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Literature Reviews

Atherosclerosis and Alzheimer's Disease Interconnection: Inflammation, Aβ and More

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Abstract: Despite being the leading cause of CVD and cardiovascular mortality globally, Atherosclerosis (ATH) remains underdiagnosed and undertreated. The reasons behind Alzheimer's Disease (AD) also remain unclear and there is currently no cure for it. At present, at least 55 million people are believed to be suffering from the disorder and the figures are expected to grow. At the same time, multiple data suggest that the most common risk factors for both conditions interfere and that timely risk management and effective prevention strategies could allow a significant reduction in the prevalence of the disorders, which indicates a need for more research on mechanisms underlying the conditions as well as their interconnection. In this review, the interplay between ATH and AD will be examined. We will look into both the modifiable and non-modifiable risk factors the diseases have in common. Since both disorders have complex pathophysiology, we will summarize the recent data on how associated processes in atherosclerosis affect the development of Alzheimer's disease and vice versa.

Keywords: Amyloid Beta, Alzheimer's Disease, Atherosclerosis, Neurodegenerative Disease

Epidemiologic Evidence and Imaging

Epidemiological studies involving the entire population have considerably broadened our comprehension that the pathogenesis of Alzheimer's Disease (AD) is more extensive than what neuron research solely concentrated on Amyloid Precursor Protein (APP) and Amyloid Beta (Aβ) would suggest. There is a considerable amount of proof indicating that the risk factors for vascular conditions related to atherosclerosis, such as older age, hyperlipidemia, and diabetes, also may lead to AD development (Lukiw, 2012). For instance, a study following a group of over 1100 people without dementia at the beginning demonstrated that smoking, cardiac disorders, elevated blood pressure, and diabetes posed a threat to AD development. Furthermore, the combination of three or more of these factors together augmented the risk of manifested AD development by 3.4 times (Petrie *et al*., 2018). Besides, in the Rotterdam Scan Study, where 1015 subjects underwent MRI, researchers discovered that "silent" ischemic strokes enhanced the risk of dementia by about 2.3 times during an average of 3.6 years of follow-up and most of the cases exhibited clinical proof of AD (Ikram *et al*., 2015).

Newer research has demonstrated that particular vascular risk factors forecast not only clinically diagnosed AD but also amyloid aggregation. In cross-sectional research of subjects with non-impaired or mildly impaired cognition, Reed and colleagues evaluated *in vivo* amyloid load in the brain with 11C-Pittsburgh compound B (PIB) Positron Emission Tomography (PET) to reveal that an elevated Framingham risk score autonomously accounted for a considerable proportion of brain amyloid depositions (Reed *et al*., 2004). Similar PIB-based imaging studies have singled out high blood pressure, increased LDL-c, and low HDL-c as particular vascular risk factors that increase brain amyloidosis. Given such increasing evidence, Barnes and Yaffe have recently proposed that up to 50% of the AD

cases internationally (more than 17 million) may be potentially due to vascular risk factors and that reducing these hazards by 10-25% could avert over a million AD cases across the globe (Barnes and Yaffe, 2011).

Clinical-Pathological Evidence

Further clinical-pathological investigations have established a correlation between AD and ischemic brain lesions. For instance, when the Nun study conducted an autopsy analysis of the brains of 61 females with neuropathologic AD manifestation, women who had concomitant ischemic strokes showed impaired cognition and increased occurrence of dementia compared to women without strokes (Snowdon, 2003). Specifically, subjects with lacunar strokes in the thalamus, basal nuclei, or white matter lesions showed an almost 20 times higher chance of dementia than subjects without strokes. At the same time, the 41 participants without clinical signs of AD, but with brain stroke demonstrated only a weak connection with dementia and poor cognitive function. In spite of the fact that the vascular disorder causing the ischemic lesions was not determined, these results propose that the clinical manifestation of AD may be caused by cerebrovascular impairment (Cannistraro *et al.*, 2019). In another broad cross-sectional study, the data was examined of more than 1000 patients in the database of the United States National Alzheimer's coordinating center. It was discovered that atherosclerosis of main cerebral vessels was significantly linked with neuritic plaques, a primary pathologic AD expression (Gupta and Iadecola, 2015). Nevertheless, other studies have not discovered a connection between AD and atherosclerotic impairment of cerebral vessels, which may be a result of different selection of research subjects. Still, the accumulated evidence endorses the idea that ischemic cerebral lesions intensify cognitive impairments in AD and implies that vascular disorder and AD are closely related to the manifestation of dementia (Roher *et al*., 2011a).

