designed randomized controlled trials have failed to find both cognitive impairing, and the beneficial effects. Two randomized controlled trials with 26.340 participants 40 to 82 years of age, including 11.610 individuals aged 70 years or older [60] comparing simvastatin and pravastatin with placebo over 5 and 3.2 years, respectively, with all of the participants in both study populations of a moderate to high vascular risk, found no differences in the number of patients who developed dementia or cognitive decline between those on statins or placebo. Both the studies were at low risk of bias, and there were no differences in the number of adverse effects leading to discontinuation [61]. It seems that firm conclusions about whether mid-life or long-term statin use has an impact on cognitive decline and dementia remain elusive. Randomized controlled trials do not support a causal preventative effect of late-life statin use on cognitive decline or dementia [59]. The contradicting results may be explained by seemingly independent mechanisms that have been hypothesized for each effect.

Stronger evidence, associating cholesterol with AD causally, was brought by experimental studies demonstrating that manipulating with cholesterol levels modified the levels of APP and Aβ [62]. However, there are numerous doubts about this hypothesis. Some studies did not find significant differences or even suggested that cholesterol levels of AD patients were lower than controls [63, 64]. Interestingly, it was postulated that the decline in cholesterol levels might actually contribute to the development of dementia [65]. According to the authors, the decline was unlikely to be explained by behavioral or metabolic changes associated with MCI, and the processes underlying it may represent occurrences early in the course of the disease or may be a marker for factors underlying both physical and cognitive decline in old age. As concluded, research on associations between cholesterol levels and risk of dementia should take into account the physical health status as it may have a modifying role [65]. In this instance, hypocholesterolemia might be associated with frailty, poor general health [66], inflammatory markers and poor nutritional status [67]. Finally, the latest longitudinal study demonstrated that higher visit-to-visit variability in TC, rather than mean TC, is associated with an increased risk of dementia and AD in the general population, which infers that variability in cholesterol level may be a novel predictor of upcoming dementia [68].

Also, prospective studies on statins and AD have not fully confirmed such relationships [69-71]. Clinical statin manipulations aimed at lowering cholesterol levels in order to prevent and cure neurodegeneration proved unsuccessful [72]. In addition, it has been postulated that the beneficial effect of statins could be a result of their anti-inflammatory rather than the cholesterol-lowering action [73]. Even experimental data is open to various interpretations as cholesterol level modifications typically impact many proteins, not limited to APP and beta-amyloid [74].

Summary of the key findings concerning statin effect on cognition suggests that initiation of statin use in late life does not seem to prevent cognitive decline and dementia over the subsequent years. The current literature does not address the questions of whether mid-life or long-term statin use has beneficial effects on cognition. Many findings indicate a protective effect of statin use on cognitive decline, but it may be attributable to research bias. Future observational work must incorporate study designs that minimize the potential

for bias, especially that, which is due to confounding and reverse causation [59]. In its most recent clinical guideline, the American Academy of Neurology does not address statin use to prevent dementia [75]. In view of the current knowledge, understanding its complex effects, together with the ability to identify patients at risk for or already experiencing cognitive impairment from statin use, as well as those who could potentially decrease their risk of dementia with statins seems crucial for health care providers [57].

Circulating cholesterol cannot penetrate the Blood-Brain Barrier (BBB) [18], although - interestingly - it has been shown that in a transgenic mouse model, a small amount of cholesterol from the periphery can enter the brain through the BBB and could play a role in hypercholesterolemia and the CSF levels of brain cholesterol [76]. Generally, the above premises do not confirm the causal role of high cholesterol levels in AD or MCI [38]. Molecular mechanisms constituting neurodegeneration are still not clear and currently, we are not in disposal of any certain biomarkers for early diagnosis [77]. Over the years, along with oxidative stress and neuroinflammation, the factor that has been suspected of having associations with neurodegeneration is an altered metabolism of brain cholesterol [78]. There are studies suggesting that oxidized derivatives of cholesterol - oxysterols (OHC) - are one of the main factors triggering AD [79, 80]. OHC are biologically active cholesterol metabolites that may be formed enzymatically or by autoxidative mechanisms [81]. OHC, such as 27-OHC, 24S-hydroxycholesterol (24(S)-OHC), 7α–OHC i 7β-OHC are not only able to penetrate the BBB but also have cytotoxic and proapoptotic characteristics. Of these, 24SOHC is the most abundant oxysterol in the brain, and potentially predominantly involved in neurodegenerative disorder pathogenesis [82].

1.4. 24(S)-Hydroxycholesterol

Defects in brain cholesterol metabolism were described in certain neurodegenerative diseases such as Sclerosis Multiplex and Huntington's Disease [83]. Because BBB effectively blocks cholesterol transport from circulation to cerebrospinal fluid, *de novo* synthesis is responsible for almost the entire cholesterol present in the brain [84]. The conversion of cholesterol to 24SOHC is catalyzed by cholesterol 24-hydroxylase (CYP46A1), which is predominantly expressed in the brain [32]. In the absence of neurodegeneration, concentrations of 24-OHC are relatively stable between the third and seventh decades of life. Beyond the six-decade of life, plasma levels of 24-OHC begin to decline with age [85] which parallels the decline in total brain volume with age [86]. Because the vast majority of circulating 24(S)-OHC originate in the brain, it is suggested that their concentrations in the CSF and/or plasma can pose peripheral neuronal degeneration markers of neurodegenerative diseases [87]. 24(S)-OHC is therefore an interesting, but a possible marker of neurodegeneration in general, probably also useful for AD [88].

