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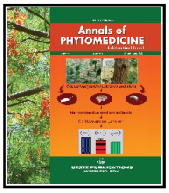

ReviewArticle : Open Access

Cholesterol and obesity: A marker for Alzheimer's disease

M. Sumithra* and P.M. Ancy,◆**

**Department of Pharmacology, SRM Institute of Science and Technology, Chennai-603203, Tamil Nadu, India*

***Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom-695124, Kerala, India*

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Abstract

Modern lifestyle and fast-food consumption nature increase the cholesterol consumption and deposition in our body. It is becoming one of the key risk factors in AD development. Several genes and receptors play crucial roles in such developments. Consumption of high-fat diet and absence of physical activity can lead to obesity. Higher BMI is the indicator of obesity. Higher BMI accelerates AD development due to brain atrophy, neuroinflammation, and oxidative stress in the hippocampus. Obesity in childhood and adolescence leads to dementia and AD in later life. COVID harmfully affects Alzheimer's patients, and it is also reported that COVID related dementia and neurodegeneration is one of the prominent post-COVID complications. This review summarises the role of cholesterol in Alzheimer's disease development and the importance of genes, receptors, and diet behind this.

1. Introduction

Modern lifestyle and western food habits are aggressively altering the day-to-day life of the common man (Mahumud *et al*., 2021). Many are attracted to junk foods, because of to its extreme taste, appearance, odour, and time-saving nature. Such food items are rich in saturated fat, salt/sugar contents and they can not impart any nutritional value. Regular consumption of these food products can progressively lead to obesity and worsens both the cardiovascular as well as nervous systems.

In India, it is estimated that the percentage of the adult population with obesity doubled in the interval 1975 to 2010 and is expected to triple by 2040 (Luhar *et al*., 2020). Recently updated data from WHO confirmed that the rate of obesity is even faster in other parts of the world. The prevalence of obesity is high in USA, Saudi Arabia (>35%), Turkey, Egypt, Iraq, Australia, Canada and Europe (>20%) (Stefan *et al*., 2021). The prevalence of Alzheimer's disease is high in various states in America along with highest obesity prevalence. Around 5.8 million Americans aged 65 and older are living with Alzheimer's disease in 2020. The number of AD patients might increase considerably from 5.8 million to 13.8 million by 2050 (Zhang *et al*., 2021). It is the sixth leading cause of death in America.The trend is not different all around the world. This data suggests that the increase in percentage of population with Alzheimer's disease has a close connection with food habits and obesity.

Key risk elements present in junk foods are saturated fat, salt, and sugar. Food rich in fructose and fat act as toxic in brain due to increase insulin resistance by altered PI3K-Akt pathway and signal transduction. This also consists of dietary advanced glycalation products, which has the potential to impart oxidative stress and inflammatory responses, and can cause neurodegeneration and permanent memory loss which may eventually lead to AD. Hypercholesteremia related oxidative stress in brain is due to increased level of oxysterol specifically 27-OHC and 7α-OHC. This may impart neuroinflammation and amyloid beta accumulation, usually seen before AD development (Figure 1), and hence can be used as future biomarker target for AD (Dias *et al*., 2014).

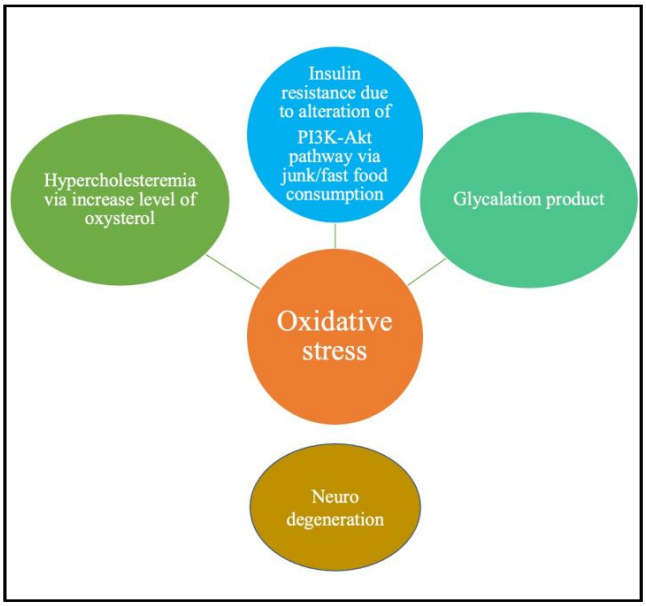

Figure 1: Diagrammatic representation of neurodegeneration due to oxidative stress.

Recent studies indicate that cholesterol also has a significant role in the development and progression of AD (Di Paolo *et al*., 2011).