Other clinical investigations have concentrated on more immediate evaluations of vascular atherosclerosis. Aspects of atherosclerosis in the circle of Willis were examined in an autopsy study of 32 patients with AD and 22 subjects in the control group. The study identified cases of intracranial artery stenosis on the grounds of histopathological image analysis of vessels cut into cross-sections and scrutinized under a dissecting microscope to define narrowed vessels due to atheroma (Yang *et al*., 2017). Results indicated that in AD patients, the cerebral arterial circle showed considerably more frequent and serious intracranial stenosis compared to the control group. Additionally, the study revealed that a generalized measurement of the intracranial atherosclerosis burden had a strong association with various AD neuropathology markers, like neurofibrillary tangles, atheromas, and braak scores. Later, neuropathological studies on a larger scale substantiated the significant, independent correlation between AD and cerebral atherosclerotic disease after adjusting for sex, age, and APOE4 allele status (Bang, 2014). Recently, a study involving 1000 subjects with macroscopic and microscopic neuropathology demonstrated that 77 percent of AD patients had grossly manifested atherosclerotic impairments in the circle of Willis, which is a considerably higher percentage than that among healthy people or individuals with non-AD conditions (Graff-Radford *et al*., 2021). While there is extensive histopathologic research endorsing a connection between AD and atherosclerotic impairments in large vessels, the degree to which AD is related to arteriolosclerosis in small vessels, which is identified as thickening and hardening of arterioles, is still to be defined. For instance, recently arteriolosclerosis could not be identified in the frontal cortex of patients with AD (Kalaria, 2016). Another study showed proof of hypoxia-related gene expression in AD brains, which was not connected with any changes in the arteriole structure or with amyloid-beta accumulation, but was due to an elevated release of endothelin-1, a potent vasoconstrictor. Whereas the effect of hypoperfusion due to plaques in large vessels could not be evaluated, these findings suggest that AD brains suffer from hypoxic stress, which has critical consequences for amyloid-beta aggregation (Love and Miners, 2016).

In addition to clinical-pathological studies, contemporary brain imaging techniques provide a comprehensive assessment of macrovascular atherosclerosis. Traditionally, *in vivo* clinical analysis of vascular disorders was based on the placement of a catheter into the lumen of an artery, injecting contrast in the blood, and detecting it by means of angiography. Although very precise in detecting strictures in the lumen, these methods are invasive, pose considerable possible risks, and do not give an immediate visual picture of vessel walls or atheroma (Kantor *et al*., 2009). Newer cross-cutting imaging technologies, like Computed Tomographic Angiography (CTA) and Magnetic Resonance Angiography (MRA), are now commonly applied in medical practice. They enable the visualization of main arteries inside and outside the scull and allow for differentiation between arterial walls, lumen, and atherosclerotic atheroma. Furthermore, techniques that measure cerebral blood flow (like CT and MR to evaluate cerebral perfusion pressure) or flow velocities in vessels (like carotid ultrasound and transcranial Doppler