Plasma concentrations of 24(S)-OHC depend on the balance between their production in the brain and elimination from the liver, and are associated with the number of metabolically active neurons. They are modified by cholesterol turnover factors, plasma lipoprotein metabolism, genetic

factors, and lifestyle [89]. It has been postulated that plasma levels of 24(S)-OHC can potentially be used as an early biochemical marker of altered cholesterol homeostasis in the Central Nervous System (CNS) [90]. Following studies brought conflicting results, finding normal [87] or lowered [91-93] levels of 24(S)-OHC in dementia compared to controls. Zuliani *et al.* suggest that plasma levels of 24(S)-hydroxycholesterol can be elevated in early phases of AD due to systemic inflammation [94]. Those findings support the hypothesis that higher levels of 24(S)-OHC in early AD occur when neurodegeneration coefficient is higher than normal, but the extent of neuron loss and brain atrophy remains relatively small, and these levels decrease with the disease progression, when neuronal damage provides higher levels of cholesterol to be converted into 24S-OHC [90, 91]. The exact mechanisms leading to an increase in plasma 24(S)-OHC levels in early stages of AD are not known. It is possible that cholesterol turnover is elevated due to neuronal degradation [94]. There are evidence that lowered plasma 24(S)-OHC levels in advanced stages of dementia are associated with the loss of metabolically active nerve cells and the atrophy degree of cell membranes. Blood-brain barrier dysfunctions, presence of inflammation, or elevated cholesterol turnover can all counteract this tendency, resulting in elevation, or, sometimes, alteration of those levels [87].

Unlike plasma 24S-OHC concentrations, the CSF levels seem to be more sensitive to modifications in the brain and not affected by hepatic clearance [95]. Therefore, they may be better markers for neurodegenerative diseases and disruptions of the BBB [96, 97]. It has been demonstrated that CSF 24S-OHC levels are significantly higher in the early stages of AD, and decrease with its progression, suggesting increased cholesterol turnover in the CNS during degeneration [87, 98], and reflecting the loss of cells expressing cholesterol 24-hydroxylase as the disease advances [99].

In spite of existing evidence on associations of oxysterols with neurodegenerative diseases, very few studies have focused on the assessment of the relationship between oxysterols and MCI, providing promising preliminary results suggesting that elevated levels of 24(S)-hydroxycholesterol [97] or 27-hydroxycholesterol [38] in CSF can be a sensitive marker of neurodegeneration in patients with MCI. The latest meta-analysis [100] points out that cholesterol, 24-OHC, and 27-OHC levels in CSF are elevated in MCI patients compared to controls, and that there is a significant dysfunction of cholesterol metabolism in the CSF of AD subjects. This indicates that in addition to the available biomarkers in the CSF, 24(S)-OHC, 27-OHC, and cholesterol appear to be sensitive biomarkers for the evaluation of MCI and AD. Authors postulate a mechanism in which cholesterol homeostasis is disturbed in preclinical AD, whereas metabolite dysregulation occurs throughout the disease process; changes in cholesterol and its metabolites might serve as additional biomarkers for the diagnosis and screening of AD. Most importantly, they might help identify a sub-group of AD patients with lipid metabolism dysregulation who might have different clinical presentations and clinical courses.

1.5. Cholesterol, ApoE and AD

Cholesterol's role in AD remained largely ignored until the discovery of Apolipoprotein E (ApoE) as the primary

genetic risk factor for sporadic AD (> 95% cases) [101]. The human ApoE gene exists as three different alleles, ε2, ε3, and ε4 [102], of which homozygous ApoE4 carriers are approximately 15-times more likely to develop the disease. With 25% of the population being ApoE4 carriers, understanding the role of this allele in AD pathogenesis and pathophysiology is crucial [103]. ApoE plays a pivotal role in lipoprotein metabolism in both the brain and periphery. The situation in the brain and in the periphery differs significantly; while CNS lipids are necessary for normal function, peripherial lipids are associated with risk of atherosclerotic lesions [104]. While ApoE is known to be the major mechanism of cholesterol transport within the brain, its direct involvement in AD pathogenesis is unknown and remains an important topic in AD research [88]. The association between ApoE, cholesterol and AD has been reviewed by several researchers [95, 105-112]. Among several mechanisms that have been proposed to explain that link, interesting hypotheses of impaired delivery of cholesterol from astrocytes to neurons, such that ApoE4 performs this activity less efficiently [113], and that of the three isoforms, ApoE4 is responsible for increasing cholesterol in the brain to a greater extent than ApoE3 [114], have been presented. The latter is supported by clinical findings and suggests that it could be a potential therapeutic target for disease prevention [115]. Converging evidence indicates a role of the relationships between ongoing deterioration of brain lipid homeostasis and vascular changes as risk factors for cardiovascular disease, such as high midlife plasma cholesterol, diabetes, stroke, obesity and hypertension, in the AD pathophysiology [115].

