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REVIEW

A Potential Link Between Visceral Obesity and Risk of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common type of dementia characterized by the deposition of amyloid beta (Aβ) plaques and tau-neurofibrillary tangles in the brain. Visceral obesity (VO) is usually associated with low-grade inflammation due to higher expression of pro-inflammatory cytokines by adipose tissue. The objective of the present review was to evaluate the potential link between VO and the development of AD. Tissue hypoxia in obesity promotes tissue injury, production of adipocytokines, and release of pro-inflammatory cytokines leading to an oxidative-inflammatory loop with induction of insulin resistance. Importantly, brain insulin signaling is involved in the pathogenesis of AD and lower cognitive function. Obesity and enlargement of visceral adipose tissue are associated with the deposition of Aβ. All of this is consonant with VO increasing the risk of AD through the dysregulation of adipocytokines which affect the development of AD. The activated nuclear factor kappa B (NF-κB) pathway in VO might be a potential link in the development of AD. Likewise, the higher concentration of advanced glycation end-products in VO could be implicated in the pathogenesis of AD. Taken together, different inflammatory signaling pathways are activated in VO that all have a negative impact on the cognitive function and progression of AD except hypoxia-inducible factor 1 which has beneficial and neuroprotective effects in mitigating the progression of AD. In addition, VO-mediated hypoadiponectinemia and leptin resistance may promote the progression of Aβ formation and tau phosphorylation with the development of AD. In conclusion, VO-induced AD is mainly mediated through the induction of oxidative stress, inflammatory changes, leptin resistance, and hypoadiponectinemia that collectively trigger Aβ formation and neuroinflammation. Thus, early recognition of VO by visceral adiposity index with appropriate management could be a preventive measure against the development of AD in patients with VO.

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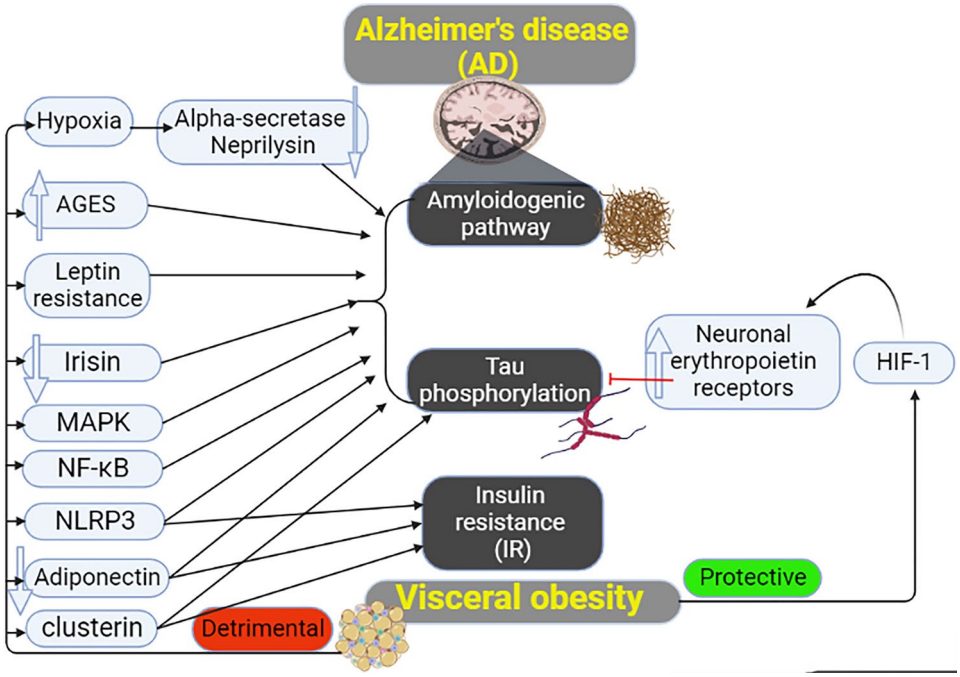
Graphical Abstract



Keywords Alzheimer's disease · Visceral obesity · Leptin resistance · Oxidative stress · Inflammatory changes

Introduction

Alzheimer's disease (AD) is the most frequent type of dementia. AD was first identified in 1907 by Alois Alzheimer [1]. AD is recognized as a single neurological entity; its frequency is very much increased after the age of 65 [2, 3]. AD should be distinguished from other types of dementia including reversible dementia, Parkinson-associated dementia, vascular dementia, and frontotemporal dementia [1]. AD represents 70% of all dementia types; it upsurges with age, doubling every 10 years. It has been reported that AD prevalence is 3% in individuals aged 65–74, to about 50% in subjects aged 85 years and older [4, 5]. The prevalence of AD was about 5 million in 2007 that is suspected to increase to 13 million in 2050 [6]. Furthermore, head trauma, female sex, low education level, cardio-metabolic disorders, and vascular diseases are considered risk factors for the progress of AD [7]. Nonetheless, till now there is no specific biomarker that differentiates AD from other types of dementia. As well, brain biopsy and brain positron emission tomography were used in the diagnosis of AD but with conflicting findings [4].

The pathologic findings of AD include senile and neuritic plaques with noteworthy dendritic loss, dystrophic neuritis, neuropil threads, and cerebrovascular amyloid [8]. However, synaptic loss, amyloid pathway, and Lewy body deposition are the main pathological feature of AD [8, 9]. Also, AD is characterized by the deposition of amyloid beta (Aβ) plaques and tau-neurofibrillary tangles (TNTs) in the brain. Remarkably, deposition of Aβ occurs earlier than the pathology of cortical tau. Deposition of Aβ-induces tau-mediated neuronal and synaptic loss in AD, though tau neuropathology can progress independently of Aβ accumulation [8–10]. The neuropathological changes in AD are related to the deposition of amyloid plaques, neurofibrillary tangles, and progression of neuroinflammation, neuronal mitochondrial dysfunction, autophagy dysfunction, and cholinergic synaptic dysfunction [11, 12] (Fig. 1).

The clinical presentation of AD patients is characterized by cognitive dysfunction, speech dysfunction, sensorymotor disorders, memory loss, and personality disorders. However, some AD patients stay stable for several years and may improve with time [13]. Additionally, early-onset AD is more progressive and characterized by less memory loss with higher psychosocial disorders [13, 14]. Authentic AD patients presented with apraxia, judgment dysfunction, speech abnormalities, disorientation, and personality changes [13, 14]. The main clinical findings in AD patients are related to neuropsychiatric disorders (Fig. 2).