sonography) help to reveal hemodynamic anomalies that indirectly indicate vessel disorders (Green and Parker, 2003). With age, vessel pathology is usually associated with atherosclerosis causing lumen narrowing. In a recent study involving 42 AD patients and 50 subjects in the control group, transcranial Doppler sonography was used to assess the pulsatility index of the large vessels in the cerebral arterial circle. The pulsatility index was identified as the difference between the peak systolic flow and minimum diastolic flow velocity, divided by the mean velocity recorded throughout the cardiac cycle (Rivera-Rivera *et al*., 2016). As in previous studies, subjects with AD demonstrated lowered mean flow velocity in the arteries and elevated pulsatility index in the vessels fed by the Willis circle. This research also reported that AD patients, unlike subjects without dementia, demonstrated lowered diastolic flow velocity in the main neck arteries (carotid arteries). It was likely caused by the loss of elasticity in large cerebral arteries due to the vessel wall stiffening (Roher *et al*., 2011b).

To establish a connection between imaging indicators of AD and physiological measurements of arteriosclerosis, researchers examined *in vivo* amyloid accumulation and its correlation with arterial rigidity in a group of 81 elderly subjects without dementia. This prospective observational study utilized a PIB-PET scan to assess the amyloid presence at the beginning and again in two years of follow-ups (Hughes *et al*., 2015). Furthermore, a waveform analysis was employed, which is a non-invasive automated technology, to assess arterial stiffness in central and peripheral vessels. The study demonstrated that the growth in the share of subjects with amyloid dispositions from 48-75% was significantly linked with aggravation of arterial stiffness in the course of time (Salvi *et al*., 2022). Hence, arterial rigidity is closely related to advancing cerebral deposition of amyloid beta, as evidenced by previous studies demonstrating that AD was connected with both carotid intima-media thickness and disorders of peripheral vessels. A few similar studies have verified the interaction of AD with the deterioration of cerebral blood flow and progressive stiffness of arterial walls. These findings collectively propose that the latest noninvasive neuroimaging technologies could help to assess advanced atherosclerosis and detect patients who are most likely to develop dementia and AD and who are in need of vasoprotective treatments and close monitoring of vascular risk factors (Baradaran *et al*., 2022).

Vascular Involvement

Atherosclerosis and Alzheimer's are seemingly different diseases, with ATH identified by cholesterol buildup on artery walls and AD by neuron degeneration, neurofibrillary tangles, and atheroma formation (Wolters and Ikram, 2019). Nevertheless, there is mounting evidence that AD is also connected with endothelial dysfunction (Fig. 1). In spite of a slight difference in the formation of brain arteries and arterioles from main blood vessels, they also contain smooth muscle and endothelial cells. Research using AD mice has proved that the disease progression is characterized by deposits in brain arteries (Di Marco *et al*., 2015). In AD humans, amyloid deposits outside the brain cells are mostly found in brain arteries and the density of these deposits decreases as one moves towards smaller vessels. It has been hypothesized that the impairment of endothelial cells that line brain vasculature is a driving force in triggering the loss of neurons (Gireud-Goss *et al*., 2021).

Brain imaging showed that AD is linked with lowered blood flow in the brain, a finding also observed in AD mice. Roher studied the brain arteries of patients with AD and subjects of the same age without dementia in the control group (Roher *et al*., 2017). Besides atheroma and neurofibrillary tangles, AD patients demonstrated a greater level of blockage in the cerebral arterial circle than controls and there was a direct association between the extent of arterial narrowing and neurofibrillary tangles score. Hofman and colleagues verified these results in research where they compared sonograms of AD subjects and controls for indicators of atherosclerosis, such as the thickness of artery walls (Lathe *et al*., 2014). All ATH indicators were more frequent in AD subjects compared to controls and the AD odds ratio for subjects with advanced ATH was 3.0 (CI 1.5-6) compared to subjects without it. The principal results of these studies have been extensively replicated, indicating that the connection between cerebral ATH and AD is not a fiction composed of diagnostic errors (Gireud-Goss *et al*., 2021). The Baltimore Longitudinal Study of Aging (BLSA) revealed that atherosclerosis in the aorta or coronary arteries without the intracranial ATH is not a high-risk factor for AD. At the same time, cerebral atherosclerosis was proved to be a significant hazard factor for dementia (Dolan *et al*., 2010).