In spite of decades of intensive research, molecular mechanisms of ApoE4 promoting Alzheimer's disease, as well as processes mediated by this lipoprotein, which could be attractive pharmaceutical targets for the prevention and treatment of AD, are still unknown [103, 116]. Nonetheless, available findings suggest that ApoE status needs to be considered when assessing the relationship between lipid levels and AD risk in population studies [117] and that cholesterol transport may play an important role in the progression of AD [103].

CONCLUSION

If the expected lifespan elongation pace in the civilized countries maintains, the majority of newborns after the year 2000 will celebrate their 100 birthday [118]. The key question is: will this growth in life expectancy be accompanied by cognitive wellbeing or impairment? This debate, fueling decades of research on cholesterol in the context of cognitive performance, still remains open. Despite the plethora of studies on the relationships between both circulating cholesterol as a risk factor for cognitive decline, and brain cholesterol metabolism and dementia, so far no single trusted indicator of an early cognitive deterioration has been identified. The causal role of high cholesterol levels in AD or MCI has not been confirmed. It remains to be determined and a challenge to establish if brain cholesterol structure and functions are altered in dementia patients [74]. Future research aimed at identifying the mechanisms that underlie the effects of its metabolism and transport not only may provide important insight into the causes and interdependencies of cognitive impairment and dementia, but also inspire novel strategies

for treating and preventing these disorders. However, the current state of knowledge makes the use of cholesterol markers of cognitive decline in clinical practice impossible [119].

REFERENCES

[1]   Alzheimer's Disease Facts and Figures, an annual report released by the Alzheimer's Association. Available at: https://www.alz.org/alzheimers-dementia/facts-figures (Accessed May 2019).

[2]   World Health Organization, Dementia Factsheet. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia (Accessed May 2019).

[3]   Wimo A, Guerchet M, Ali GC, *et al*. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimers Dement 2017; 13(1): 1-7.
http://dx.doi.org/10.1016/j.jalz.2016.07.150 PMID: 27583652

[4]   American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed (DSM-5). Arlington, VA: American Psychiatric Publishing 2013.

[5]   World Health Organization. ICD-10 International Statistical Classification of Diseases and Related Health Problems 10. New York: World Health Organization 2008.

[6]   Chertkow H, Feldman HH, Jacova C, Massoud F. Definitions of dementia and predementia states in Alzheimer's disease and vascular cognitive impairment: Consensus from the Canadian conference on diagnosis of dementia. Alzheimers Res Ther 2013; 5(Suppl. 1): S2.
http://dx.doi.org/10.1186/alzrt198 PMID: 24565215

[7]   Sheehan B. Assessment scales in dementia. Ther Adv Neurol Disorder 2012; 5(6): 349-58.
http://dx.doi.org/10.1177/1756285612455733 PMID: 23139705

[8]   Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol 2012; 3: 73.
http://dx.doi.org/10.3389/fneur.2012.00073 PMID: 22586419

[9]   Chertkow H. Diagnosis and treatment of dementia: Introduction. Introducing a series based on the third Canadian consensus conference on the diagnosis and treatment of dementia. CMAJ 2008; 178(3): 316-21.
http://dx.doi.org/10.1503/cmaj.070795 PMID: 18227452

[10]   Arneson D, Zhang Y, Yang X, Narayanan M. Shared mechanisms among neurodegenerative diseases: From genetic factors to gene networks. J Genet 2018; 97(3): 795-806.
http://dx.doi.org/10.1007/s12041-018-0963-3 PMID: 30027910

[11]   Alzheimer's Association. Alzheimer's disease facts and figures. Alzheimers Dement 2012; 8(2): 131-68.
http://dx.doi.org/10.1016/j.jalz.2012.02.001 PMID: 22404854

[12]   Alzheimer Society of Canada. Lewy body dementia. Available at: www.alzheimer.ca/en/About-dementia/Dementias/Lewy-Body-Dementia (accessed May 2019).

[13]   Alzheimer Society of Canada. Front temporal dementia. Available at: www.alzheimer.ca/en/About-dementia/Dementias/ Frontotemporal-Dementia-and-Pick-s-disease (Accessed May 2019).

[14] Alzheimer Society of Canada. Vascular dementia. Available at: www.alzheimer.ca/en/About-dementia/Dementias/Vascular-Dementia (Accessed May 2019).

[15] Wiederkehr S, Simard M, Fortin C, van Reekum R. Validity of the clinical diagnostic criteria for vascular dementia: A critical review. Part II. J Neuropsychiatry Clin Neurosci 2008; 20(2): 162-77. http://dx.doi.org/10.1176/jnp.2008.20.2.162 PMID: 18451187

[16] Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci 2011; 12(12): 723-38. http://dx.doi.org/10.1038/nrn3114 PMID: 22048062

[17] Kling MA, Trojanowski JQ, Wolk DA, Lee VM, Arnold SE. Vascular disease and dementias: Paradigm shifts to drive research in new directions. Alzheimers Dement 2013; 9(1): 76-92. http://dx.doi.org/10.1016/j.jalz.2012.02.007 PMID: 23183137

[18] Björkhem I, Meaney S. Brain cholesterol: Long secret life behind a barrier. Arterioscler Thromb Vasc Biol 2004; 24(5): 806-15. http://dx.doi.org/10.1161/01.ATV.0000120374.59826.1b PMID: 14764421