Management of AD patients is mostly symptomatic by treatment with cholinesterase inhibitors like donepezil, rivastigmine, tacrine, and galantamine. Also,

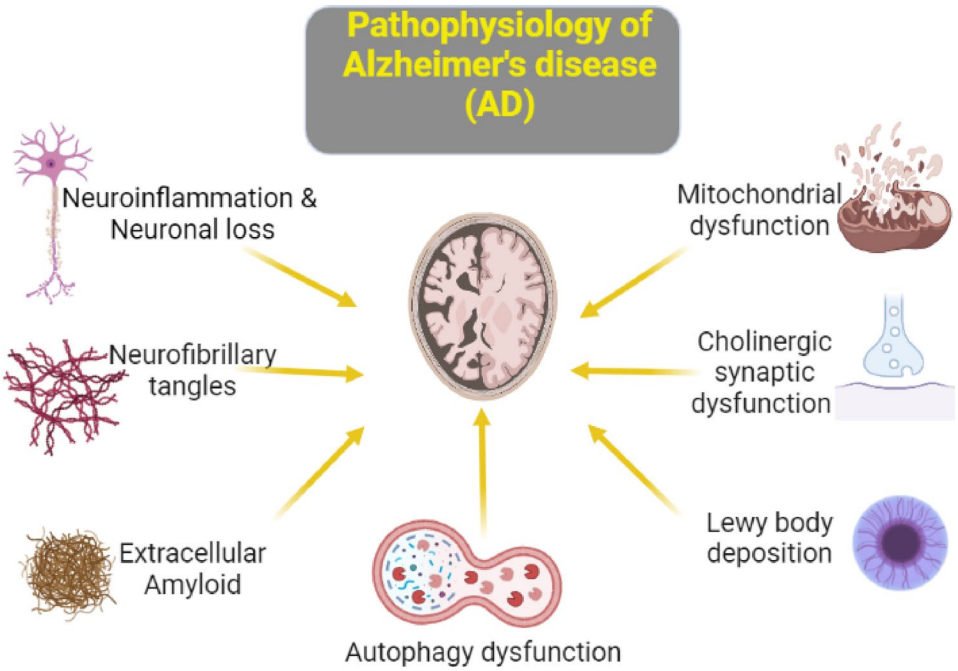


Fig. 1 Pathophysiology of Alzheimer's disease (AD)

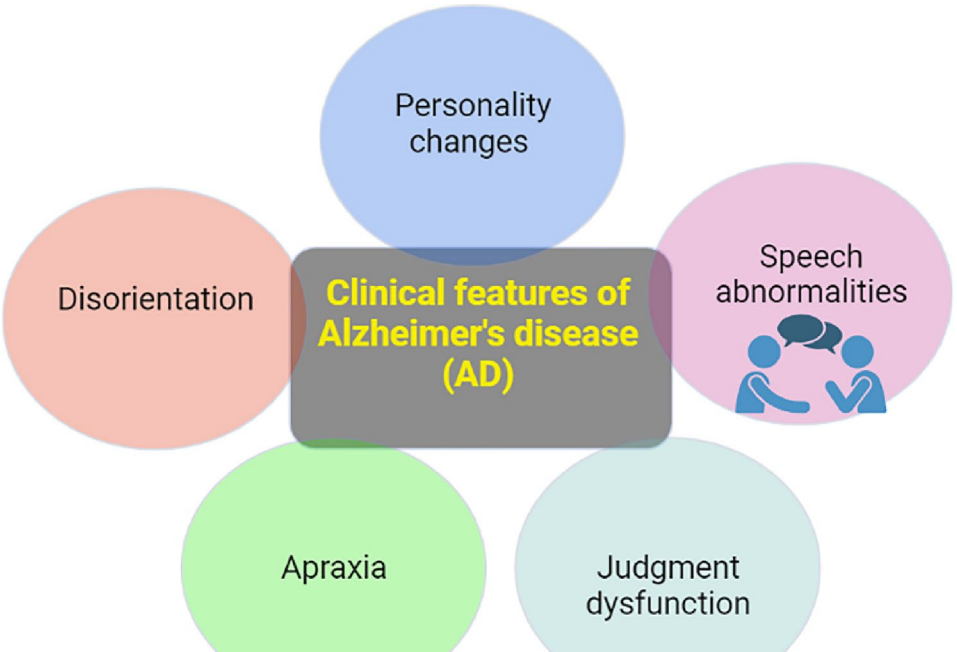


Fig. 2 Clinical features of Alzheimer's disease (AD)

N-methyl-D-aspartate (NMDA) antagonists like memantine are used in treating cognitive deficits in AD patients [15, 16]. Nonetheless, these agents provide symptomatic relief without affecting the etiopathologic progression of AD [15, 16] (Fig. 3).

It has been shown that different metabolic disorders including obesity, insulin resistance (IR), and related inflammatory disorders are associated with an increased risk for the development of AD [17, 18]. Notably, central obesity is associated with the early-onset development of AD due to increased inflammation and IR [19, 20]. The visceral adiposity index (VAI, please see below for its calculation) reflects adipose tissue dysfunction and central obesity. Thus, this review is aimed to evaluate the potential link between VO and the development of AD.

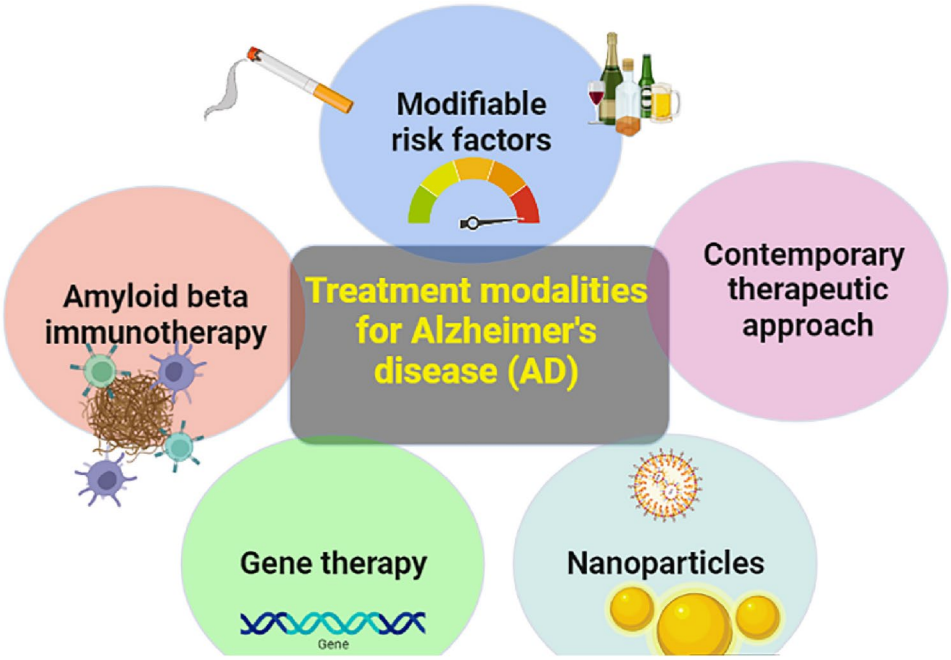


Fig. 3 Management of Alzheimer's disease (AD)

Obesity and VAI

Obesity is a medical condition due to the excessive accumulation of body fat which adversely affects health [21]. Obesity is defined as body mass index (BMI) ≥ 30 kg/m^2. Obesity is correlated with the development of cardiometabolic disorders and other diseases including dyslipidemia, hypertension, IR, type 2 diabetes mellitus (T2DM) and coronary heart diseases as well as malignancies respectively [22, 23]. Different indicators and predictors of obesity are used; one of the most common one is BMI. It has been shown that BMI is incorrectly regarded as a suitable indicator of body fat and obesity as it shows a non-linear correlation with the percentage of body fats in both sexes [24]. Many factors affect the validity of BMI including age, race, gender, hydration status and muscle mass [25]. A retrospective study conducted by Flegal et al. [26] showed that BMI was not a good indicator for assessing the association between obesity and mortality. Furthermore, a meta-analysis and cohort studies illustrated that BMI was not to be used as a predictor of primary and secondary preventions of cardiovascular diseases, as it does not differentiate between body fat and lean mass [27]. Notably, BMI is correlated significantly with indicators of true body fat and does not consider the effect of age, race, and sex [27]. Besides, BMI was not correlated significantly with abdominal obesity and related cardiovascular risk factors as other indicators like waist circumference (WC) and VAI. However, WC cannot differentiate between visceral and subcutaneous fats [28].