Presumably, AD comprises two different disorders: A major class with the impairment of brain vessels and a minor category without it, but it is not evident. Ellis and colleagues reported cerebral angiopathy in the major class of AD (83%). Senility, which is classified as cerebral angiopathy, is directly linked to amyloid lesions of brain vessels and shares strong similarities with both AD and atherosclerosis (Viswanathan and Greenberg, 2011). Additional research is necessary to classify AD-associated old age dementias according to the type of vessels involved. Nevertheless, collective research suggests that most clinically manifested AD cases show a considerable involvement of vasculature (Iadecola *et al*., 2019).

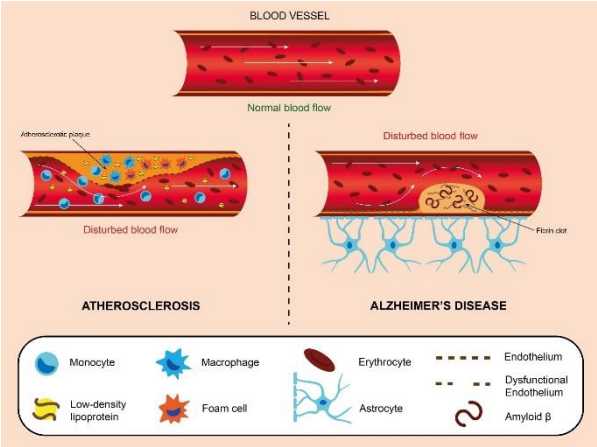

Fig. 1: Vascular involvement in atherosclerosis and Alzheimer's disease. atherosclerosis is a chronic inflammatory disease marked by the accumulation of cholesterol-laden macrophages (foam cells) in arterial walls, leading to partial occlusion. The rupture of plaques increases the risk of myocardial infarction and stroke. Alzheimer's disease is characterized by neuronal loss, thickening of brain vessel walls, amyloid deposits of Aβ near the cerebrovasculature, and fibrin clot formation. Both atherosclerosis and Alzheimer's disease involve vessel wall thickening and blood blockage, resulting in blood flow disturbances and impaired delivery of oxygen and nutrients to vital organs

To summarize, the basic types of atherosclerotic and Alzheimer's diseases are connected with the thickening of vessel walls and blood blockage, although the principal sites (cerebral arteries in AD, main arteries in ATH) and the course of the diseases differ. In ATH, cholesterol deposits in vessels compromise heart function and pose a hazard of getting into circulation, resulting in an infarction (Steinman *et al*., 2021). In AD, cerebral hypoperfusion is considered to be the cause of the disease. Presumably, the thickening of the brain vessel walls results in impaired cerebral delivery of oxygen and nutrients, increasing the likelihood of neuron death. These courses are not necessarily separate: Atherosclerosis alone may jeopardize nutrient and oxygen supply to the brain, while processes characteristic for AD in essential brain locations may unbalance the circulatory system (De Montgolfier *et al*., 2020)

Taken together, the data indicate that AD and ATH comprise a variety of associated disorders, with the involvement of vasculature being a common precondition, despite the differing locations of the involvement in the two diseases. Below various genetic hazard factors will be described and how they shed light on the interconnection between AD and atherosclerosis (Huang *et al*., 2020).