[19] Chari D, Ali R, Gupta R. Reversible dementia in elderly: Really uncommon? J Geriatr Ment Health 2015; 2: 30-7. http://dx.doi.org/10.4103/2348-9995.161378

[20] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: Clinical characterization and outcome. Arch Neurol 1999; 56(3): 303-8. http://dx.doi.org/10.1001/archneur.56.3.303 PMID: 10190820

[21] Jack CR, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7(3): 257-62. http://dx.doi.org/10.1016/j.jalz.2011.03.004 PMID: 21514247

[22] Auld DS, Kornecook TJ, Bastianetto S, Quirion R. Alzheimer's disease and the basal forebrain cholinergic system: Relations to β-amyloid peptides, cognition, and treatment strategies. Prog Neurobiol 2002; 68(3): 209-45. http://dx.doi.org/10.1016/S0301-0082(02)00079-5 PMID: 12450488

[23] Selkoe DJ. American college of physicians. American physiological society. Alzheimer disease: Mechanistic understanding predicts novel therapies. Ann Intern Med 2004; 140(8): 627-38. http://dx.doi.org/10.7326/0003-4819-140-8-200404200-00047 PMID: 15096334

[24] Giaccone G, Arzberger T, Alafuzoff I, et al. New lexicon and criteria for the diagnosis of Alzheimer's disease. Lancet Neurol 2011; 10(4): 298-9. http://dx.doi.org/10.1016/S1474-4422(11)70055-2 PMID: 21435593

[25] Piaceri I, Nacmias B, Sorbi S. Genetics of familial and sporadic Alzheimer's disease. Front Biosci (Elite Ed) 2013; 5(1): 167-77. http://dx.doi.org/10.2741/E605 PMID: 23276979

[26] Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med 2012; 367(9): 795-804. http://dx.doi.org/10.1056/NEJMoa1202753 PMID: 22784036

[27] Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, Dekosky ST. Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9): 1133-42. http://dx.doi.org/10.1212/WNL.56.9.1133 PMID: 11342677

[28] Petersen RC, Lopez O, Armstrong MJ, et al. Practice guideline update summary: Mild cognitive impairment: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology 2018; 90(3): 126-35. http://dx.doi.org/10.1212/WNL.0000000000004826 PMID: 29282327

[29] Hildreth KL, Church S. Evaluation and management of the elderly patient presenting with cognitive complaints. Med Clin North Am 2015; 99(2): 311-35. http://dx.doi.org/10.1016/j.mcna.2014.11.006 PMID: 25700586

[30] Gauthier S, Reisberg B, Zaudig M, et al. International psychogeriatric association expert conference on mild cognitive impairment. Mild cognitive impairment. Lancet 2006; 367(9518): 1262-70. http://dx.doi.org/10.1016/S0140-6736(06)68542-5 PMID: 16631882

[31] Petrov AM, Kasimov MR, Zefirov AL. Brain cholesterol metabolism and its defects: Linkage to neurodegenerative diseases and synaptic dysfunction. Acta Naturae 2016; 8(1): 58-73. http://dx.doi.org/10.32607/20758251-2016-8-1-58-73 PMID: 27099785

[32] Russell DW, Halford RW, Ramirez DM, Shah R, Kotti T. Cholesterol 24-hydroxylase: An enzyme of cholesterol turnover in the brain. Annu Rev Biochem 2009; 78: 1017-40. http://dx.doi.org/10.1146/annurev.biochem.78.072407.103859 PMID: 19489738

[33] Herz J, Bock HH. Lipoprotein receptors in the nervous system. Annu Rev Biochem 2002; 71: 405-34. http://dx.doi.org/10.1146/annurev.biochem.71.110601.135342 PMID: 12045102

[34] Mahley RW, Rall SC. Apolipoprotein E. far more than a lipid transport protein. Annu Rev Genomics Hum Genet 2000; 1: 507-37. http://dx.doi.org/10.1146/annurev.genom.1.1.507 PMID: 11701639

[35] Sparks DL, Hunsaker JC, Scheff SW, Kryscio RJ, Henson JL, Markesbery WR. Cortical senile plaques in coronary artery disease, aging and Alzheimer's disease. Neurobiol Aging 1990; 11(6): 601-7. http://dx.doi.org/10.1016/0197-4580(90)90024-T PMID: 1704106

[36] Sparks DL, Scheff SW, Hunsaker JC, Liu H, Landers T, Gross DR. Induction of Alzheimer-like beta-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. Exp Neurol 1994; 126(1): 88-94. http://dx.doi.org/10.1006/exnr.1994.1044 PMID: 8157129

[37] Anstey KJ, Ashby-Mitchell K, Peters R. 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): 215-28. http://dx.doi.org/10.3233/JAD-160826 PMID: 27911314

[38] Liu Q, An Y, Yu H, et al. Relationship between oxysterols and mild cognitive impairment in the elderly: A case-control study. Lipids Health Dis 2016; 15(1): 177. http://dx.doi.org/10.1186/s12944-016-0344-y PMID: 27724967

[39] Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. Lancet 2000; 356(9242): 1627-31. http://dx.doi.org/10.1016/S0140-6736(00)03155-X PMID: 11089820

[40] Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme: A reductase inhibitors. Arch Neurol 2000; 57(10): 1439-43. http://dx.doi.org/10.1001/archneur.57.10.1439 PMID: 11030795