Currently, VAI is used to estimate central visceral obesity (VO) which is more correlated with cardiovascular risk factors in the development of cardiovascular diseases [29]. VAI is regarded as an independent indicator associated with 10 years of cardiovascular risk in men with little association in women [29]. Thus, VAI can be routinely used to recognize men obese individuals at risk for cardiovascular complications. A prospective study in Europe found that VAI is an additional indicator to detect cardiovascular risk in men without previous cardiovascular diseases [29]. Amato et al. [30] illustrated that VAI was a reliable indicator of central obesity and visceral fat dysfunction, and was associated with cardiometabolic risk. A retrospective study involved 315 non-obese individuals revealed that VAI was correlated with cardiovascular risk [OR 2.45, 95% CI 1.5–3.95, $P < 0.0001$]. In addition, VAI was negatively correlated with insulin sensitivity [$Rs = -0.72$, $P < 0.001$] [30]. This observation suggests that VAI is a valuable predictor and indicator of central obesity and IR in patients with cardiometabolic disorders. To date, many studies have shown that VAI is linked with VO-induced inflammation, atherosclerosis, and coronary heart diseases [31, 32]. Li and colleagues [31] in a retrospective study observed that neutrophil-lymphocyte ratio (NLR) and VAI are increased in patients with carotid atherosclerosis which predict 10 years of cardiovascular risk. In Chinese patients with coronary heart disease, VAI was higher.

Of note, VAI can be easily calculated by the following equation according to Nusrianto et al. [33] that depends on many variables including WC, BMI, high-density lipoprotein (HDL), and triglyceride (TG) levels.

$$\text{Males: VAI} = \left[\frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})}\right] \times \left[\frac{\text{TG}}{1.03}\right] \times \left[\frac{1.31}{\text{HDL}}\right]$$

$$\text{Females: VAI} = \left[\frac{\text{WC}}{36.58 + (1.89 \times \text{BMI})}\right] \times \left[\frac{\text{TG}}{0.81}\right] \times \left[\frac{1.52}{\text{HDL}}\right]$$

VAI is an empirical mathematical method for the assessment function and distribution of body fat [33]. VAI is regarded as a potential indicator of cardiometabolic risk and the development of metabolic syndrome [34]. Furthermore, VAI is considered a better predictor for the development of T2DM and hypertension [35, 36]. VAI is also superior to WC and BMI in predicting the function and distribution of visceral fats in post-menopausal women with low-calorie diets [37]. All this taken together points to VAI being an accurate potential predictor of cardiovascular risk in obese patients. The cut-off value of VAI and associated adipose tissue dysfunction (ATD) according to age is illustrated in Table 1 [20].

Despite this valuable role of VAI, the application of this method is incorrect in small sample size, patients with morbid obesity and obese children less than 16 years. In addition, VAI is affected by fibrate drugs which reduce TG level [20, 38].

Visceral Obesity (VO) and Inflammation

VO is commonly associated with low-grade inflammation due to higher expression of pro-inflammatory cytokines by adipose tissue [39, 40]. An experimental study illustrated that visceral adipose tissue (VAT) affects the reactivity of immune cells within visceral lymph nods. Inflammatory cytokines promote the migration of dendritic cells (DCs) from small intestines to the visceral lymph nodes in mice with a high-fat diet [39]. Thus, visceral lymph nodes seem to be the potential nexus between adipose tissue and intestinal inflammation with exacerbation of systemic inflammation [39].

There is an emerging body of work indicating that genes, epigenetics, and the in-utero environment can impact whether or not a child is obese [41]. While certain genes have been identified that increase one's risk for becoming obese, other factors such as excess gestational weight gain, gestational diabetes mellitus, and smoking can also influence this risk [41, 42]. However, further research is needed to determine which efforts are effective at decreasing the incidence of obesity and to develop new methods of prevention. Over the past several years, many discoveries have been made regarding the genetic variation that influences complex diseases like cardiovascular disease and obesity [43]. These new discoveries have largely resulted from genome-wide association studies where the application of high-throughput genotyping of millions of genetic markers enables researchers to examine genetic associations on a genome-wide basis. Recent reports indicate that at least 32 genes contribute to common forms of obesity [44]. A number of these have also been confirmed as contributors to pediatric obesity [44]. Many of these genes are thought to be related to the development of obesity through the dysregulation of leptin or other metabolic hormones in the body. A majority of the newly discovered genes are expressed in the brain, emphasizing the role of the central nervous system in obesity risk [43–45].

Various studies confirm that VO is connected with abnormal cytokine production and activation of inflammatory signaling pathways [46, 47]. An observational study involved 600 obese patients demonstrated that VAT but not subcutaneous adipose tissue (SAT) is associated with systemic inflammation as evidenced by high levels of c-reactive protein (CRP) and NLR [47]. VAT is regarded as a possible source of inflammation due to the infiltration of macrophages, the main source of pro-inflammatory cytokines. It has been documented that obese patients had a higher level of tumor necrosis factor alpha (TNF-α) as compared to lean subjects [47, 48]. A previous experimental study showed that TNF-α increased exponentially with the development of VAT in obese mice [49]. Obesity and associated metabolic disorders promote macrophage accumulations with the induction of abnormal immune response. Interestingly, TNF-α activates hormone-sensitive lipase with further release of non-esterified fatty acids into the circulation with impairment of insulin sensitivity [50, 51]. Obesity-induced inflammation is linked with the progression of systemic disorders like atherosclerosis, endothelial dysfunction (ED), and hypertension [52]. Of note, obese subjects have high circulating levels of interleukin (IL)-6, TNF-α, CRP and pro-inflammatory adipocytokines like leptin. Pro-inflammatory adipocytokines trigger chronic inflammation [53, 54]. The anti-inflammatory adiponectin plays a crucial role in the mitigation of VO-induced inflammation by inhibiting the expression of nuclear factor kappa B (NF-κB) and TNF-α [55–58]. Of interest, adiponectin serum level is reduced in obese subjects [59]. A prospective study involving 193 obese subjects showed that adiponectin serum level was low

Table 1 The cut-off value of visceral adiposity index (VAI) and associated adipose tissue dysfunction (ATD) [20]

ATD	VAI according to the age				
	<30 years	30–42 years	42–52 years	52–66 years	> 66 years
Mild	2.53–2.58	2.24–2.53	1.93–2.16	1.94–2.32	2.01–2.41
Moderate	2.59–2.73	2.54–3.12	2.17–2.77	2.32–3.25	2.42–3.17
Severe	> 2.73	> 3.12	> 2.77	> 2.25	> 3.17

mainly in subjects with high VAI and VAT [59]. Therefore, increasing visceral fat in overweight and obese subjects augments the risk for the development of systemic inflammation due to the reduction in the circulating anti-inflammatory adiponectin level.

