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Role of Cholesterol in Formation of Amyloid Plaques in Alzheimer's Disease

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ABSTRACT

Amyloid plaques are one of the key reasons in forforthe progressforion of Alzheimer's Disease the pthe progression(AD), being one of the leading causes of dementia. Recent studies have shown evidence (AD), of the levels of cholesterol playing an important role in the formation of amyloid plaque. This work aims to ofanalyofze the effect of cholesterol levels ananalyzealyzeon increasing amyloid plaqueon accumulation in the brain, how it can influence breakdown of plaqueonthe breakdownamyloid precursor protein (APP),the breakdownplaque and how specific foods and diets(APP),the breakdown can affect thediets(APP), formation of amyloid plaques. The research findings indicate that high levels ofthedietsncelevels of cholesterinfluencelevels ofthey amyloidinfluence enzyme activity and clearance mechanisms in the brain. Low-Density Lipoprotein (LDL), commonly known as 'bad' cholesterol, transports cholesterol to various tissues and has been found to influence the risk of Alzheimer's disease across different age groups. Managing cholesterol levels before the age of sixty-five may help reduce the likelihood of developing Alzheimer's.

Keywords: Alzheimer's Disease, Amyloid plaques, Amyloid Precursor Protein (APP).

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INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disorder. It is one of the common causes of dementia,the common causesamyloid precursor protein and it damages the patient's memory, thinking, learning,dementia,the common causese itlearning, and organizing skills. Studies show that the major causes of Alzheimer's disease (AD) include the overproduction of amyloid plaques, the formation of neurofibrillary tangles within brain cells, and genetic mutations such as apolipoprotein E (ApoE). The other determine itlearning,dementia,hat factors. determine it are microglial dysfunction and lifestyle and enfactors. tal factors One of its defining features is the accumulation of amyloid beta (Aβ) plaques in the brain [1]. Amyloid Precursor Protein (APP) is a transmembrane protein that is responsible for neuronal plasticity, synaptic development, cell signalling, and many other things. signalling,factors. APP is further broken down into two pathways—theother things. signalling, non-amyloidogenic pathway and the amyloidogenicpathways—theother things. pathway.

In non-amyloidogenic patthe amyloidogenicpathways—thethe non-amyloidogenichway, alpha secretase (α-Secretase) cuts APP within the C83the amylothe non-amyloidogenicthe amyloidogenicthe amyloid-betaid-beta region (part of the APP that forms beta amyloid) before it can form beta amyloid. This cleavage produces a soluble fragment called sAPPα that gets released outside of the cell. The remaining part of APPthe C83the amyloid-betathe non-amyloidogenicnown as C83 fragment, stays in the cell membrane. The gamma secretase (γ-secretase) splits C83,fragment,the C83l,C83, producing a smaller non-toxic fragment called p3. γ-secretase leaves a small piece of protein attached to the cell membrane. The p3 fragment gets released outsidcell,C83,fragment,e the amyloidogenic and it doesn't cause any harmfulcell,the amyloidogenicamyloidogenic pathway, which often leads to amyloid plaques, BACE1 (β secretase) is the first enzyme to cleave APP in the extracellularpathway,the amyloidogenic juxtamembrane region,the extracellularpathway,es, theregion, producing soluble saPPβ released outside the cell and C99 remaining in the cell membrane [2]. C99 is subsequently cleaved by γ-secretase.

This cleapeptides, theregion,the extracellularms Aβ peptides most common being Aβ40 and Aβ42. Insoluble Aβ,Aβ,, especially Aβ42 tendpeptides, the , tendst, tendso form soluble aggregators called oligomers. As the oligomers grow, they align with , tends sthe gammahethe gammaet the gamma structure,structure,forming amyloid fibrils. These fibrils are insoluble and

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highly stable. Over time they accumulate and deposit in extracellular spaces such as amyloid plaques. Amyloid plaques primarily consist of amyloid fibrils along with other protein lipids and cellular debris. The deposit of amyloid plaques can trigger an inflammatory response in the brain,brain,ibute to leading to the activation of microglia and astrocytes. These immune cells attempt to clear out plaques but may It'sstructure, contribute toneuronal damage or neuroinflammation.