Corresponding author: Ms. P.M. Ancy

Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom-695124, Kerala, India

E-mail: ap6760@srmist.edu.in

Tel.: +91-8547943958

Cholesterol is a wax-like organic compound in the steroid family with the molecular formula $C_{27}H_{46}O$ (Albuquerque *et al*., 2019). Cholesterol is essential for the development and synthesis of corticosteroids and sex steroids. It involves in the development of cell membrane and components for the synthesis of vitamin D and bile acids. Diet and *de novo* biosynthesis are the most common sources of cholesterol in humans (Lu *et al*., 2020). Cholesterol biosynthesis is a complex biochemical process, all nucleated cells can perform it (Jin *et al*., 2019). The two important pathways behind cholesterol homeostasis are the Bloch pathway and the Kandutsch-Russel pathway.

Cellular cholesterol levels are based on *de novo* biosynthesis, cholesterol uptake, transport and storage. The liver shows an important role in cholesterol homeostasis (Luo *et al*., 2020). It is the main delivering site of both endogenous synthesized and exogeneous acquired cholesterol.

The liver releases cholesterol into the blood as very-low-density lipoprotein (VLDL) and then it got modified into low-density lipoprotein (LDL). This LDL is taken up to peripheral tissues by receptor-based endocytosis. The liver is the only organ responsible for cholesterol removal by two mechanisms. The G5/G8 (ABCG5/G8) receptor which belongs to the subfamily of ATP- binding cassette (ABC) is responsible for the removal of cholesterol and later it got expelled into the gall bladder and form bile acids. Cellular efflux of oxysterol is another way of cholesterol removal (Russell *et al*., 2003).

LDL receptor has greater role in the trapping of amyloid beta in association with apolipoprotein E. It imparts in low density lipoprotein clearance in blood and supply cholesterol to cells. Increase in the level of cholesterol promote amyloidogenesis (de Oliveira *et al*., 2020). Peroxisome proliferator-activated receptor γ, LDL receptor and APOE receptor, TREM 2, CD36, N-methyl-D-aspartate receptors (NMDARs) are the receptors that have greater importance in cholesterol homeostasis (Figure 2).

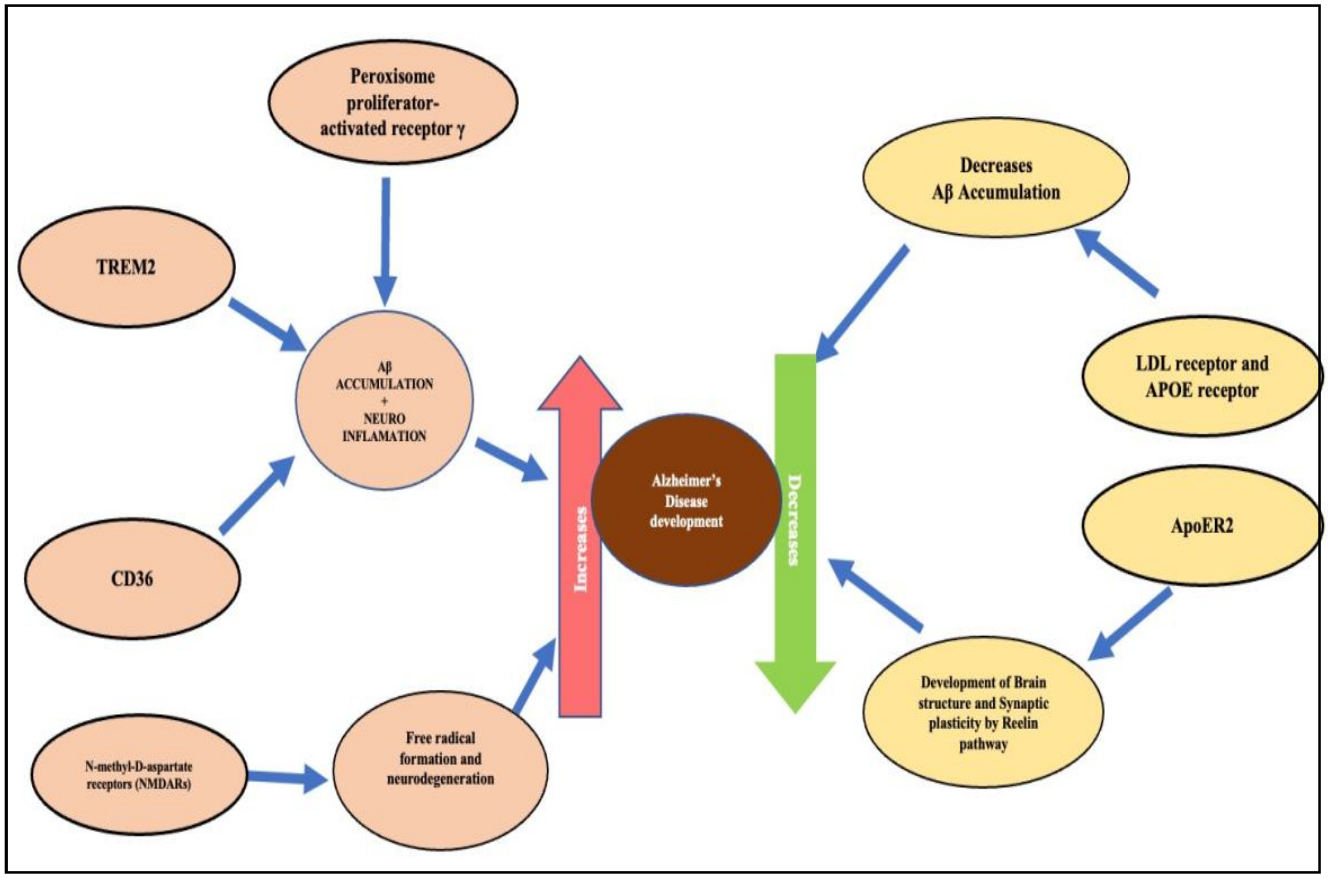

Figure 2: Receptors involved in Alzheimer's disease development in relation with cholesterol.