Taken together, the development of VO is associated with the augmentation of pro-inflammatory and proatherogenic mediators leading to ED, IR and atherosclerosis (Fig. 4).

Visceral Obesity (VO) and Insulin Resistance (IR)

IR represents glucose intolerance with a reduction of physiological response to insulin resulting in the development of hyperinsulinemia with euglycemia [60]. Obesity is the major contributor to the progression of IR which interrupts many intracellular signaling [61]. IR induces the over-production of non-esterified fatty acids with the progression of inflammation, oxidative stress, and mitochondrial dysfunction [62, 63]. VAT-induced oxidative stress triggers IR through the modulation of insulin receptors and insulin action [64]. High-fat diet activates the generation of reactive oxygen species (ROS) which impairs insulin sensitivity and triggers inflammatory changes with the development of hyperinflammation [48, 65, 66]. In addition, tissue hypoxia in obesity promotes tissue injury, production of adipocytokines and release of pro-inflammatory cytokines leading to an oxidative-inflammatory loop with induction of IR [63, 66]. Oxidized low density lipoprotein (LDL) and free fatty acids induce the development of IR and associated cardiometabolic changes like atherosclerosis [63, 66]. The precise mechanisms of IR in obesity seem to be multifactorial including glucolipotoxicity, endoplasmic reticulum stress, and oxidative stress [67, 68]. Hardy et al. [69] found that VAT is mainly associated with the development of IR due to inflammatory and oxidative stress interactions. In addition, the accumulation of VAT is thought to affect whole-body insulin sensitivity, unlike peripheral adipose tissue accumulation which does not affect the development of IR [70]. The molecular mechanism of IR in obesity is mainly related to the upregulation of peroxisome proliferator activator receptor gamma (PPARγ) [71, 72]. PPARγ deficient mice are protected from the development of IR following a high-fat diet. Therefore, targeting PPARγ could be a possible therapeutic option for IR [71]. Furthermore, metabolic inflammation could be the main cause of the propagation of IR in obesity [73]. Notoriously, VAT promotes the polarization of immune and inflammatory cells towards skeletal muscle, liver, adipose tissue, brain and pancreatic islets causing metabolic derangement and development of IR [73]. Thus, anti-inflammatory agents by targeting inflammatory cells might attenuate VAT-induced metabolic disorders and related diseases like T2DM and atherosclerosis.

These findings proposed a strong link between VO and IR through the creation of an inflammatory/oxidative loop that disturbs the insulin signaling pathway (Fig. 5).

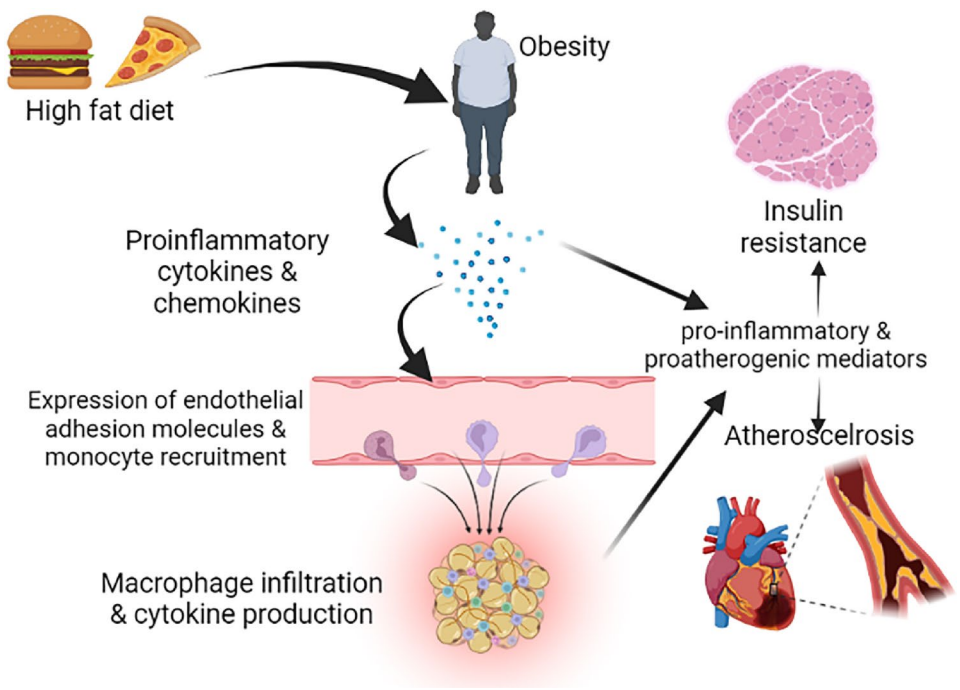


Fig. 4 Visceral obesity and development of systemic inflammation

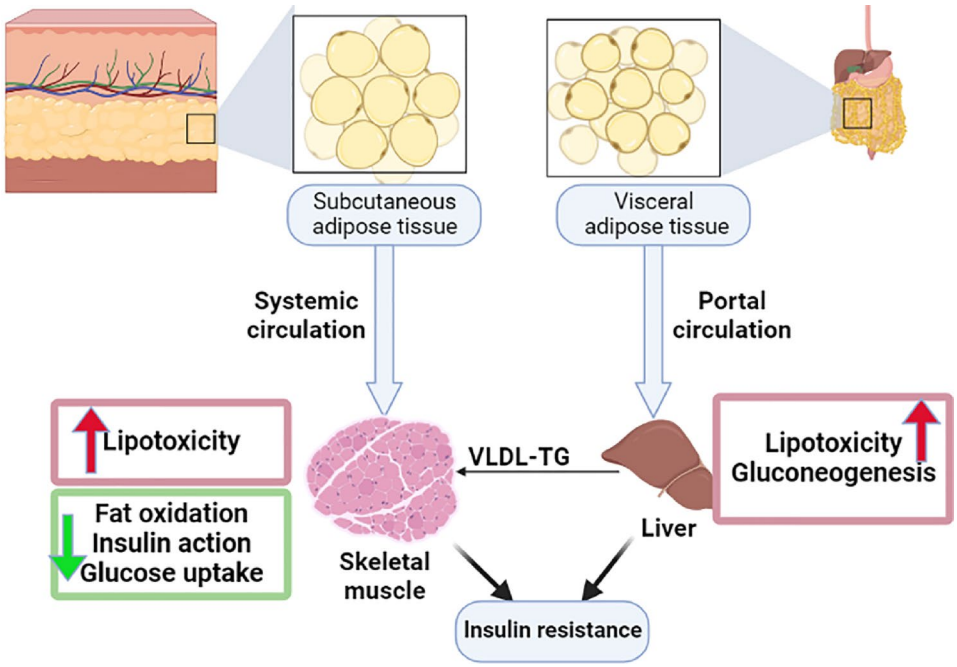


Fig. 5 Visceral obesity and development of insulin resistance

Visceral Obesity (VO) and Brain IR

It has been shown that brain insulin signaling is involved in the pathogenesis of AD through AKT phosphorylation which induces AD pathology and lowers cognitive function [74]. A community-based clinic-pathological cohort study involving 150 old patients with and without T2DM reported that insulin signaling was severely disturbed by postmortem analysis [74]. Interestingly, activation of neuronal insulin signaling has been observed to prevent memory loss in an AD model consonant with neuroprotection[75]. Also, the expression of insulin-like growth factor 1 receptor (IGF1R) was increased in postmortem hippocampal tissue from AD patients [75]. Of note, brain IGF1 signaling was severely impaired in AD patients. Thus, boosting brain insulin and IGF1 signaling could be a promising therapy for AD. It has been shown that the administration of intranasal insulin improves memory performance through the enhancement of synaptic plasticity and neurotransmitter function and could be a good treatment for AD [76].