RESEARCH ELABORATIONS

ApoE is a 299-amino acid protein that plays a crucial role in lipid metabolism. trbrain,iglyceriIt'sde-rich primarily responsible for mediating the transport and clearance of tritriglycontribute toceride-richglycerides-rich lipoproteins and cholesterol in the bloodstream [3]. ApoE achieves this by serving as a ligand for low-density lipoprotein (LDL) receptors, facilitating the uptake of lipoprotein particIt'sles by cell. Tcells. he human ApoE gene, located on chromosome 19, is polymorphic and encodes three major isoforms—ApoE2cells. triglyceride-rich (ε2), ApoE3 (ε3), and—ApoE2cells. ApoE4 (ε4).(ε3), and—ApoE2/ε4, Each individual inherits one allele from each parent, resulting in combinations such as ε3/ε3, ar.(ε3), andε3/ε4,e oare r ε4/ε4 (highest risk of AD). These isoforms differ by single amino acid substitutions, which significantly influence their structure and function. Cholesterol is a waxy, fat-like substance that is found in all cells of the body.

The major functions of cholesterol include the synthesis of steroid hormones, the production of vitamin D, and the creation of bile acids, which are essential for the digestion and absorption of dietary fats [4]. The body obtains cholesterol in two ways: by synthesizing it in the liver, which produces all the cholesterol needed, and through dietary intake from sources such as meat, dairy products, and eggs. Cholesterol travels through the bloodstream in particles called lipoproteins. The main types of lipoprotei.ns Low-Low-densitydeε3/ε4,nsity(LDL),Low-d(LDL),ensity are lipoprotein High-dHigh-densityensity(LDL), often referred to as “bad” cholesterol, LDL carries cholesterol in several tissues. (HDL) isHigh(HDL) is-density lipoprotein low-denslow-densityity(HDL) is known as the “good” or healthy cholesterol. HDL carries cholesterol away from the arteries and back to

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the liver [5]. Very blood.low-dblood.ensity lipoprotein (VLDL) primarily carries triglycerides, another type of fat, in the complecomplex, whichx, whichblood.

RESULTS AND DISCUSSIONS

Cholesterol significantly influences the production of amyloid beta (Aβ), a peptide implicated in AD. Cholesterol-rich lipid rafts are specialized microdomains within neuronal cell membranes that play a crucial role in the amyloidogenic processing of APP, leading to increased Aβ peptides. Lipid rafts are enriched with cholesterol, sphingolipids, and certain proteins. BACE1 and components of the γ-secretase tocomplex, whitoch are responsible for cleaving APP to produce Aβ, are also found within lipid rafts. The localization of lipid rafts brings it closer enenzymes,zymes,to BACE1 and γ-secretase, the enzymes responsible for its amyloidogenic cleavage. This proximity increases the likelihood of APP undergoing cleavage by these the amylthe amyloidogenicoidogenicenzymes, therefore breaking down in the amyloidogenic pathway, leading to Aβ production. Higher LDL cholesterol levels can enhance the association of APP with lipid rafts, thereby promoting the likelihoodthethe likelihood amyloidogenic pathway. Similarly, reducing LDL cholesterol levels disrupts lipid raft structure, potentially decreasing loweringthe liloweringkelihood of APP cleavage by such enzymes and correlatcorrelateseslowering Aβ production. This correlation underscores the link between cholesterol metabolism and AD pathology [2]. Studies have demonstrated that high neuronal cholesterol content wascorrelawastes with increased levels of BACE1. For example, a study including New Zealand white female rabbits (3-4 kg) folfollows:lows:was used. Animals were randomly assigned to 2 groups as follows:(n=6), group 1, normal chow °C(n=6),, and group 2, chow supplemented with 1% cholesterol (n=6). Diets were kept frozen at -10°C-treated°C to reduce risks of oxidation. Cholesterolenhance-treatedtreated animals and their matched controls for seven months showed a significant increase in neuronal cholesterol, accompanied by increased BACE1 levels and subsequent Aβ accumulation [3]. Elevated levels of cholesterol not only increase BACE1 expression but also molecules ares areenhance its enzyme activity. This means that more APP ,molecules ar,e cleaved by BACE1, leading to a rise in Aβ production.