High-density, intermediate, low-density, and very-low density lipoproteins and chylomicrons are various lipoproteins in the blood. Among them, HDL and LDL are considered as the major lipoproteins. LDL is major transporters of cholesterol which regard as bad cholesterol and HDL is responsible for cholesterol excretion so regard as good cholesterol. Elevation of cholesterol in the bloodstream is known as hypercholesterolemia (Baik *et al*., 2020). Blood cholesterol level is one of the indicators of various disorders. Total cholesterol lower than 200 mg/dl, LDL level lower than 130 mg/dl (Grundy *et al*., 1990) and HDL above 40/50 mg/dl in men/women (Priya *et al*., 2013) are considered as a good healthy lipid profile. The factors such as age, gender, race, hereditary factors, obesity and diabetes influences the healthy cholesterol content in a person (Piste *et al*., 2006). Animal studies have indicated that diet-induced hyper-cholesterolemia increases the accumulation of Aβ, which is one of the biomarkers of AD. This can accelerate AD pathology in rabbit brains and similar transgenic mouse models (Chenjia Xua *et al*., 2016). The present review focuses on the importance of cholesterol in the development of AD. It also looks for ApoE, hFABP3, ApoH, vitamin D which can act as cholesterol biomarkers for AD development.

ApoE, clusterin (CLU), ABCA7, TREM2 and PLCy2, Glial LOAD risk genes are the genes related to cholesterol and AD development.

2. Brain and cholesterol

The human brain is a sophisticated organ in the body with high cholesterol content (Agarwal *et al*., 2020). It contains about 23 % present of cholesterol in the body (Dai *et al*., 2021). Since the blood-brain barrier blocks the free flow of cholesterol from the blood to the brain, the brain synthesizes its cholesterol based on demand (Agarwal *et al*., 2020). The major type of cholesterol seen in the brain is unesterified cholesterol. The lipid droplets (about 1%) are the esterified form of cholesterol and excess cholesterol store intracellularly. With the help of acyl-coenzyme A: cholesterol acyltransferase 1(ACAT1/SOAT1), the cholesterol esterification takes place in the endoplasmic reticulum. The astrocytes become active in situations such as deficiency of ApoE and overload of exogenous cholesterol. Other forms of brain lipids are glycerophospholipids and sphingolipids (Schreurs *et al*.,2010). Cholesterol plays a prominent part in the normal physiology of the brain. It is needed for the formation of synapse and dendrite, it acts as a signalling molecule and source of energy (Hussain *et al.,* 2019). It involves axonal and neuronal transmission. Cholesterol depletion leads to failure of neurotransmission and synaptic plasticity (Orth *et al*., 2012). This will become one of the factors for central nervous system diseases (Zhang *et al.*, 2015). Astrocytes are one of the major sites in which brain cholesterol production mainly takes place. ApoE and ApoA 1 are the main apolipoproteins responsible for cholesterol metabolism and transport in the brain. Stress and other damages increase the production of ApoE but ApoA 1 is obtained *via* SR-BI mediated uptake with the help of choroid plexus. The receptors that work behind the cholesterol uptake are VLDLR, LDLR, LRP1,LRP1B, LRP4/MEGF7, megalin/LRP2 and APOER2/LRP8. LDLR family receptors have a key role in cholesterol uptake (Orth *et al.*,2012). LRP1 and LDLR is prominent members of the LDLR receptor family in the brain. In the adult brain, astrocytes synthesize cholesterol then transport it to neurons functions. Transport of cholesterol in brain mediated as APOE-cholesterol complex with the help of ABCA-1 (García-Sanz *et al.*, 2021). This complex undergoes endocytosis by neurons, then hydrolyzed to get free cholesterol. Esterification of this free cholesterol happens with the help of the acyl-coenzyme A: cholesterol acyltransferase 1. Some of the free forms of cholesterol influence the cholesterol synthesizing enzymes and lipoprotein receptors like the liver X receptor. It increases the transport of cholesterol from cells to apolipoproteins which is then converted to 24S-HC by CYP46A1 (Sims *et al.,* 2020). Cholesterol has a long life about 6 months to 5 years in the brain. Cholesterol removal in the brain takes place in the form of oxysterol. ABC transporters also play a significant role in cholesterol removal.