Insulin receptors are widely expressed in certain brain regions involved in the regulation of cognition, appetite, olfaction, and autonomic function [77]. Insulin receptors regulate neuronal plasticity and metabolism and afford a neuroprotective effect. The functional activity of insulin receptors in the brain is distinct from peripheral metabolic effects. Dysfunction of insulin receptors and insulin signaling pathways promote the progression of various brain disorders [77]. Insulin concentration in different brain areas like the brain cortex, hypothalamus, and hippocampus is higher than plasma [78]. Of note, insulin does not affect neuronal glucose transport and expression of glucose transporter 4 (GLUT-4) [78].

Interestingly, insulin in the brain is involved in the regulation of cognitive function rather than glucose uptake as in the peripheral tissues. It exerts neuromodulatory and neuroprotective effects with a positive impact on memory function through the modulation of synaptic activity and neurotransmitter release [79]. Peripheral glucose uptake and cognitive function are reduced with age by an unknown mechanism. Dysregulation of peripheral glucose signaling may affect hippocampal functional activity and stability [79, 80]. Different studies have shown that insulin decreases the risk for the progression of AD. Insulin increases Aβ clearance [74, 81]. In contrast, disturbances in brain insulin levels may lead to detrimental effects through the phosphorylation of tau protein (Fig. 6).

In this context, VO-induced IR may also promote brain IR with impairment of cognitive function and development of AD [82]. Moreover, high-fat diet (HFD)-induced obesity increases deposition of Aβ with significant impairment of cognitive function in mice via deregulation of the brain insulin signaling pathway [83]. Development of brain IR promotes neurodegeneration and neuroinflammation with progress to AD through activation of neuronal mitogen-activated protein kinase (MAPK) which enhances aggregation of Aβ and formation of neurofibrillary tangles (NFTs) [74, 82]. In turn, high Aβ and NFTs reduce the expression of neuronal insulin receptors with the development of IR and further deterioration of AD pathology [84]. Activated neuronal MAPK triggers neuroinflammation and tau phosphorylation via inhibition of adenosine monophosphate (AMP)

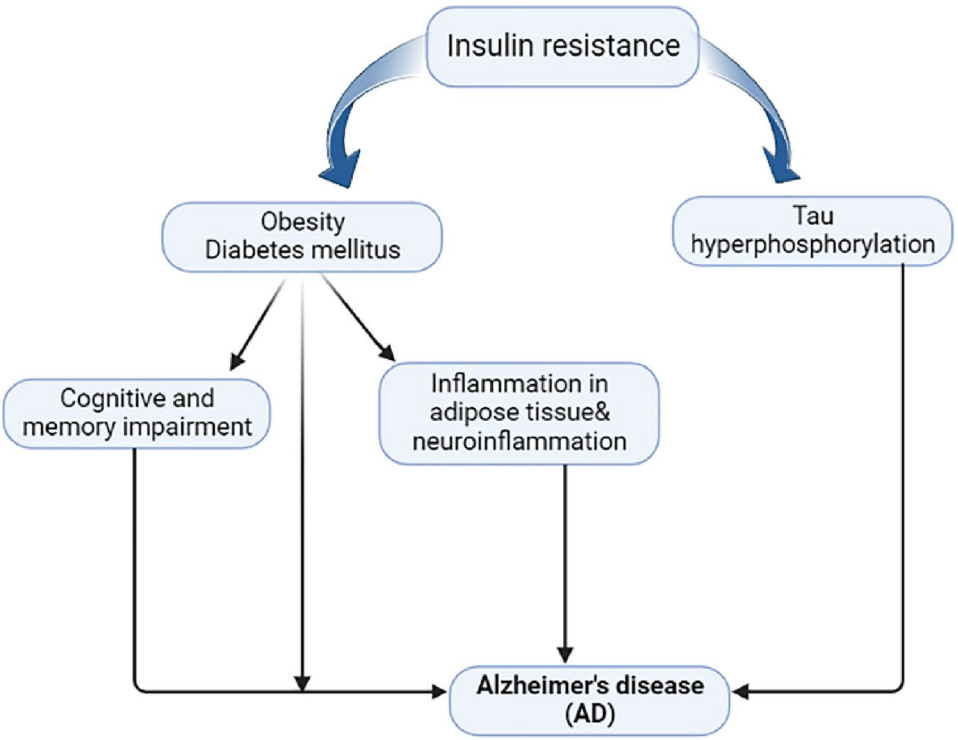


Fig. 6 Visceral obesity and brain IR

and activation of glycogen synthase kinase (GSK) leading to Aβ accumulation and progression of the pathogenesis of AD [85]. Thus, regulation of brain insulin function enhances neuronal activity and prevents the development of AD neuropathology [82].

The possible mechanisms of insulin in the enhancement of cognitive function in AD are related to various regulations of neuronal signaling pathways. Insulin improves catecholamine release and uptake, regulates the expression of NMDA and gamma-Aminobutyric Acid (GABA) receptors, and enhances the cerebral cortex AMP pathway and cortisol circadian rhythm [76, 85] (Fig. 7).

These findings suggest that insulin plays a critical role in the promotion of cognitive function and the prevention

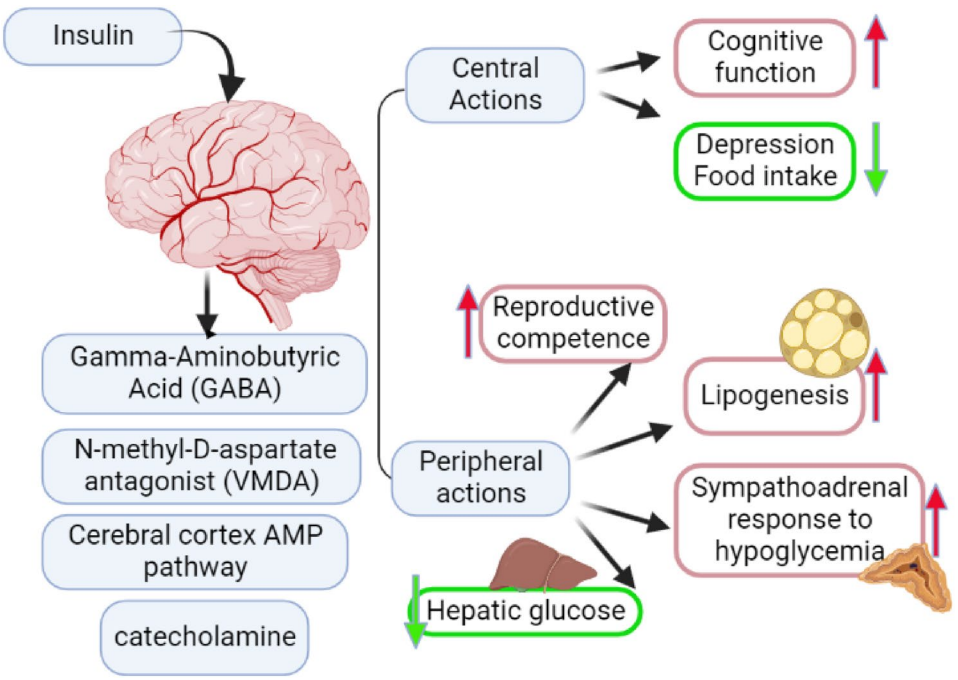


Fig. 7 Cognitive enhancing effects of insulin

progression of AD. Thus, VO-induced IR could be one of the important pathways in the pathogenesis of AD.