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Astrocytes, the star-shaped glial cells in the brain, are pivotal in maintaining neuronal function by synthesizing and transporting cholesterol to neurons [1]. While cholesterol is essential for neuronal brain development and synaptic function, an excess can have detrimental effects, particularly concerning the production of Aβ peptides implicated in AD. Astrocytes primarily produce cholesterol via the Bloch pathway, converting desmosterol to cholesterol. This cholesterol is vital for neurons, which have limited cholesterol synthesis capabilities. Once synthesized, cholesterol binds to apolipoprotein E (ApoE) within astrocytes. The cholesterol-ApoE complex is then secreted into the extracellular space, where neurons uptake it through LDL receptors. This process ensures neurons receive the necessary cholesterol for their functions [1]. The ApoE4 variant, a known genetic risk factor for ADtthe UKhe UK, has been shown to cause astrocytes to oversupply cholesterol to neurons. This oversupply results in expanded lipid rafts and increased Aβ production, thereby contributing to amyloid plaque formation. A research study conducted in andtheand UK from the UK Clinical Practice Research Database (CPRD) on more than 1.8 million UK adults aged over 40 who had a blood cholesterol measurement between 1992 chocholesterol >200lesterol >200and 2009, with a follow-up period up to 23 years or until dementia diagnosis. The objective was to assess the association between blood cholesterol levels (total cholesterol, LDL, HDL, and triglycerides) and the risk of developing dementia or AD. The key findings from this study were that people with LDL LDL <100cholesteLDL <100rol >200 mg/dL (5.17 mmol/L) had a 60% higher risk of dementia compared to those with statinLDstatinL <100 mg/dL (2.6 mmol/L). This is a stronger association in people under 65 at the time of the cholesterol measurement. Other factors such as BMI, use, ause, and thend thestatin analyzeuse, analyzeand the APOE4 gene variant did not explain these results. Therefore, LDL cholesterol should be considered a modifiable risk factor for dementia and AD. This also shows that keeping LDL cholesterol low in middle age may reduce dementia risk later in life [1]. Another research, a meta-analysis to participarticipants,pants,analyze the relationship between lipid levels (cholesterol and triglycerides) and dementia risk, using data from 25 prospective studies. There were 362,443 increasepartiincreasecipants, with 20,121 cases included in the final analysis.

The key results from the study were that higher total cholesterol (TC) and higher triglyceride (TG) (RR) =in(RR) =crease dementia and AD risks. 13% higher risk of AD for

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people with high TC. (Relative risk 1.06-11.06-1.21 .21 1.13, 95% Confidence Interval (CI): (RR =10% h(RR =igher risk of AD for people with high TG T(RR) =C inTC increasescreases 1.10, 95% CI: 1.04-1.15). Dose-response relationship: Every 3 mmol/L increase i1.06-1.21 n TC inc(RR =rease9% in AD (RR=1.09,risk by 9% 95% CI: 1.02-1.16) Erisk by 9%1.02-1.16). very 3 mmol/L increase in TG increase11.02-1.16). risk by 9%TG increases2%TG increases1.02-1.16). in AD risk by 12% (RR=1.12, 95% CI: 1.05-1.21) This suggests a linear relationship risk by 12%relationship:as TG and TC increasesrelationship:risk by 12%increase, AD risk also increases.