3. Relation of cholesterol in Alzheimer's pathology

Ageing-related cholesterol content changes occur in brain regions, which may be morphological or neurochemical alterations, especially occurs in the hippocampus which is responsible for memory. Ageing and metabolic stress are the factors responsible for membrane cholesterol content change that further cause cognitive deficient. According to the Cambridge team with researchers at Lund University in Sweden, they found out that amyloid-beta normally does not aggregate to form plaque but the presence of cholesterol that helps to bind together, hence speed up the aggregation and cause the formation of amyloid plaque. This is one of the hallmarks of Alzheimer's disease. Elevated cholesterol levels promote the development of early onset of Alzheimer's disease (EOAD) and it is due to the genetic factors related to cholesterol. APOE E4 is a well-known genetic factor responsible for EOAD, this factor increases the level of circulating cholesterol such as LDL. According to Thomas. S. Wingo, another gene APOE B can increase the chance of EOAD development (Wingo *et al.*, 2019). Hyperlipidemia causes increased production of free radicals which damage the blood-brain barrier and promote amyloidogenesis in the brain. This leads to AD development by the accumulation of beta-amyloid plaque (Ribes-Navarro *et al.*, 2019). Cholesterol has an important role in the formation of fibrillary plaques. It was experimentally proved on transgenic mice and assesses the relation of cholesterol and apolipoprotein E with b-amyloid immunoreactivity and thioflavin S immunofluorescence (Burns *et al.*, 2003). Obesity causes a decrease in blood flow in CNS that leads to neuronal death (Bracko *et al.*, 2020). Free radicals, oxidative stress (Li *et al.*, 2020), increased inflammation, abnormal APP processing causes neuronal death and AD development. Latest studies showed that changes in cholesterol level increase Tau accumulation that leads to the formation of neurofibrillary tangles (Bloom *et al.*, 2014), Which is another hallmark of AD (Noble *et al*., 2003). Hence, cholesterol has a promising role in Alzheimer's development.

Studies showed that the presence of cholesterol in AD patient's plasma membrane is higher than a normal one, it also increases with disease progression (Martín *et al.,* 2014). Aβ production accelerated by BACE-1 mediated APP cleavage due to the presence of excess cholesterol at plasma membrane in primary cultured neurons. It causes an increased release of APP intracellular domain. Which decreases low density lipoprotein related protein1 transcription. It promotes exogenous cholesterol capture at plasma level and decreases cholesterol level in cells.

The high fat diet promotes amyloid beta accumulation and neuronal inflammation in the brain (Ribes-Navarro *et al.*, 2019; Refolo *et al.*, 2000). Latest findings showed that high fat diet cause changes in the gut microbiome and this linked to inflammatory responses in hippocampus further cause short term memory defect. Obesity causes a decrease in cerebral blood flow, it increases the incidence of AD development (Bracko *et al.*, 2020). Antioxidants like polyphenols protect the brain from oxidative damage while a fat-rich diet promotes oxidative stress (Li *et al.*, 2020). Saturated fat consumption increases the risk for both vascular events and cognitive impairments (Lam *et al.*, 2019).

4. Obesity and Alzheimer's disease

Obesity increases the risk of AD development (Knight *et al.*, 2014). Consumption of high-fat diet and absence of physical activity can lead to obesity (Nissankara Rao *et al.,* 2021). Higher BMI is the indicator of obesity. Higher BMI accelerates AD development due to brain atrophy in the hippocampus. Obesity in childhood and adolescence leads to dementia and AD in later life. Adolescence is a critical period in brain maturation that takes place, any drastic changes such as obesity or other factors that alter brain structure especially in the hippocampus region and cause AD development. High-fat diet consumption studies in the rat in adolescence to adulthood showed that decline in memory and hippocampus neurogenesis (Boitard *et al.*, 2016) occurs progressively in adolescent rats. Obesity, lack of

exercise, high fat diet are risk factors for AD as well as the cardiovascular system and diabetes development (Rollins *et al.*, 2019). The consumption of added sugars, a high-fat diet, and adoption of western food habits aggregate the development of memory impairment (Figure 3). Unsaturated fat is healthier than saturated fats and trans fats (Lam *et al.*, 2019). The new treatment strategy focuses on both the cholesterol-lowering effect and improvement of memory (Nissankara Rao *et al.*, 2021).