[41] Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. Arch Neurol 2002; 59(3): 378-84. http://dx.doi.org/10.1001/archneur.59.3.378 PMID: 11890840

[42] Wolozin B, Wang SW, Li NC, Lee A, Lee TA, Kazis LE. Simvastatin is associated with a reduced incidence of dementia and Parkinson's disease. BMC Med 2007; 5: 20. http://dx.doi.org/10.1186/1741-7015-5-20 PMID: 17640385

[43] Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD. Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology 2008; 71(5): 344-50. http://dx.doi.org/10.1212/01.wnl.0000319647.15752.7b PMID: 18663180

[44] Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity: The rotterdam study. J Neurol Neurosurg Psychiatry 2009; 80(1): 13-7. http://dx.doi.org/10.1136/jnnp.2008.150433 PMID: 18931004

[45] Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. JAMA 1996; 275(1): 55-60. http://dx.doi.org/10.1001/jama.1996.03530250059028 PMID: 8531288

[46] Vaughan CJ. Prevention of stroke and dementia with statins: Effects beyond lipid lowering. Am J Cardiol 2003; 91(4A): 23B-9B. http://dx.doi.org/10.1016/S0002-9149(02)03270-8 PMID: 12615295

[47] Cucchiara B, Kasner SE. Use of statins in CNS disorders. J Neurol Sci 2001; 187(1-2): 81-9. http://dx.doi.org/10.1016/S0022-510X(01)00529-9 PMID: 11440749

[48]   Zhang X, Wen J, Zhang Z. Statins use and risk of dementia: A dose-response meta analysis. Medicine (Baltimore) 2018; 97(30): e11304.
http://dx.doi.org/10.1097/MD.0000000000011304 PMID: 30045255

[49]   Miida T, Takahashi A, Ikeuchi T. Prevention of stroke and dementia by statin therapy: Experimental and clinical evidence of their pleiotropic effects. Pharmacol Ther 2007; 113(2): 378-93.
http://dx.doi.org/10.1016/j.pharmthera.2006.09.003 PMID: 17113151

[50]   Bifulco M, Malfitano AM, Marasco G. Potential therapeutic role of statins in neurological disorders. Expert Rev Neurother 2008; 8(5): 827-37.
http://dx.doi.org/10.1586/14737175.8.5.827 PMID: 18457539

[51]   Sierra S, Ramos MC, Molina P, Esteo C, Vázquez JA, Burgos JS. Statins as neuroprotectants: A comparative *in vitro* study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. J Alzheimers Dis 2011; 23(2): 307-18.
http://dx.doi.org/10.3233/JAD-2010-101179 PMID: 21098985

[52]   Wanamaker BL, Swiger KJ, Blumenthal RS, Martin SS. Cholesterol, statins, and dementia: What the cardiologist should know. Clin Cardiol 2015; 38(4): 243-50.
http://dx.doi.org/10.1002/clc.22361 PMID: 25869997

[53]   Pollen DA, Baker S, Hinerfeld D, *et al*. Prevention of Alzheimer's disease in high risk groups: Statin therapy in subjects with PSEN1 mutations or heterozygosity for apolipoprotein E ε 4. Alzheimers Res Ther 2010; 2(5): 31.
http://dx.doi.org/10.1186/alzrt55 PMID: 21062519

[54]   Li G, Larson EB, Sonnen JA, *et al*. Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. Neurology 2007; 69(9): 878-85.
http://dx.doi.org/10.1212/01.wnl.0000277657.95487.1c PMID: 17724290

[55]   Stroes E. Statins and LDL-cholesterol lowering: An overview. Curr Med Res Opin 2005; 21(Suppl. 6): S9-S16.
http://dx.doi.org/10.1185/030079905X59102 PMID: 16138936

[56]   Chong PH, Seeger JD, Franklin C. Clinically relevant differences between the statins: Implications for therapeutic selection. Am J Med 2001; 111(5): 390-400.
http://dx.doi.org/10.1016/S0002-9343(01)00870-1 PMID: 11583643

[57]   Schultz BG, Patten DK, Berlau DJ. The role of statins in both cognitive impairment and protection against dementia: A tale of two mechanisms. Transl Neurodegener 2018; 7: 5.
http://dx.doi.org/10.1186/s40035-018-0110-3 PMID: 29507718

[58]   Gu Q, Paulose-Ram R, Burt VL, Kit BK. Prescription cholesterol-lowering medication use in adults aged 40 and over: United States, 2003-2012. NCHS Data Brief 2014; 177(177): 1-8.
httpMID: 25536410

[59]   Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia-systematic review and methodological commentary. Nat Rev Neurol 2015; 11(4): 220-9.
http://dx.doi.org/10.1038/nrneurol.2015.35 PMID: 25799928

[60]   McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2016; 1: CD003160.
httpMID: 26727124

[61]   Bunt CW, Hogan AJ. The effect of statins on dementia and cognitive decline. Am Fam Physician 2017; 95(3): 151-2.
httpMID: 28145677

[62]   Friedhoff LT, Cullen EI, Geoghagen NS, Buxbaum JD. Treatment with controlled-release lovastatin decreases serum concentrations of human beta-amyloid (A beta) peptide. Int J Neuropsychopharmacol 2001; 4(2): 127-30.
http://dx.doi.org/10.1017/S1461145701002310 PMID: 11466161