Atherosclerosis and Associated Immune Response

ATH is a multifaceted, inflammatory disorder characterized by lipid accretion, impairment of vasculature, and immune response to inflammation in most medium to large arteries, including those providing blood to the brain. It remains the primary cause of cardiovascular disease. Vascular impairment due to ATH leads to small vessel disorder, a disabled clearance of amyloid beta, blood-brain barrier disrupture, inflammation, and, eventually, neurodegenerative disorders (Stahr and Galkina 2022). Many factors raising the risk of cardiovascular disease, such as old age, high blood pressure, inflammation, hypercholesterolemia, and vascular impairment, also increase the likelihood of developing AD. The development of atherosclerosis is facilitated by persistent aortic inflammatory processes with the participation of innate and adaptive immunity. The role of various cells such as Th1, NK, NKT, T follicular helper, and neutrophils in promoting atherosclerosis is well-known, as well as the protective function of Tregs, while the contribution of Th2 and Th17 is still under discussion (Björkegren and Lusis, 2022). B cell participation in atherosclerosis is complicated and varies according to the subset. Follicular and innate response activator B cells promote ATH by facilitating Th1 response and the release of immunoglobulins and pro-inflammatory cytokines, whereas B1a and B1b cells play a protective role in expressing natural antibodies that inhibit oxidized LDLs captured by macrophages (Ma *et al*., 2021). Recently the anti-ATH effect of marginal zone B cells through control over the development of T follicular helper cells was reported. Regulatory B cell participation is contentious. In general, the immune system plays a crucial role in atherogenesis, generating a distinct and complicated immune response that could impact the progression of other disorders related to atherosclerosis. Here we present evidence for atherosclerosis involvement in facilitating AD and describe potential processes by which an exceptional immune response generated during atherogenesis could impact AD development (Douna *et al*., 2022).

Alzheimer's Disease and Associated Immune Response

Alzheimer's disease is a progressively worsening degenerative condition of the nervous system characterized by the cerebral accumulation of Amyloid Beta (Aβ), which leads to neuron loss and considerable deterioration of cognitive functions. Despite various hypotheses being put forward to explain AD, the predominant theory, the Amyloid Hypothesis, proposes that Aβ aggregation is the primary cause of neuron degeneration (Solis Jr *et al*., 2020). In normal cases, Aβ is

eliminated through a variety of mechanisms, like Aβ capture by microglia and astrocytes, flow-dependent discharge of interstitial fluid into cerebrospinal fluid and the activity of transport proteins such as LDL receptor-related protein 1, very LDL receptor and P-glycoprotein and proteases including insulin-degrading enzymes, neprilysin, glutamate carboxypeptidase II and matrix metalloprotease-9. However, there are several processes that can cause cerebral Aβ aggregation, including Aβ overproduction and reduced Aβ elimination from the brain (Schreiner and Popescu, 2021).

AD developing at an early age, also called familial Aβ AD, is the result of one or several mutations in APP or presenilin1/2, subunits of the γ-secretase enzyme, which can cause AD occurrence in homozygous dominant individuals already at the age of 30-50. These mutations raise amyloidogenic pathway activity, causing increased Aβ generation. The more common AD type, AD developing later in life and also called sporadic AD, seems to be triggered by the interplay between genetic and environmental factors, which may facilitate either Aβ excessive production or a decrease in its elimination (Weggen and Beher, 2012). Various genetic factors have been linked to AD, like, for example, different isoforms of the APOE gene and heterozygous mutations in TREM-2. It is worth noting that mutations in APOE and TREM-2 are also closely connected with atherosclerosis by disrupting macrophage autophagy, which makes them possible candidates for treatment against both diseases. While the development of late-onset AD seems to be primarily caused by genetic factors, with some researchers suggesting a 70:30 proportion between genetics and the environment in the disease triggering, various vasculature risk factors are also linked to heightened chances of dementia, such as ATH, DM, smoking and elevated blood pressure (Wolfe *et al*., 2018).