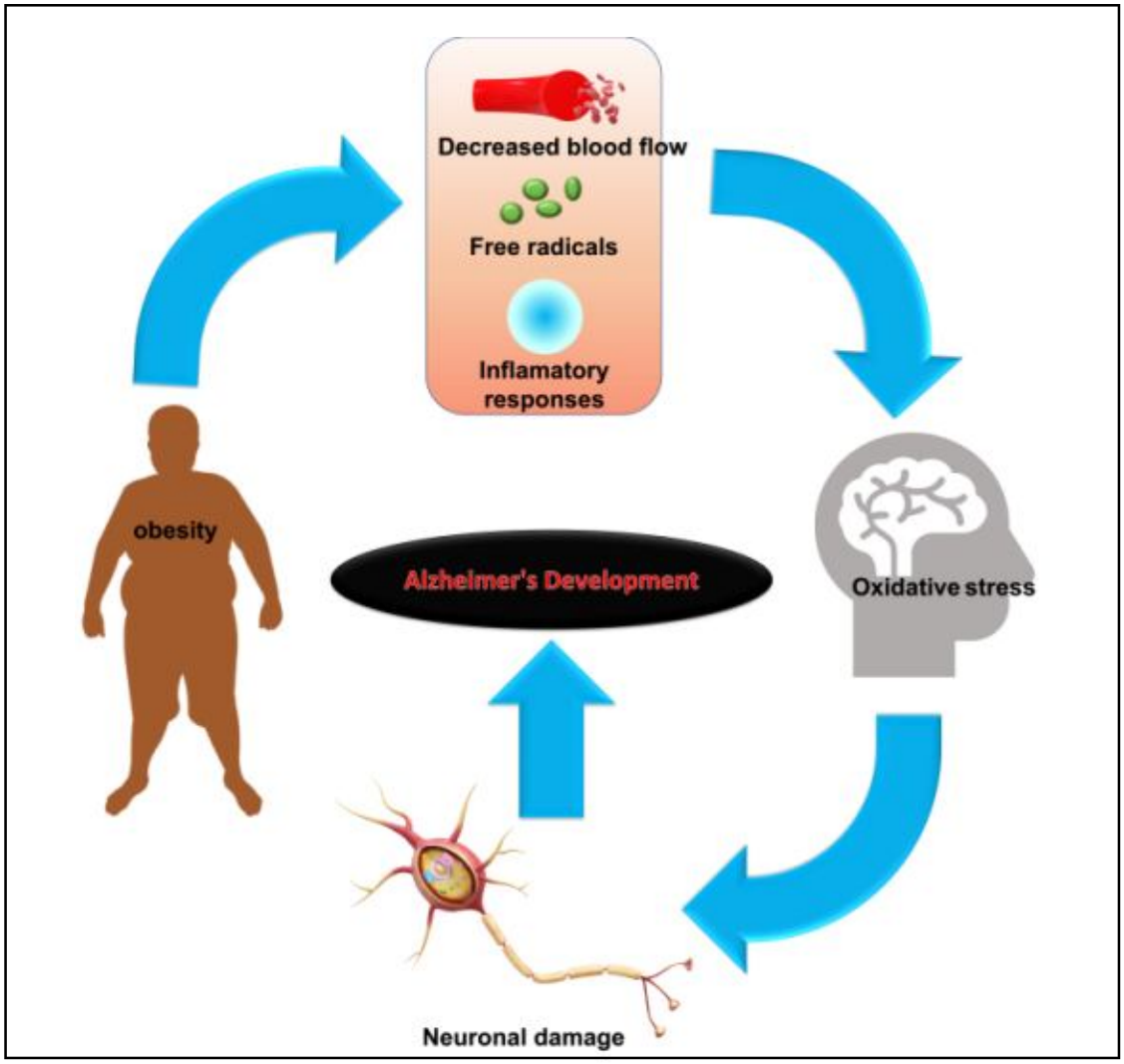

Figure 3: Role of obesity in Alzheimer's disease development.

5. Importance of diet in cognitive impairment

The high fat consumption is higher, especially in western food habits. This increases the risk of stress, sleep deprivation, memory impairment, and progression of the development of dementia in AD (Alzoubi *et al.*, 2019; Arika *et al.*, 2019). Mediterranean diet (McGrattan *et al.*, 2019) is accepted as a healthy diet in case of age related memory improvement worldwide (Arnoldo *et al.*, 2017; de Leeuw *et al.*, 2020). Recent studie shows that consumption of fish (Morris *et al.*, 2005; Kalmijn *et al.*, 1997; Breijyeh *et al.*, 2020), food rich in mono/poly unsaturated fat, dietary EPA, and DHA helps to prevent dementia (Chew *et al.*, 2020). The Rotterdam study revealed that while the consumption of omega-3-fatty acid rich fish decreases the risk for dementia, saturated fat consumption increases the risk. Diet rich in Eicosapentaenoic acid (EPA) possesses an antioxidant effect that decreases age related oxidative stress (Bourre *et al.*, 2009). A diet with fat content has a key role in the development of memory impairments which can modify the progression of the disease also (Bourre *et al.*, 2008; Solfrizzi *et al.*, 2005).

6. Role of apolipoprotein in Alzheimer's disease pathology

Apolipoprotein E is the main 39 k Da apolipoprotein in CNS and is mostly found in the brain (Linton *et al.*, 1991). It was identified in 1970 (Chen *et al.*, 2021) and actively participating in cholesterol homeostasis in the brain (Wolfe *et al.*, 2019). The various sources of apolipoprotein in the brain are astrocytes, oligodendrocytes, microglia and epidermal layer cells. Excitotoxic injury is responsible for apolipoprotein expression in neurons. The intercellular transport of cholesterol and similar lipids between neuronal and glial cells are mediated by the transport protein, ApoE (Behl *et al.*, 2021; Lahiri *et al.*, 2004). The single gene ApoE is situated at chromosome 19q 13.2