Visceral Obesity (VO) and Risk of AD

Of note, AD is developing due to Aβ accumulation via the amyloidogenic pathway with the formation of Aβ plaques. The processing and production of Aβ plaques affect neuronal activity through the interruption of synaptic activity and induction of cell death [86]. Obesity and enlargement of VAT are associated with the deposition of Aβ [87]. Obesity is regarded as an independent risk factor for the development of AD, and 7.3% of AD patients over the age of 65 years are directly attributed to previous midlife central obesity [87]. Interestingly, apolipoprotein J known as clusterin which is involved in the pathogenesis of AD is increased in various cardiometabolic disorders including obesity [87]. Oh et al. [88] illustrated that the expression of clusterin is involved in the pathogenesis of early-stage AD via enhancement of Aβ-induced neurotoxicity and advancement of cognitive impairments in mice. Besides, adipose tissue-clusterin promotes IR via the induction release of pro-inflammatory cytokines and oxidative stress [89]. Thus, there is a potential link between obesity and the development of AD through the clusterin pathway [89].

On the other hand, high-fat diet-induced obesity promotes brain Aβ pathology. Shie et al. [90] demonstrated that hepatic steatosis and obesity are linked with high circulating Aβ in metabolically stressed mice. Furthermore, increasing circulating levels of Aβ in T2DM and obesity promote the development of ED due to impairment of the nitric oxide (NO) pathway [91]. An experimental study demonstrated that leptin resistance in obese mice promotes the deposition of tau protein [92]. Thus, leptin resistance-induced obesity enhances tauopathy and the development of NFT [92]. Remarkably, VAT triggers the activation of MAPK which is involved in tau pathology and neuroinflammation [93]. Hyperphosphorylation of tau proteins by MAPK promotes the generation of NFT which trigger neuroinflammation and neurodegeneration with subsequent cognitive impairment [93]. Herein, an activated MAPK signaling pathway in obese patients could a possible association between VO and the development of AD.

Moreover, irisin which is a myokine produced from adipose tissue, muscles and hippocampus has a neuroprotective role against the development of AD. Irisin improves neuronal synaptic plasticity with a positive impact on the cognitive function and development of dementia [94–96]. Notably, irisin level is reduced in the AD model in both hippocampus and cerebrospinal fluid (CSF). The deficiency of irisin enhances tau pathology and Aβ formation [97]. It has been reported that irisin level is positively correlated with fat mass and BMI and negatively correlated with adiponectin serum level. Thus, the irisin level is reduced following weight loss and bariatric surgery [98]. Leung et al. [99] observed that irisin level was reduced in Chinese adults with obesity due to uncontrolled inflammatory changes. Therefore, the reduction of irisin activity in obese patients may exacerbate neuroinflammation and the development of AD.

Indeed, central obesity with a high waist-height ratio (WHR) is regarded as a high-risk factor for the development of late-onset AD [19]. In addition, high BMI in middle age is correlated with a higher incidence of AD in late life. In contrast, low BMI was also reported to be a risk factor for the development of AD [100]. Loss of olfaction is the initial manifestation of AD that cause poor appetite and weight reduction [101]. Thus, weight loss and reduction of BMI are the consequences of AD, and the reverse is not true. Likewise, the reduction of lean body mass and the increase in body fat percentage may increase the risk of AD [102]. Loss of lean mass is accelerated in AD and is associated with brain atrophy and cognitive performance, perhaps as a direct or indirect consequence of AD pathophysiology or through shared mechanisms common to both AD and sarcopenia [102]. In particular, the percentage of fat was positively associated with cortical thickness and the highest WHR group showed significantly decreased cortical thickness in men compared with the reference group. WHR showed an inverted U-shaped association with total cortical thickness and frontal lobe thickness in men, this association was not detected in women [103]. As well, the increase in body fat percentage is associated with the risk of AD [104]. Therefore, the increase of BMI and body fat percentage may increase the risk of AD development through the induction of Aβ accumulation and release of pro-inflammatory cytokines which promote the development of neuroinflammation.

In this state of affairs, VAI which includes both WC and BMI might be more appropriate in the estimation of VO and its relation with the development of AD. Adiposity indices have a strong relationship with cognitive decline in AD patients [105]. An elegant study revealed that high adiposity indices like the VAT ratio are correlated with abnormal white matter hyperdensity. Thus, higher VAI which reflects VO is regarded as an independent risk factor for cognitive dysfunction in AD patients [105].

These findings are consonant with VO increasing the risk of AD through the dysregulation of adipocytokines which affect the development of AD (Fig. 8).

Taking into account all these mechanisms, one is tempted to propose that targeting obesity-induced IR and inflammation reduces the risk of AD through modulation of systemic inflammation, neuroinflammation and brain IR. An experimental study revealed that administration of natural raspberry ketone in obese rats reduced body weight, BMI and

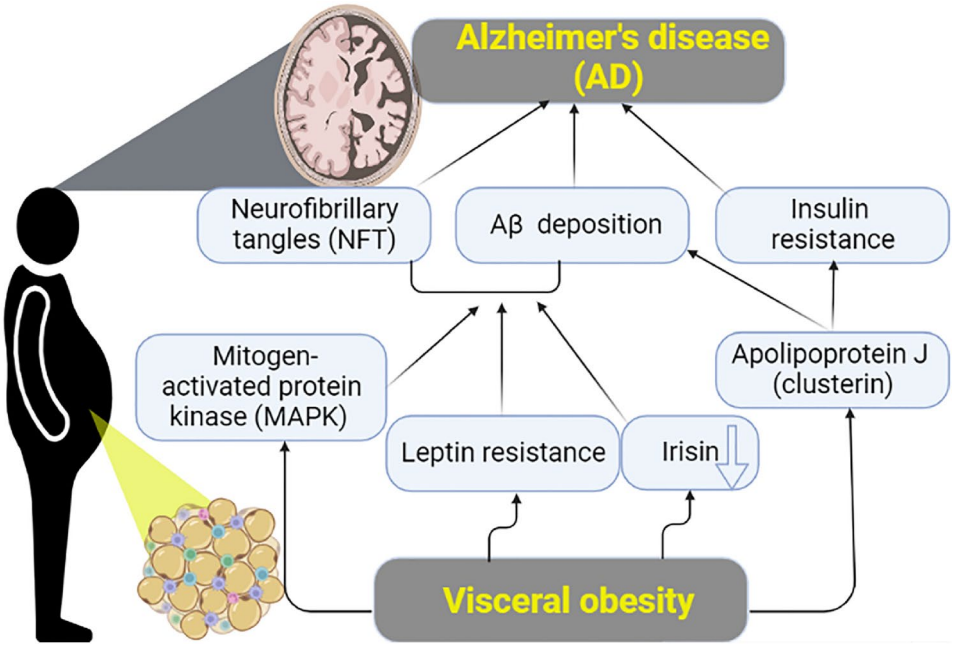


Fig. 8 Visceral obesity and risk of Alzheimer's disease (AD)