[63]   Romas SN, Tang MX, Berglund L, Mayeux R. APOE genotype, plasma lipids, lipoproteins, and AD in community elderly. Neurology 1999; 53(3): 517-21.
http://dx.doi.org/10.1212/WNL.53.3.517 PMID: 10449113

[64]   Knittweis JW, McMullen WA. The effect of apoE on dementia is not through atherosclerosis: The Rotterdam study. Neurology 2000; 54(12): 2356-8.
http://dx.doi.org/10.1212/WNL.54.12.2356-a PMID: 10881278

[65]   Stewart R, White LR, Xue QL, Launer LJ. Twenty-six-year change in total cholesterol levels and incident dementia: The Honolulu-Asia aging study. Arch Neurol 2007; 64(1): 103-7.
http://dx.doi.org/10.1001/archneur.64.1.103 PMID: 17210816

[66]   Corti MC, Guralnik JM, Salive ME, *et al*. Clarifying the direct relation between total cholesterol levels and death from coronary heart disease in older persons. Ann Intern Med 1997; 126(10): 753-60.
http://dx.doi.org/10.7326/0003-4819-126-10-199705150-00001 PMID: 9148647

[67]   Hu P, Seeman TE, Harris TB, Reuben DB. Does inflammation or undernutrition explain the low cholesterol-mortality association in high-functioning older persons? MacArthur studies of successful aging. J Am Geriatr Soc 2003; 51(1): 80-4.
http://dx.doi.org/10.1034/j.1601-5215.2002.51014.x PMID: 12534850

[68]   Chung HS, Lee JS, Kim JA, *et al*. Variability in total cholesterol concentration is associated with the risk of dementia: A nationwide population-based cohort study. Front Neurol 2019; 10: 441.
http://dx.doi.org/10.3389/fneur.2019.00441 PMID: 31133961

[69]   Zandi PP, Sparks DL, Khachaturian AS, *et al*. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. Arch Gen Psychiatry 2005; 62(2): 217-24.
http://dx.doi.org/10.1001/archpsyc.62.2.217 PMID: 15699299

[70]   Rea TD, Breitner JC, Psaty BM, *et al*. Statin use and the risk of incident dementia: The cardiovascular health study. Arch Neurol 2005; 62(7): 1047-51.
http://dx.doi.org/10.1001/archneur.62.7.1047 PMID: 16009757

[71]   McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Cochrane review on 'statins for the treatment of dementia'. Int J Geriatr Psychiatry 2013; 28(2): 119-26.
http://dx.doi.org/10.1002/gps.3797 PMID: 22473869

[72]   McGuinness B, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. Cochrane Database Syst Rev 2014; 7(7): CD007514.
httpMID: 25004278

[73]   Ledesma MD, Dotti CG. Amyloid excess in Alzheimer's disease: What is cholesterol to be blamed for? FEBS Lett 2006; 580(23): 5525-32.
http://dx.doi.org/10.1016/j.febslet.2006.06.038 PMID: 16814780

[74]   Wood WG, Li L, Müller WE, Eckert GP. Cholesterol as a causative factor in Alzheimer's disease: A debatable hypothesis. J Neurochem 2014; 129(4): 559-72.
http://dx.doi.org/10.1111/jnc.12637 PMID: 24329875

[75]   Doody RS, Stevens JC, Beck C, *et al*. Practice parameter: Management of dementia (an evidence-based review). Report of the quality standards subcommittee of the American academy of neurology. Neurology 2001; 56(9): 1154-66.
http://dx.doi.org/10.1212/WNL.56.9.1154 PMID: 11342679

[76]   Refolo LM, Malester B, LaFrancois J, *et al*. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiol Dis 2000; 7(4): 321-31.
http://dx.doi.org/10.1006/nbdi.2000.0304 PMID: 10964604

[77]   Agrawal M, Biswas A. Molecular diagnostics of neurodegenerative disorders. Front Mol Biosci 2015; 2: 54.
http://dx.doi.org/10.3389/fmolb.2015.00054 PMID: 26442283

[78]   Martín MG, Pfrieger F, Dotti CG. Cholesterol in brain disease: Sometimes determinant and frequently implicated. EMBO Rep 2014; 15(10): 1036-52.
http://dx.doi.org/10.15252/embr.201439225 PMID: 25223281

[79]   Popp J, Lewczuk P, Kölsch H, *et al*. Cholesterol metabolism is associated with soluble amyloid precursor protein production in Alzheimer's disease. J Neurochem 2012; 123(2): 310-6.
http://dx.doi.org/10.1111/j.1471-4159.2012.07893.x PMID: 22845771

[80]   Popp J, Meichsner S, Kölsch H, *et al*. Cerebral and extracerebral cholesterol metabolism and CSF markers of Alzheimer's disease. Biochem Pharmacol 2013; 86(1): 37-42.
http://dx.doi.org/10.1016/j.bcp.2012.12.007 PMID: 23291240

[81]   Dias IHK, Milic I, Lip GYH, Devitt A, Polidori MC, Griffiths HR. Simvastatin reduces circulating oxysterol levels in men with hypercholesterolaemia. Redox Biol 2018; 16: 139-45.
http://dx.doi.org/10.1016/j.redox.2018.02.014 PMID: 29501047