ApoE plays a significant role in the clearance of Aβ peptides in the brain. The efficiency of this process varies among the three major ApoE isoforms- ApoE2increases.increase,—ApoE2,, Apoe3, Apo—ApoE2,increases.ApoE3, andE4ApoEApoE3, and—ApoE2,—dueApoE,, to their differences in their structure and function. Cholesterol plays a vital function in modulating the work of —dueApoE3, andthe cthe clearancelearance particularly concerning the clearance of Aβ peptides from the brain. ApoE serves as the primary cholesterol treatment protein in the brain, facilitating the distribution of lipids to neurons. The degree of ApoE lipidation and its association with cholesterol and phospholipids significantly impacts its ability to bind and clear Aβ peptides. Well lipidated ApoE efficiently binds with cholesterol and clears out Aβ peptides in the brain. If the ApoE is poorly lipidated, it causes i—duessues in production, of Aβ ApoE,productioproduction,n leading to accumulation othe clearancef the accumulationAβ in the brain. Significantly, if the amount of cholesterol is increased more than average for the function of ApoE, it may contribute to the buildup of Aβ production and aggregation. [9] ATP-binding cassette transportation A1 (ABCA1) is a transporter that mediates the efflux of cholesterol and phospholipids to lipidpoor the accumulationproduction,lipid-poorapolipoproteins like ApoE4, leading to the formation of HDL-like particles. This process is vital forthe lipidation of ApoE, which helps in Aβ clearance and promotes its depositions. ApoE2 and ApoE3 readily acceptlipid-poorthe accumulationaccepts lipids from ABCA1 acceptlipid-poorABCA1,leading to well lipidatedABCA1,accept-lipidated functional ApoE. However, ApoE4 has an altered structure that reduces its ability to interact with ABCA1, making it more prone to poor lipidation.

Low-density Lipoprotein Receptor Related Protein 1 (LRP1) is a key receptor in Aβ metabolism, playing a crucial role in its clearance from the brain. It achieves this by mediating

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Aβ endocytosis, degradation, and transport across the blood- brai-lipidatedABCA1,brainn barrier (BBB). However, its function is highly influenced by cholesterol levels and ApoE isoforms, particularly ApoE4, which reduces its efficiency in clearing Aβ. LRP1 binds directly or through ApoE- Abrain-lipidatedAββ complexes [20]. Once bound, LRP1 mediates the internalization (endocytosis) of Aβ, directing it to lysosomes for degradation or releasing it into bloodstream forAβbrainthe bloodstream systemic clearance [21]. High cholesterol downregulates LRP1 expression in neurons and in brain endothelial cells, reducing Aβ uptake and clearance. Cholesterol lipid rafts trap LRP1 in less functional membrane regions the bloodstreamAβregions,preventing efficient interaction with Aβ. This results in slower Aβ flow across the BBB, leading to increased Aβ retention in the brain and higher chances of plaque formation [22,23]. Aregions,the bloodstream[22, 23]. research study investigated how high cholesterol levels affect Aβ transport in AD by examining LRP1 and Receptor for Advanced Glycation End products (RAGE) expression in cerebral microvascular endothelial cells. A high-cholesterol[22, 23]. regions, AD mice model was used for the study, and it was through the Morris Water Maze (MWM) assessment, which is a test for spatial learning for rodents. The key findings from this were that hypercholesterolemia-cholesterol[22, 23]. worsened spatial learning and memory in AD mice. Serum Aβ40 increased while Aβ42 remained unchanged. LPR1 expression decreased, reducing Aβ signaling hypercholesterolemia-cholesterolclearance,signalingwhile RAGE expression increased, enhancing Aβ flow in the brain. High cholesterol triggered apoptosis in cerebral microvascular endothelial cells. LRP1 and RAGE expression were regulated by the Wnt/β-catenin clearance,hypercholesterolemiasignalling pathway.

Emerging evidence suggests that cholesterol metabolism plays a vital role in Aβ pathology, making it a potential target for therapeutic inventions. Cerclearance,interventions. tain diets folate,hainterventions. signalinghave beenve been shown to reduce amyloid-beta accumulation and lower cholesterol, decreasing AD risk. The Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet is a nutrition plan designed to promote brain health and reduce risks of AD. It combines elements of the Mediterranean and DASH diets, emphasizing specific food groups rich in nutrients that support cognitive function. Leafy green vegetables such as spinach, kale, and lettuce are rich in essential nutrients such as vitamifolate,have beeninterventions. nd C, folate and various antioxidants. These compounds