improved cholinergic neuron activity [106] suggesting that concomitant supplementation of natural raspberry ketone with calorie restricted regimen effectively modulate the neurodegenerative changes induced by obesity and delay of the progression of AD. In addition, modulation of peripheral and brain IR in obesity by metformin may reduce the risk of neurodegeneration and AD [107]. Therefore, metformin could be a promising therapeutic agent in the management of AD [107]. Furthermore, quercetin (QT) is one of the most abundant polyphenolic flavonoids, which is present in fruits and vegetables and displays many biological, health-promoting effects in a wide range of diseases. In vitro, in vivo, and clinical evidence regarding the anti-Alzheimer, anti-diabetic and anti-obesity effects of QT were approved [108]. Thus, mitigation of T2DM-induced systemic inflammation by metformin and QT may reduce the risk for development of AD.

Signaling Pathways Link Visceral Obesity and AD

Different signaling pathways are involved in the pathogenesis of VO and AD, and they might be a potential link between VO and AD is summarized in Table 2.

MAPK and mTOR

In VO, different inflammatory and metabolic pathways are more active which in direct or indirect ways could affect the development of AD. It has been reported that MAPK is implicated in obesity-mediated complications [109]. Activation of MAPK in obesity triggers systemic inflammation and apoptosis causing peripheral and central effects [109]. Obesity-induced IR and hyperinsulinemia through IGF promote the expression of MAPK and mechanistic targets of rapamycin (mTOR) are involved in the development of systemic complications [109]. Notably, MAPK plays a crucial role in the pathogenesis of AD through the induction of neuroinflammation [110]. MAPK promotes excitotoxicity, synaptic dysfunction and tau phosphorylation. Besides, mTOR is also involved in the pathogenesis of AD and other types of dementia through the modulation of neuronal lysosomal and autophagy processes [110]. The administration of rapamycin in mice after the development of Aβ deposition was effective in the reduction of Aβ plaque accumulation [111]. In addition, the beneficial effects of glucagon-like peptide (GLP-1) in treating AD are mediated through the induction of mTOR [127]. This may explain the double-edge effects of mTOR in the pathogenesis of AD. Therefore, targeting mTOR and MAPK pathways could be effective in the management of AD. Thus, mTOR and MAPK pathways could be a potential link between VO and the development of AD.

NLRP3 Inflammasome

Furthermore, activation of nod-like receptor pyrin 3 (NLRP3) inflammasome is intricate with the progression of the inflammatory process in obesity [112]. Chronic inflammation in obesity may be mediated by activated NLRP3 inflammasome which induces expression cleavage of caspase 1 and release of IL-1β and development of lipotoxicity

Table 2 Different signaling pathways are involved in the pathogenesis of visceral obesity (VO) and Alzheimer's disease (AD)

References	Study type	Findings
Donohoe et al. [109]	Review study	MAPK and mTOR pathways are implicated in obesity-mediated complications
Munoz et al. [110]	Review study	MAPK plays a crucial role in the pathogenesis of AD through the induction of neuroinflammation
Lin et al. [111]	Experimental study	Rapamycin was effective in the reduction of Aβ plaque accumulation
Vandanmagsar et al. [112]	Experimental study	Activation of NLRP3 inflammasome is intricate with the progression of the inflammatory process in obesity
Hanslik et al. [113]	Review study	NLRP3 inflammasome activation results in microglia stimulation, assembly and aggregation of Aβ, and enhancement of tau-associated neurobiology
Halle et al. [114]	In vitro study	Deposition of Aβ and NFT were linked with the activation of NLRP3 inflammasome in the microglia
Ising et al. [115]	Experimental study	NLRP3 inflammasome activation was associated with tau aggregation and exacerbation of AD in mice
Shoelson et al. [116]	Experimental study	NF-κB is implicated in the development of inflammation and IR in obesity
Granic et al. [117]	Review study	The NF-κB pathway is involved in the pathogenesis of AD and could be a potential link between T2DM and the progression of AD
Lukiw [139]	Experimental study	The NF-κB pathway was involved in the induction of pro-inflammatory miRNA in AD
Kong et al. [145]	Experimental study	Forsythoside B could prevent NF-κB-mediated neuroinflammation in mice with experimental AD
Egaña-Gorroño et al. [118]	Review study	Obesity is associated with augmentation of AGEs levels which mediate oxidative stress and inflammation
Beeri et al. [119]	Case-control study	AGEs/RAGEs are implicated in the progression of neuroinflammation and AD
Gaspar et al. [120]	Review study	Dysregulation of hypoxia-inducible factor 1 (HIF-1) is intricate in the development of obesity and related complications
Hassan et al. [121]	Review study	Transcription of HIF-1 is augmented as a compensatory mechanism in AD
Zhang et al. [122]	Experimental study	HIF-1 inhibits the expression of neprilysin and increases the cleavage of amyloid precursor proteins
Lall et al. [123]	Experimental study	HIF-1 exerts a neuroprotective effect against the development of AD via suppression of oxidative stress and neuroinflammation induced by Aβ toxicity
Mariani et al. [124]	Experimental study	SIRT1 has a protective effect against VO, and it reduced in obesity
Kuang et al. [125]	Review study	SIRT-1 inactivation is associated with defective Aβ clearance and AD
Sousa et al. [126]	Review study	SIRT1 activators could be effective potential therapeutic treatments against aging and aging-related disorders including AD

and IR [112]. Ablation of NLRP3 inflammasome in VAT and liver reduced inflammation and increase insulin sensitivity in mice. As well, the removal of NLRP3 inflammasome reduces VAT interferon-gamma (INFγ) and increases native T cell count in mice [112]. This finding suggests that activation of NLRP3 inflammasome is linked with obesity-induced obesity and the development of IR. A systematic review indicates that excess nutrients trigger activation of NLRP3 inflammasome with subsequent pro-inflammatory response and development of IR [128]. Legrand-Poels revealed that the toxic effects of free and saturated free fatty acids induce the development of ROS and inflammatory reactions which promote the activation of NLRP3 inflammasome [129]. It is of interest that omega-free fatty acids inhibit NLRP3 inflammasome activation and the development of hyperinflammation in obesity.

Different studies implicate NLRP3 inflammasome activation in the pathogenesis of AD [113, 130]. Recently, it has been shown that NLRP3 inflammasome activation results in microglia stimulation, assembly and aggregation of Aβ, and enhancement of tau-associated neurobiology [113]. In an in vitro study it has been found that the deposition of Aβ and NFT was linked with the activation of NLRP3 inflammasome in the microglia [114]. Different experimental studies revealed that NLRP3 inflammasome activation was associated with tau aggregation and exacerbation of AD in mice [115, 131]. Notably, caspase-1 activation and release of pro-inflammatory cytokines precede AD neuropathology implying that activation of NLRP3 inflammasome could be the initial pathogenic event in AD [132]. These findings support that VO-induced NLRP3 inflammasome activation might be a possible cause for the development of AD neuropathology.