[82]   Testa G, Staurenghi E, Zerbinati C, *et al*. Changes in brain oxysterols at different stages of Alzheimer's disease: Their involvement in neuroinflammation. Redox Biol 2016; 10: 24-33.

http://dx.doi.org/10.1016/j.redox.2016.09.001 PMID: 27687218

[83] Karasinska JM, Hayden MR. Cholesterol metabolism in Huntington disease. Nat Rev Neurol 2011; 7(10): 561-72.
http://dx.doi.org/10.1038/nrneurol.2011.132 PMID: 21894212

[84] Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH. Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B,E(LDL) receptors in the brain. J Biol Chem 1987; 262(29): 14352-60.
httpMID: 3115992

[85] Björkhem I. Crossing the barrier: Oxysterols as cholesterol transporters and metabolic modulators in the brain. J Intern Med 2006; 260(6): 493-508.
http://dx.doi.org/10.1111/j.1365-2796.2006.01725.x PMID: 17116000

[86] Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. Neurology 2005; 64(6): 1032-9.
http://dx.doi.org/10.1212/01.WNL.0000154530.72969.11 PMID: 15781822

[87] Schönknecht P, Lütjohann D, Pantel J, et al. Cerebrospinal fluid 24S-hydroxycholesterol is increased in patients with Alzheimer's disease compared to healthy controls. Neurosci Lett 2002; 324(1): 83-5.
http://dx.doi.org/10.1016/S0304-3940(02)00164-7 PMID: 11983301

[88] Hughes TM, Rosano C, Evans RW, Kuller LH. Brain cholesterol metabolism, oxysterols, and dementia. J Alzheimers Dis 2013; 33(4): 891-911.
http://dx.doi.org/10.3233/JAD-2012-121585 PMID: 23076077

[89] Leoni V, Caccia C. 24S-hydroxycholesterol in plasma: A marker of cholesterol turnover in neurodegenerative diseases. Biochimie 2013; 95(3): 595-612.
http://dx.doi.org/10.1016/j.biochi.2012.09.025 PMID: 23041502

[90] Lütjohann D, Papassotiropoulos A, Björkhem I, et al. Plasma 24S-hydroxycholesterol (cerebrosterol) is increased in Alzheimer and vascular demented patients. J Lipid Res 2000; 41(2): 195-8.
httpMID: 10681402

[91] Bretillon L, Sidén A, Wahlund LO, et al. Plasma levels of 24S-hydroxycholesterol in patients with neurological diseases. Neurosci Lett 2000; 293(2): 87-90.
http://dx.doi.org/10.1016/S0304-3940(00)01466-X PMID: 11027840

[92] Kölsch H, Heun R, Kerksiek A, Bergmann KV, Maier W, Lütjohann D. Altered levels of plasma 24S- and 27-hydroxycholesterol in demented patients. Neurosci Lett 2004; 368(3): 303-8.
http://dx.doi.org/10.1016/j.neulet.2004.07.031 PMID: 15364416

[93] Solomon A, Leoni V, Kivipelto M, et al. Plasma levels of 24S-hydroxycholesterol reflect brain volumes in patients without objective cognitive impairment but not in those with Alzheimer's disease. Neurosci Lett 2009; 462(1): 89-93.
http://dx.doi.org/10.1016/j.neulet.2009.06.073 PMID: 19560513

[94] Zuliani G, Donnorso MP, Bosi C, et al. Plasma 24S-hydroxycholesterol levels in elderly subjects with late onset Alzheimer's disease or vascular dementia: A case-control study. BMC Neurol 2011; 11: 121.
http://dx.doi.org/10.1186/1471-2377-11-121 PMID: 21970714

[95] de Chaves EP, Narayanaswami V. Apolipoprotein E and cholesterol in aging and disease in the brain. Future Lipidol 2008; 3(5): 505-30.
http://dx.doi.org/10.2217/17460875.3.5.505 PMID: 19649144

[96] Leoni V, Masterman T, Mousavi FS, et al. Diagnostic use of cerebral and extracerebral oxysterols. Clin Chem Lab Med 2004; 42(2): 186-91.
http://dx.doi.org/10.1515/CCLM.2004.034 PMID: 15061359

[97] Leoni V, Shafaati M, Salomon A, Kivipelto M, Björkhem I, Wahlund LO. Are the CSF levels of 24S-hydroxycholesterol a sensitive biomarker for mild cognitive impairment? Neurosci Lett 2006; 397(1-2): 83-7.
http://dx.doi.org/10.1016/j.neulet.2005.11.046 PMID: 16406316

[98] Leoni V, Masterman T, Patel P, Meaney S, Diczfalusy U, Björkhem I. Side chain oxidized oxysterols in cerebrospinal fluid and the integrity of blood-brain and blood-cerebrospinal fluid barriers. J Lipid Res 2003; 44(4): 793-9.
http://dx.doi.org/10.1194/jlr.M200434-JLR200 PMID: 12562838

[99] Papassotiropoulos A, Lütjohann D, Bagli M, et al. 24S-hydroxycholesterol in cerebrospinal fluid is elevated in early stages of dementia. J Psychiatr Res 2002; 36(1): 27-32.
http://dx.doi.org/10.1016/S0022-3956(01)00050-4 PMID: 11755458