and has apo E2, apoE3, and apoE4 variations (Lanfrancoet *al.*, 2020). The amino acids at positions 112 and 158 alter the structure and activity of the three allelic variations. Structurally ApoE consist of two domains. One is an N-terminal four helix domain at136-150 and the other is AC terminal lipid-binding domain at 244-272 (Wolfe *et al.*, 2019). In the case of isoforms, the amino acid difference is responsible for the difference in lipid and receptor binding. The apo E4 is reported to have an active contribution on sporadic AD development (Kate Shannon *et al.*, 2016). This gene can easily bind with Aβ and leads to its deposition (Balez *et al.*, 2016). The Aβ binding capacity of various isomers of ApoE are E2>E3>E2, where apo E2 and E3 isoforms are easily lipid dated than E4 it based on affinity for soluble Aβ. ApoE based Aβ clearance is believed to be due to the competitive binding of apoE and Aβ for low-density lipoprotein receptor related protein (LRP) (Vitali *et al.*, 2014).

Recent studies reported that in human neurons non-canonical mitogen-activated protein (MAP) kinase signalling pathway influences the APP transcription and Aβ6. Production by ApoE isoforms (apoE4>apoE3>apoE2) (Chen *et al.*, 2021; Zhao *et al.*, 2018). Post mortem studies revealed the relation between ApoE and amyloid deposition such as ApoE4 carrier accumulate more amyloid deposition than ApoE4 non-carrier AD patients. The fibrillogenic action of ApoE is needed for the maturation of diffuse Aβ to senile plaque. Aβ deposition varies in brain regions based on the ApoE effect. ApoE and apo act as inflammatory mediators after brain injury. Thus each ApoE isoforms have specific molecular and functional effects. Many studies on large-scale genome-wide association and genome-wide association meta-analyses stated that ApoE4 increases the genetic risk for AD development (Puglielli *et al.*, 2003), while ApoE2 shows protective genetic factors (Suidan *et al.*, 2019).

7. Cholesterol biomarkers for Alzheimer's disease diagnosis

Research on early diagnosis is the most active area in Alzheimer's study. Biomarkers help to predict AD development. The most used biomarkers are Aβ and tau neurofibrils. Research is ongoing for finding out another biomarker. Biomarkers change in disease progression, and it is difficult to identification and prediction of AD early stage. The following biomarkers are related to both AD and cholesterol.

7.1 ApoE

ApoE level increases in the case of AD patients (Zhao *et al.*, 2018). Presence of ApoE in CSF analysis helps to understand the AD development progression (Kate Shannon *et al.*, 2016).

7.2 hFABP3

Heart-type fatty acid-binding protein 3 is expressed in the cerebral neocortex, hippocampal CA1, CA2 regions, dopaminergic, acetyl cholinergic, glutamatergic neurons, and heart. The main functions of hFABP3 are membrane fluidity, synapse formation, and lipid transport. It is one of the essential proteins responsible for lipid metabolism and neurodegeneration. FABP3 in arachidonic acid-mediated relation indirectly causes the aggregation of Aβ and alfa-synuclein (αSyn), this progressively causes Aβ plaque formation. Increased concentration of FABP3 causes tau formation (Chiasserini *et al.*, 2017). Recent findings showed that the alteration of FABP3 occurs in CSF of AD patient (Dulewicz *et al.*, 2021). So, it can be used as a lipid-related biomarker.

7.3 ApoH

Apolipoprotein H (beta 2- glycoprotein I) is present as lipoproteins in plasma. It actively participates in metabolism of lipids, coagulation, and the production of antiphospholipid autoantibodies (Hoekstra *et al.*, 2021).

7.4 Vitamin D

The fat soluble vitamin, vitamin D is responsible for the formation and growth of bone by the regulation of calcium, phosphorus, *etc.* It is considered as neuroprotective hormone. Recent studies showed that it has beneficial effects in brain health (Bivona *et al.*, 2019; Sultan *et al.*, 2020) and neurodegenerative disease as Alzheimer's disease (Estadella *et al.*, 2021; Yang *et al.*, 2020). Esra Ertilav and her team scientifically suggested that a reduced level of vitamin D increases the risk for AD development (Ertilav *et al.*, 2021).

8. Receptors involved in cholesterol homeostasis

Cholesterol homeostasis in the brain does not clearly understand yet. Various research findings suggested many postulates. Receptors influence cholesterol homeostasis in the brain. Various receptors run behind this. Some of them are listed in the (Table 1) and genes responsible for AD development listed in (Table 2).