In spite of the well-recognized importance of Aβ in AD, there is growing evidence that the immune response and related inflammation also significantly influence the initiation and development of AD. It has been established that AD is closely linked to elevated levels of C-reactive protein and pro-inflammatory cytokines such as TNFα, IL-6, and IL-1β. Researchers do not have a unified point of view on the AD correlation with subjects' age and their status of peripheral inflammation (Kinney *et al*., 2018). Moreover, some studies indicate that high levels of peripheral inflammation in middle to old age are connected with a higher AD risk and are associated with progressive cognitive retrogression and vascular risks. Notably, inflammation within the central nervous system is an early sign of AD, as evidenced by increased TNFα levels and decreased TGFβ production found in the cerebrospinal fluid of subjects with mild cognitive disorders. The doubling of the cognitive impairment rate within six months is also connected with elevated levels of TNFα (Bettcher *et al*., 2021). There is also evidence that systemic inflammation caused either by a critical disease or by an acute or chronic infection may lead to nervous system disorders of AD type in mouse models and cognitive impairments in aged humans. This suggests that systemic inflammation may be a predecessor of an AD-like disorder and take part in its initiation/progression. So far, results of preclinical, genetic, as well as animal studies endorse the idea that all phases of AD development are characterized by activated immunity. In AD animals, infiltrating monocytes and neutrophils lead to a pathology; and a marker of immune response to AD is the dominant response of Th1 and Th17 cells (Bathini *et al*., 2023). However, the role of B cells and Tregs is still a matter of debate. It has yet to be defined how the peripheral immune system may influence the beginning of AD-specific degeneration and at which phases of AD development the immune system and related inflammation are crucially important.

Atherosclerosis and Aβ Clearance

Despite the attention given to the rise in Aβ production resulting from the consequences of atherosclerosis of brain arteries, mounting evidence proposes that disruption of Aβ elimination may also present another connection between ATH and AD pathology. Processes crucial to Aβ elimination from the brain comprise reabsorption of cerebrospinal fluid, degradation through Aβ-degrading enzymes, and discharge through perivascular drainage and vessels such as transfer into the bloodstream through the LRP1 receptor (Gupta and Iadecola, 2015). Proteins, peptides, and soluble metabolites are discharged from the brain via perivascular drainage and finally, they get into the neck lymph nodes. On the way, interstitial fluid penetrates by mass flow into the perivascular space around the walls of vessels, known as the Virchow-Robin space. To date, it has not been possible to assess the pressure gradient controlling the process, as the molecular flow in vessel walls moves in the opposite direction from the blood flow (Tarasoff-Conway *et al*., 2015). Besides, it is difficult to study in vivo the drainage in perivascular routes because of its rapidity and microscopic size. Nevertheless, the proportionate share of the major Aβ elimination pathways was calculated in humans and it was discovered that 50% of Aβ elimination could be credited to cerebrospinal fluid and vascular-perivascular drainage, indicating the significance of vascular Aβ elimination in the human brain (Kim *et al*., 2020).

Research utilizing mathematical models of cerebral perivascular solute transfer indicates that the force

propelling this molecular transport is the arterial wall movement of reflection or recoil type following the normal pulse wave. A model proposing that solute drainage happens through a thin stratum between endothelium and astrocytes demonstrates that solutes like Aβ are most likely drained during discrete, momentary periods in every pulse cycle when fluid and dissolved matter are moved in the direction reverse of blood flow in the Virchow-Robin space (Vinje *et al*., 2021). Additionally, efficient fluid drainage in this model is probably facilitated by solutes attaching to the perivascular space lining, which creates a one-way valve effect. According to this model, in conditions reducing the amplitude of vascular wall movements, such as hypoperfusion due to arterial stenosis or wall rigidity in microangiopathic ATH, the time of solutes adherence to the lining of the perivascular space will be prolonged. In this case, if Aβ is one of the solutes, this reduction in the amplitude would likely decrease its clearance and potentially contribute to Aβ accumulation in vessels and parenchyma, as observed in AD (Mahmajeva *et al*., 2010). Another study using mathematical models to assess fluid movements in the perivascular space demonstrated that peristaltic movement of vascular walls is necessary to promote solute and fluid transportation in the Virchow-Robin space. These results align with Aβ allocation in the walls of large arteries in cortical and leptomeningeal cerebrovascular pathology characteristic of Cerebral Amyloid Angiopathy (CAA), which suggests that Aβ is probably deposited in the perivascular routes of cerebral fluid drainage. Murine models also endorse this hypothesis, indicating that Aβ introduced into the interstitial fluid of a mouse allocates in the basal lamina in the same pattern as in CAA in humans, which can further impede cerebral perivascular drainage (Troili *et al*., 2020).