[100] Wang HL, Wang YY, Liu XG, et al. Cholesterol, 24-hydroxycholesterol, and 27-hydroxycholesterol as surrogate biomarkers in cerebrospinal fluid in mild cognitive impairment and alzheimer's disease: A meta-analysis. J Alzheimers Dis 2016; 51(1): 45-55.
http://dx.doi.org/10.3233/JAD-150734 PMID: 26836015

[101] Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993; 261(5123): 921-3.
http://dx.doi.org/10.1126/science.8346443 PMID: 8346443

[102] Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: The alzgene database. Nat Genet 2007; 39(1): 17-23.
http://dx.doi.org/10.1038/ng1934 PMID: 17192785

[103] Holly CH, Priyanka DP, Warren S, Vishnu S, Miranda NR. The role of APOE4 in Alzheimer's disease: Strategies for future therapeutic interventions. Neur Sig 2019; 3(2): NS20180203.
http://dx.doi.org/10.1042/NS20180203

[104] Rasmussen KL. Plasma levels of apolipoprotein E, APOE genotype and risk of dementia and ischemic heart disease: A review. Atherosclerosis 2016; 255: 145-55.
http://dx.doi.org/10.1016/j.atherosclerosis.2016.10.037 PMID: 28340945

[105] Michikawa M. Role of cholesterol in amyloid cascade: Cholesterol-dependent modulation of tau phosphorylation and mitochondrial function. Acta Neurol Scand Suppl 2006; 185: 21-6.
http://dx.doi.org/10.1111/j.1600-0404.2006.00681.x PMID: 16866907

[106] Shobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. Lancet Neurol 2005; 4(12): 841-52.
http://dx.doi.org/10.1016/S1474-4422(05)70248-9 PMID: 16297842

[107] Poirier J. Apolipoprotein E represents a potent gene-based therapeutic target for the treatment of sporadic Alzheimer's disease. Alzheimers Dement 2008; 4(1): S91-7.
http://dx.doi.org/10.1016/j.jalz.2007.11.012 PMID: 18632009

[108] Hirsch-Reinshagen V, Wellington CL. Cholesterol metabolism, apolipoprotein E, adenosine triphosphate-binding cassette transporters, and Alzheimer's disease. Curr Opin Lipidol 2007; 18(3): 325-32.
http://dx.doi.org/10.1097/MOL.0b013e32813aeabf PMID: 17495608

[109] Poirier J. Apolipoprotein E, cholesterol transport and synthesis in sporadic Alzheimer's disease. Neurobiol Aging 2005; 26(3): 355-61.
http://dx.doi.org/10.1016/j.neurobiolaging.2004.09.003 PMID: 15639314

[110] Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: A causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci USA 2006; 103(15): 5644-51.
http://dx.doi.org/10.1073/pnas.0600549103 PMID: 16567625

[111] Mahley RW, Huang Y, Weisgraber KH. Detrimental effects of apolipoprotein E4: Potential therapeutic targets in Alzheimer's disease. Curr Alzheimer Res 2007; 4(5): 537-40.
http://dx.doi.org/10.2174/156720507783018334 PMID: 18220516

[112] Fenili D, McLaurin J. Cholesterol and apoe: A target for Alzheimer's disease therapeutics. Curr Drug Targets CNS Neurol Disord 2005; 4(5): 553-67.
http://dx.doi.org/10.2174/1568007057743220085 PMID: 16266288

[113] Pfrieger FW. Outsourcing in the brain: Do neurons depend on cholesterol delivery by astrocytes? BioEssays 2003; 25(1): 72-8.
http://dx.doi.org/10.1002/bies.10195 PMID: 12508285

[114] Castellano JM, Kim J, Stewart FR, et al. Human apoE isoforms differentially regulate brain amyloid-β peptide clearance. Sci Transl Med 2011; 3(89): 89ra57.
http://dx.doi.org/10.1126/scitranslmed.3002156 PMID: 21715678

[115] Leduc V, Jasmin-Bélanger S, Poirier J. APOE and cholesterol homeostasis in Alzheimer's disease. Trends Mol Med 2010; 16(10): 469-77.
http://dx.doi.org/10.1016/j.molmed.2010.07.008 PMID: 20817608

[116]   Lahiri DK. Apolipoprotein E as a target for developing new thera-
        peutics for Alzheimer's disease based on studies from protein,
        RNA, and regulatory region of the gene. J Mol Neurosci 2004;
        23(3): 225-33.
        http://dx.doi.org/10.1385/JMN:23:3:225 PMID: 15181251
[117]   Hall K, Murrell J, Ogunniyi A, *et al*. Cholesterol, APOE genotype,
        and Alzheimer disease: An epidemiologic study of Nigerian
        Yoruba. Neurology 2006; 66(2): 223-7.

        http://dx.doi.org/10.1212/01.wnl.0000194507.39504.17 PMID:
        16434658
[118]   Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing popu-
        lations: The challenges ahead. Lancet 2009; 374(9696): 1196-208.
        http://dx.doi.org/10.1016/S0140-6736(09)61460-4 PMID:
        19801098
[119]   Humpel C, Hochstrasser T. Cerebrospinal fluid and blood biomark-
        ers in Alzheimer's disease. World J Psychiatry 2011; 1(1): 8-18.
        http://dx.doi.org/10.5498/wjp.v1.i1.8 PMID: 24175162