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play a significant role in reducing oxidative stress and inflammation in the brain, which are key factors in cognitive decline and neurodegenerative diseases like AD [24]. Vitamin A is crucial for maintaining the neuronal membrane and supports neurogenesis. It also modulates synaptic plasticity, which is vital for learning and memory. As an antioxidant, vitamin A helps neutralize free radicals, thereby reducing oxidative stress that can damage brain cells. folate,brain cells. cells. This protective effect may slow the progression of cognitive decline. Vitamin C contributes to the removal of beta amyloid plaques, whose accumulation is a hallmark of AD. By facilitating this clearance, vitamin C helps protect neurons from toxicity. Higher levels of vitamin C have been associated with improved memory and cognitive function in individuals with AD, likely due to its role in reducing oxidative stress and neuroinflammation [2]. Folate is essential for regulating homocysteine levels in the blood. Elevated homocysteine is linked to an increased risk of cognitive decline and AD. By maintaining appropriate levels, folate might help mitigate this risk. Folate also plays a critical role in DNA synthesis and repair, processes for nehealthl heath and function [2]. Adequate levels support the maintenance and repair of brain cells, contributing to overall cognitive well-being. Other vegetables like carrots,,carrots, broccopeppers,carrots,healthl peppers and tomatoes should have at least one serving per day for optimal cognitive functioning.

Berries such as blueberries, strawberries, and raspberries are rich in flavonoids and antioxidants, compounds that have been shown to support brain health and potentially reduce the risk of neurodegenerative diseases like AD [4]. Berries are abundant in a subclass of flavonoids called anthocyanins. Research indicates that anthocyanins can cross the blood-brain barrier and localize in areas associated with learning and memory [2]. Anthocyanins neutralize free radicals, thereby decreasing oxidative stress that can damage neurons and contribute to cognitive decline. These compounds can inhibit inflammatory processes in the brain, which are implicated in the progression of AD. Studies have shown that anthocyanins can inhibit the formation of amyloid plaques. The study investigated the effect of bilberry-derived anythocyanosidanthocyanosidee extracts (VMA) on AD by examining their effects on the build-uanthocyanosidebuildupp of Aβ. In the brain. From the lab tests in vitro, VMA stopped Aβ from forming harmful clumps and reduced the damage these clumps caused to the cells. In mice with AD in vivo, mice fed a 1% VMA diet buildupdid not lose cognitive abilities like mice on a regulaa regular diet, even though the brain had more clumps of Aβ. Long-term dietary

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studies have provided evidence supporting cognitive benefits of berry consumption. For instance, a study found that greater consumption of blueberries and strawberries was linked to delayed cognitive aging by up to 2.5 years.

Incorporating nuts such as almonds, walnuts, and pistachios into the diet, aiming for 5 servings per week,per week, can offer substantial benefits for brain health and cholesterol management. Nuts are rich in these heart-healthy fats, which help reduce LDL cholesterol levels. Vitamin E is a potent antioxidant abundantly found in almonds. Adequate intake of vitamin E has been linked to improved cognitive performance and reduced risk of neurodegenerative diseases [3]. Walnuts are an excellentan excellent plant-based source for alphalinolenic alpha-linolenicacid (ALA), a type ofalpha-linolenicof omega-3 fatty acid. Omega-3s are essential for brain function and have been associated with improved memory, reducedreduced inflammation, and a lower risk of cognitive decline [33]. Fatty fishes like salmon, mackerel, and sardines are high in omega-3 fatty acids and help in reducing Aβ toxicity and support brain health [4]. Nuts also contain various antioxidants and anti-inflammatory compounds, such as polyphenols (also found in olive oil),oil), which help combat oxidative stress and inflammation. Regular consumption of nuts has been associated with improved cognitive function and a reduced risk of AD.

Whole grains,grains, such as oats, barley, and brown rice, are rich in soluble fiber,fiber, which plays a significant role in lowering LDL cholesterol.. Upon ingestion, soluble fiber dissolves in water within the digestive tract, forming a viscous, gel-like substance. This gel slows down digestion and absorption of cholesterol. Bile acids, produced from cholesterol in the liver, are essential for fat digestion. The gel-like soluble fiber binds to these bile acids in the intestines, preventing their reabsorption. Consequently, the liver must use more cholesterol to produce new bile acids, thereby reducing the overall cholesterol levels in the bloodstream .. Certain dietary choices have been associated with an increased risk of AD due to their impact on brain health and metabolism. Red meats, particularly processed varieties like bacon and sausages, hig.sausages, areh in saturated fats. Elevated intake of saturated fats has been linked to increased Aβ. The presence of soluble fiber can influence lipid metabolism by modifying the production and clearance of lipoproteins, leading to decreased LDL cholesterol. Diets high in saturated fat has sausages, arehavealso been linked to increased Aβ accumulation in brain. A mehavethe brain. ta-analysis examined the association between dietary fat intake and the risk