Table 1: Role of receptors in cholesterol homeostasis

Receptors	Function	References
PPAR-γ	Homeostasis of lipid and glucose in the brain, reduction in the production of Aβ (beta-amyloid plaques), and control mitochondrial biogenesis inhibition of neuroinflammation,	Kotha *et al.*, 2021
LDL receptor	Promote absorption of ApoE-containing lipoprotein particles in the brain	Nikolakopoulou *et al.*, 2021
Apoer2	Development of brain structure and synaptic plasticity in the adult brain. ApoER2 works as Sepp1 receptor	Dlugosz *et al.*, 2018
TREM2	Transmembrane receptor for lipids. It is found on amyloid cells plasma membrane and microglia. It has an active role in the innate immune response	Atagi *et al.*, 2015
CD36	Scavenger receptor, act as fatty-acid transporter, phagocytosis of apoptotic cells,	Yutuc *et al.*, 2020

Table 2: Genes in AD development in connection with cholesterol

S.No.	Gene	Role in AD development
1	ApoE (ApoE2, ApoE3 and ApoE4)	These are considered as basic allele for LOAD risk
2	Clusterin (CLU)	Clusterin (ApoJ) encoded by CLU gene is expressed in astrocytes. It has significant role on cholesterol and lipid transport. It is the level increase in AD patients
3	ABCA7	Intracellular cholesterol- and lipid transport remains unclear, transcription of ABCA7 is down regulated when cholesterol levels are high in the cell
4	TREM2 and PLCy2	Work with microglial lipid metabolism and showcase this pathway for LOAD development
5	Glial LOAD risk genes	Affect (micro) glial cholesterol metabolism could impact AD pathology

8.1 Peroxisome proliferator-activated receptor γ

Peroxisome proliferator-activated receptor γ is categorised under nuclear receptors. This receptor is responsible for the control of lipid, glucose, *etc*., in the brain. It helps to reduce the production of beta-amyloid plaque and inhibit neuroinflammation. This produces the cognitive enhancing effect in Alzheimer's disease (Kotha *et al*., 2021;Wagner *et al*.,2020;Wójtowicz *et al*.,2020).

8.2 LDL receptor and APOE receptor

The central nervous system has several cholesterol-regulated receptors such as LDL receptor (Grundy *et al*., 1990), VLDL receptor, apo ER2/LRP8, LRp4, LRP2 (megalin) (Basak *et al*., 2012), LRP1B, LRP5/LRP6 and LRP11/SORL1. Lipids and lipoproteins in ApoE are the ligands for these receptors. LDL receptor and LRP1 are the most prominent lipoprotein ApoE receptors in the brain (Wolfe *et al*., 2019) and helps in the uptake of apoE containing lipoprotein in the brain. LRP1 is expressed in neurons and highest transport capacity due to rapid endocytic rates than LDLR. LRP1 in the abluminal side of BBB acts as a scavenger receptor and helps to clearance of Aβ from interstitial fluid (Nikolakopoulou *et al*., 2021). The agonistic action of LRP1 increases the clearance of Aβ and is further eliminated with the help of the liver (Kim *et al*., 2020). In AD patients, LRP1 downregulated and decrease Aβ clearance. It causes the accumulation of Aβ.

8.3 ApoER2

ApoER2 was seen in humans and chickens. It is under the category of low-density lipoprotein receptors. It is expressed in the neocortex, hippocampus, cerebellum, olfactory bulb of the central nervous system, and a small amount expressed in the sciatic nerve, swan cells of the peripheral system. It can also be seen in the placenta, testis, ovary, and platelets. The human transcript comprises an open reading frame of 2889 bp encoding a protein with 963 amino acids and a molecular weight of 105 kDa. In mammals, the proline-rich unique region composed of 59 amino acids is seen in cytoplasmic domain of ApoER2. No other member of the LDL receptor family has this region. There are two probable SH3 binding motifs, PXXP, indicating a chance of signal transduction. The possible binding on the two hybrid screen, leads to the identification of the proteins, JIP-1 and JIP-2 and it will work as a molecular signalling mechanism, which controls the cell processes like proliferation, differentiation, migration apoptosis, *etc*. This receptor causes endocytosis of macromolecules *via* interaction with clarithrin and performs signal transduction with adapter proteins. It involves in reeling pathway which helps in the development of brain structure and synaptic plasticity in the adult brain. ApoER2 works as Sepp1 receptor at the blood-brain barrier as well as within the brain provide endocytosis of Sepp1 and selenium supply. Which decrease cognitive impairment and neurodegeneration (Dlugosz *et al*., 2018)

8.4 TREM 2

TREM 2 belongs to the immunoglobulin superfamily. It is a transmembrane receptor and usually found on myeloid cells in the plasma membrane and microglia (Olsen *et al*., 2020). It is also seen in basal ganglia, corpus callosum, spinal cord, and medulla oblongata. Innate immune response takes place by the activation of TREM2. TREM 2 in humans present in chromosome 6p21.1 (Gussago1 *et al*., 2019). TREM-like genes are TREM1, TREM2, TREM3, and TREM4. TREM1 and TREM2 interact with tyrosine kinase binding protein (TYROBP) and induce cell activation, followed by phagocytosis. TREM 2 binds lipopolysaccharides, HDL, LDL, APOE, APOJ, apoptotic neurons, and phospholipids. TREM2 binds commonly with APOE and their interaction in microglia produces modulation of phagocytosis of ApoE bound apoptotic neurons. It increases the chance of AD development (Atagi *et al*., 2015; Xue *et al*., 2021). R47H variant increases AD risk 4 times more than another variant by impairment of ligand binding. Over expression of TREM 2 leads to AD. It was experimentally proved in a mouse model of beta-amyloid accumulation (Wang *et al*., 2020).