Currently, magnetic resonance imaging has been utilized to illustrate the perivascular pathways that allow for cerebral solute removal through the exchange of cerebrospinal and interstitial fluid. DCE-MRI of rat brains confirmed that CSF flows via main para-arterial pathways and the exchange between cerebrospinal and interstitial fluids is reliant on molecular size. Additionally, in a different study, interstitial solute removal was examined using fluorescent microscopy in vivo and ex vivo after Aβ introduction into the murine cerebral parenchyma (Alghanimy *et al*., 2023; Yu *et al*., 2022). Results showed that in contrast to relatively young WT mice, in old WT mice Aβ clearance from the cerebral parenchyma was reduced by 40%. The researchers discovered a 27% decrease in the pulsatility of intracortical arteriole walls, which was connected with the deterioration in Aβ exchange. This finding proposes that arterial wall rigidity may be the main inhibitor of successful Aβ removal. To determine whether the impeded Aβ clearance may be happening secondary to myocyte death without direct thrombotic plaques, further research utilizing animal models is necessary, if possible, with comparable up-to-date MRI technologies (Jessen *et al*., 2015).

If we project these data onto epidemiological and clinical evidence linking ATH and AD in humans, inadequate perivascular Aβ clearance becomes a very probable additional mechanism by which Aβ can exert a harmful impact on cerebral vasculature. Atherosclerosis could reduce distal flow and cause vascular stiffening, both of which would impede the driving force necessary to effectively remove Aβ through perivascular pathways (Greenberg *et al*., 2020). However, since methods of evaluating Aβ elimination in humans are not yet widely available, most of the evidence supporting the connection between ATH and Aβ clearance is inferential and needs further investigation. Additionally, new therapeutic strategies aimed at the enhancement of Aβ clearance, such as the use of vasopressors to raise arterial pulsatility, are worth exploring. While more accurate diagnostic and treatment strategies concentrated on Aβ clearance are being developed, it is crucial to improve our comprehension of mechanisms connecting ATH and AD on a more general level (Wildsmith *et al*., 2013). Such research is necessary to boost the relevance and resources allocated to the prevention and therapy of cardiovascular diseases, as atherosclerosis today is insufficiently diagnosed and treated. Initial studies have shown promising results, with evidence proposing that management of vascular risk factors could help decrease white matter impairments in AD as identified through MRI and may even delay disease progression in the early stages. Additionally, the recently announced decrease in the occurrence of AD has been largely attributed to an improved management of vascular risk factors (Winzer *et al*., 2018).

Aβ and Atherosclerosis

As discussed previously, there is evidence indicating that Aβ accumulation may be fostered by ATH and associated vascular impairment, but there is also confluent evidence that Aβ, in turn, can foster atherogenesis (Fig. 2). Brain autopsy data demonstrate that non-demented humans of old age with advanced atherosclerosis in the cerebral arterial circle have higher levels of Aβ42 in comparison to those with a lesser extent of brain atherosclerosis, despite similar levels of β-secretase in both groups (Vogelgesang *et al*., 2002). Although the reason for the increase in brain Aβ is unclear, several lines of research propose that Aβ is atherogenic in itself. An early study supports this idea demonstrating that Aβ and Amyloid-beta Precursor Protein (APP) are discovered in