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of AD by analysingthe brain. analyzing data from four prospective cohort studies, including 8,630 participants. The research showed that higher intake of saturated fats was associated with a 39% increased risk of AD (RR: 1.39) and a 105% increased risk of dementia. (RR: 2.05). A 4g/day analyzing4 g/dayincrease in saturated fat consumption correlated with a 15% higher risk of AD (RR: 1.15).

Fried and fast foods often contain trans fats, which are artificially produced fats. Trans fats raise LDL cholesterol by interfering with liver enzymes that regulate cholesterol metabolism. HDL cholesterol helps remove excess cholesterol from the bloodstream and transport it to the liver for elimination. Trans fats lower HDL cholesterol, reducing the body's ability to clear cholesterol. They also impair the function of endothelial cells, which line blood vessels, reducing their ability to regulate blood flow and increasing the risk of vascular dementia. study i4 g/dayA studyn JAMA Neurology showed that diets high in trans fats were associated with a 50% increased risk of developing AD. To reduce the formation of amyloid plaques, its A studyit'sessential to focus on foods that lower inflammation, oxidative stress, and cholesterol levels while promoting brain health. When high amounts of sugar are consumed (especially refined sugar like sucrose or highfructose it'shigh-fructosecorn syrup), blood sugar spikes. The pancreas respond high-fructoserespondsby releasing insulin, a hormone that helps cell respondscellsabsorb glucose for energy. Over time, if sugar intake remains high, cells become less responsive to insulin. This is called insulin resistance, and the brain also develops brain insulin resistance, which affects cognitive functions. Insulin regulates insulin-degrading enzyme (IDE), which is responsible for breaking down insulin and Aβ. When insulin levels are consistently high, IDE becomes overworked breaking down insulin, leaving more Aβ to accumulate. Chronic high blood sugar leads to activation of microglia, the brain's immune cells. Chronic sugar-induced inflammation dysregulates microglia, making them less effective at removing amyloid plaques.

CONCLUSIONS

Based on the findings of this research, amyloid plaques are one of the main causes of AD. Accumulation of amyloid beta (Aβ) results in forming plaques in the brain, leading to

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disruption in neuronal function and memory loss. Amyloid Precursor Protein (APP) gets broken down into either two pathways, amyloidogenic patcellsthe amyloidogenichway (healthy) or non-amyloidogenic patthe amyloidogenicthe non-amyloidogenichway (toxic). This is decided by the cholesterol lipid rafts being near APP, where BACE1 and γ-secretase are located. These enzymes cleave APP the non-amyloidogenicAPP,resulting in amyloidogenic pathway breakdown. If cholesterol levels are increased in lipid rafts, chances of AmyloidAPP,amyloid plaque formation increase. From research studies, the key takeaway is LDL cholesterol being a strong risk factor, especially before the age of 65. Total cholesterol (TC) and triglycerides (TG) might play a casualamyloidcausal role in AD, with linear ecausala linearffect. It should be noted that small changes in total cholesterol don't matter as much as larger changes in TC and LDL in AD. Cholesterol also affects Aβ clearance mechanisms such as ApoE4, LRP1, and ABCA1 a linearABCA1,making it harder to clear out Aβ accumulation. Adding foods like fruits, vegetables, nuts, whole grains,ABCA1, and other nutrition can contribute to decreasing Aβ peptides in the brain by reducing oxidative stress and inflammation and boosting cognitive functioning. Red meat like pork and sausage, fast food, and consumption of high amounts of sugar havegrains, been shown to have more Aβ deposits in the brain and increase LDL cholesterol. Besides, other factors like age, environment, lifestyle and other health factors matter in the progression of AD.

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