8.5 CD36

CD36 receptor is categorized under the scavenger receptor class B group. CD36 increases the chance of progression of atherosclerosis, ischemia and ischemic stroke. It involves HDL uptake and oxidation of LDL, thus related to hyperlipidemia (Dobri *et al*., 2021). Amyloid-binding with CD3 receptors leads to pro-inflammatory responses and causes AD development (Edler *et al*., 2021; Ioghen *et al*., 2021). Evidence shows that CD3 active role in neuroinflammation, neurovascular dysfunction, and subsequent neurodegeneration (Ioghen *et al*., 2021).

8.6 N-methyl-D-aspartate receptors (NMDARs)

It is a glutamate-gated ion channels. This receptor imparts in regulation of CNS excitatory synaptic functions. It participate in the cholesterol biosynthesis modulation with endoplasmic reticulum protein INSIG (insulin induced gene) and sterol regulatory element-binding protein 2 (Yutuc *et al*., 2020)

9. Treatment options in Alzheimer's disease

Alzheimer's disease is of progressive neurodegenerative disease. It is quite difficult for early diagnosis due to its complexity of disease

progression, lack of exact mechanism, various stress factors and changes that occur in biomarkers of brain and CSF. AD can not be cured completely, drugs available today such as cholinesterase inhibitors can delay its progression (Nussbaum *et al.*, 2000). Researchers focus on new drug area for AD treatment. One important point of view is lipid-lowering drugs. Scientific evidence shows that lipid-lowering drugs can promote better effects in AD treatment (Bourre *et al.*, 2008). FDA-approved lipid-lowering drug as statin particularly lipophilic statin (atorvastatin and simvastatin) can possess better effect in the improvement of cognition impairment than hydrophilic statin drugs but phase 3 clinical trial of statin therapy could not possess any relevant effect in AD management (Samant *et al.*, 2021).

PCSK9 inhibitors are another option for AD management. These drugs showed a reduction in cholesterol levels. Alirocumab and Evolocumab are acting as PCSK9 inhibitors and these are under study in AD treatment. Liver X receptor agonists (TO901317 and GW3965) or retinoid X receptor agonists (bexarotene) show better effect in cognitive improvement by reducing Aβ deposition. The natural compound obtained from plants such as quercetin shows a better effect in cognitive improvement. It is another option in the treatment of AD.

Gene therapy and antisense oligonucleotide therapy are in primitive stage studies in AD management (Pena *et al.*, 2020). Nanotechnology based on ApoE delivery and adeno associated virus (AAV) (Mendell *et al.*, 2021) mediated gene therapy are promising fields in AD management. But, these are in the developing stage (Sudhakar *et al.*, 2019) only, so various research work studies are to be needed for conformation in the treatment strategy of AD.

All these are options for AD management only, but these options can not prove the efficacy in AD management. All are under studies only. Recently (June, 2021), U.S FDA approved aducanumab (Aduhelm™) in AD treatment by focussing its Aβ effect. Besides this, healthy lifestyle, physical exercise and diet are the key factors to ameliorate the risk of AD development particularly in ApoE4 carriers (Zhao *et al.*, 2018).

10. COVID and Alzheimer's disease

COVID -19 is most dangerous pandemic in this era. It mainly affects respiratory system, but one third of population experienced neurological complications after COVID progression, mainly neurodegeneration occurs (Wang *et al.*, 2020). Neurological symptoms as dizziness, ataxia, seizure, meningoencephalitis and stroke are more prominent in COVID (Harapan *et al.*, 2021). Thus, more importance must be given to this area too. In some cases, neurological symptoms were seen earlier before respiratory-related symptoms due to direct viral attach to CNS and in other cases, neurological complications occur as post-COVID effects (Estadella *et al.*, 2021; Tousi *et al.*, 2020). People with dementia are particularly vulnerable to being infected by and spreading SARS-CoV-2 because they may not adequately comprehend, execute, or recall any of the suggested public health measures like physical distancing and use of face masks (Gil *et al.*, 2021; Justyna, 2017; Li *et al.*, 2020; Rahman *et al.*,2021). Those with agitation, wandering, or disinhibition are probably at even higher risk of catching and spreading the infection (Mok *et al.*, 2020).

11. Conclusion

Age-related issues like Alzheimer's disease, dementia, *etc*., are on the rise, day-by-day. These diseases are affecting the lifestyle of elderly ones and at times, it is becoming a life-threatening issue. Due to the slow progression nature, it is difficult to differentiate between age-related issues like Alzheimer's disease and dementia. Multiple factors are contributing to the progression of such diseases. Modern lifestyle and fast-food consumption nature increase the cholesterol consumption and deposition in our body. It is becoming one of the key risk factors in AD development. Several genes also play a crucial role in such developments. This article discusses the impact of cholesterol consumption from a high-fat diet on the development of age-related issues, especially Alzheimer's disease. It also touches on the role of several genes play in the progression of AD.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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