the small vessels encompassing a developed plaque in human carotid arteries. The authors also reported that APP derived from thrombocytes is proteolytically transformed into Aβ resulting in iNOS induction and elevated activation of macrophages, which propose that Aβ might be of great importance in the pro-inflammatory cascade of ATH. Recent studies using murine models also supported the participation of Aβ in atherosclerotic plaque formation (O'brien and Wong, 2011). Caravaggio and colleagues reported that insufficiency of insulin-degrading enzymes in IDE and lipoprotein receptor KO mice resulted in bigger atherosclerotic plaques and elevated Aβ levels within them (Caravaggio *et al*., 2013). Moreover, studies in mice models with CNS-restricted APP overexpression propose that inflammation caused by APP overexpression can result in aortic ATH even before Aβ depositions form in the cerebral parenchyma. These results support the hypothesis that while ATH-triggered vascular impairment raises Aβ formation and aggregation, Aβ, in turn, facilitates atherogenesis. Unfortunately, little information is available and further research is needed to better understand the involvement of amyloid beta in atherogenesis and the processes by which Aβ facilitates atheroma buildup (Zou *et al*., 2015).

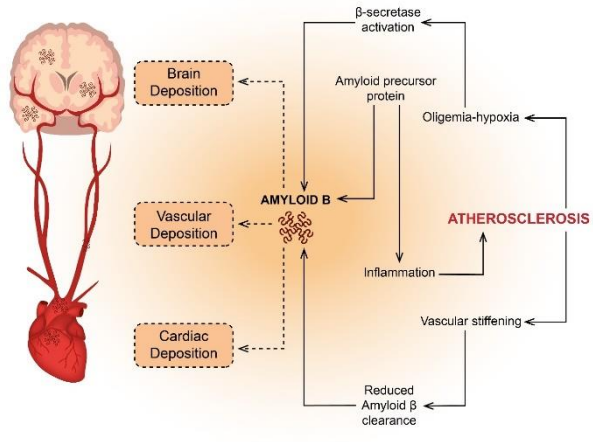

Fig. 2: Amyloid β and Atherosclerosis. Amyloid β is present in brain parenchymal and cardiac depositions as well as in vessels. Deposits of Amyloid β are primarily found in leptomeningeal and cortical vessels, cerebral microvasculature, intracerebral arteries, carotid arteries, aorta, and coronary arteries. Cardiac deposits are linked to cardiomyocyte dysfunction. Vascular Amyloid β and Amyloid precursor protein depositions foster vascular inflammation and atherosclerosis. Conversely, atherosclerosis promotes brain Amyloid β accumulation by vascular stiffening followed by reduced Amyloid β clearance, reducing cerebral blood flow (oligemia), leading to hypoxia, which in turn increases Amyloid β production by activating β-secretase

Conclusion

In this study, we have explored the link between atherosclerosis and Alzheimer's disease. Numerous studies indicate that these conditions are associated on multiple levels. Firstly, there is extensive evidence confirming a number of common risk factors for both diseases, some of which are potentially modifiable. The risk factors include smoking, a sedentary lifestyle, obesity, diabetes, hypercholesterolemia (elevated LDL and low HDL), elevated blood pressure, and aging. Timely elimination of lifestyle risk factors would significantly reduce the occurrence of the diseases. Secondly, studies have shown that about half of AD cases are due to vascular risk factors. Clinical evidence indicates that the dysfunction of cerebral vasculature in atherosclerosis, (including concurrent ischemic infarcts) is strongly associated with AD and a 10-25% decrease in these factors could prevent as much as 1 mLn. cases globally. Endothelial dysfunction has been demonstrated to accelerate atherogenesis as well as predispose neuronal death in AD. Moreover, decreased cerebral blood flow and thickening of vessel walls result in impaired O_2 and nutrient transport to the brain cells, leading to their loss. Thirdly, persistent inflammation in atherosclerosis together with elevated CRP and pro-inflammatory cytokines are associated with AD-like cognitive decline. Common genetic factors for ATH and AD are mutations in APOE and TREM2 genes. Lastly, both conditions appear to involve impaired Aβ metabolism.

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Author's Contributions

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

Conflicts of Interest

The authors declare no conflicts of interest.

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