NF-κB

NF-κB is an inflammatory signaling pathway implicated in the development of inflammation and IR in obesity [116, 133]. The NF-κB pathway is activated in insulin-sensitive tissue and highly dysregulated in obesity. Inhibition of the NF-κB pathway by aspirin improves insulin sensitivity in VAT [134]. NF-κB maintains inflammation and induces the development of IR with the progression of metabolic derangement in obesity [134]. Targeting of the NF-κB pathway by lipoxin A4 can attenuate obesity-related systemic inflammation and glomerulopathy [135, 136]. In addition, inhibition of the NF-κB pathway by major vault protein inhibits obesity and related atherosclerosis in mice treated with HFD [137]. Therefore, an activated NF-κB pathway in obesity could increase the risk of IR and systemic inflammation hallmarks of AD.

Indeed, the NF-κB pathway is involved in the pathogenesis of AD and has been reported to be a potential link between T2DM and the progression of AD [117]. Certainly, upstream regulators like Aβ, cytokine storm, and ROS activate the NF-κB signaling pathway. As well, many inflammatory signaling pathways like MAPK, AKT, PI3K and GSK3 increase the pathogenesis of AD via induction expression of NF-κB [138]. Lukiw [139] found that the NF-κB pathway was involved in the induction of pro-inflammatory miRNA in AD. An experimental study illustrated that enhancement of NF-κB immunoreactivity is linked with abnormal integrity of the cerebral cortex and hippocampus in AD [140]. Thus, NF-κB expression is higher in the brain pathological area affected by AD. Ju Hwang et al. [141] observed that NF-κB was the main mediator of neuroinflammation in AD. NF-κB involves in the amyloidogenesis process by inducing the release of chemokines, inflammatory cytokines and microglial activation [141, 142]. Thus, inhibition of the NF-κB pathway by aspirin may prevent the progression development of AD. Different studies showed that polyphenols and phytochemicals attenuate the progression of AD through the inhibition of NF-κB-induced neuroinflammation [143, 144]. Of interest, forsythoside B which is a glycoside isolated from Fructus has anti-inflammatory and prevents the pathogenesis of AD [145]. It has been shown that forsythoside B could prevent NF-κB-mediated neuroinflammation in mice with experimental AD [145]. Thus, forsythoside B and other herbal medicine might be effective in preventing the progression of AD.

Therefore, the activated NF-κB pathway in VO might be a potential link in the development of AD, so targeting of NF-κB pathway could be a possible therapeutic value in the management of AD.

Advanced Glycation End-Products

Advanced glycation end-products (AGEs) are toxic compounds produced due to the combination of glucose with protein or lipid molecules in the glycation process [146]. AGEs act on a specific receptor called receptor for AGEs (RAGEs) which is involved in body metabolism, adipose tissue macrophage content, systemic inflammation, and regulation of body mass [147]. The interaction between AGEs and RAGEs triggers vascular inflammation and the development of vascular inflammation [118, 147]. It has been observed that obesity is associated with augmentation of AGEs levels which mediate oxidative stress and inflammation. Indeed, the interaction between AGEs and RAGEs promotes the expression of inflammatory signaling pathways and adhesion molecules leading to inflammatory disorders in obesity and T2DM [118, 147]. Therefore, anti-AGEs medication attenuates hyperinsulinemia and glucose intolerance, promoting weight loss and reduction of body fat [148].

Prolonged use of a diet containing AGEs induces the development of hepatosteatosis and obesity with the increment of leptin and pro-inflammatory cytokines in mice [149]. Activation of RAGEs by AGEs promotes the development of many diseases including IR, T2DM, cancer, and diabetic neuropathy and retinopathy [149]. A study conducted by den-Engelsen et al. [150] illustrated that patients with central obesity have a higher accumulation of AGEs measured by skin autofluorescence. A systematic review revealed that low AGEs diets reduce the risk for the development of central obesity and related complications [151]. AGEs act as pro-inflammatory and pro-oxidants in the progression of AD [119].

Furthermore, AGEs/RAGEs are implicated in the progression of neuroinflammation and AD via glycoxidation of Aβ and the formation of toxic molecules [119]. AGEs /RAGEs complex is involved in the pathogenesis of AD and vascular dementia through activation of tau phosphorylation and GSK3b pathway with subsequent cognitive decline [119]. Analysis of AGEs in both serum and brain of postmortem previously diagnosed with T2DM and AD illustrated that AGEs were augmented and involved in the pathogenesis of AD [119].

Therefore, the higher concentration of AGEs in VO could be implicated in the pathogenesis of AD. Thus, a reduction of the diet containing AGEs or weight loss may reduce the risk of VO-induced AD.

Hypoxia-Inducible Factor 1

The fundamental effects of hypoxia on the progression of AD are related to the types of hypoxia. Mild and intermittent hypoxias are protective while severe and chronic hypoxias are detrimental to AD neuropathology [152].

Chronic hypoxia induces the formation and accumulation of Aβ with aggravation of Aβ neurotoxicity by increasing Ca^{+2} dyshomeostasis and generation of ROS [152]. Taken together, Aβ and chronic hypoxia provoke the progression of neuroinflammation which increase amyloidogenesis and AD pathology. Thus, restoration of normal oxygen tension or the increase of HIF-1 activity in the brain may attenuate the development of AD and other neurodegenerative brain disorders [153]. In addition, chronic hypoxia shifts amyloid precursor protein toward the amyloidogenic pathway with the generation of neuronal Aβ through suppression of alpha-secretase activity and neprilysin which degraded amyloid precursors [154].

HIF-1 is a key molecule that regulates cell response to hypoxia and inflammation as it is essential for cell survival and function [120]. HIF-1 is involved in VAT metabolism and induction of inflammation and IR. Dysregulation of HIF-1 is intricate in the development of obesity and related complications [120]. HIF-1 is regulated by hypoxia, ROS, NO, tricarboxylic acid metabolites, pro-inflammatory cytokines, and hormonal factors [155]. Notably, HIF-1 promotes the expansion of VAT and the increase of body mass with the reduction of basal body metabolic rate [156]. It has been shown that HFD induces the expression of hypothalamic HIF-1 causing hypothalamic inflammation with the development of glucose intolerance and increased body weight [156]. Thus, HIF-1 is regarded as a potential regulator of energy homeostasis and lipid metabolism, herein it is considered a possible target in the management of obesity.

Of note, brain hypometabolism in the aging process due to the gradual reduction of oxygen and glucose supply mainly in certain brain regions including the hippocampus and temporo-frontal cortex trigger AD neuropathology [157]. Brain hypometabolism promotes the expression of Aβ with a reduction of its clearance. In turn, aggregation of brain Aβ induces the progression of oxidative stress, inflammation, and neuronal cell death [157]. Among cellular adaptation mechanisms in response to the effect of Aβ-induced inflammatory changes and neuronal hypoxia, transcription of HIF-1 is augmented as a compensatory mechanism [121]. Thus, maintaining the HIF-1 level by agents like heavy metals like nickel, and iron chelators could be an effective strategy to attenuate AD-induced inflammation and oxidative stress [121, 157]. Remarkably, different studies documented that HIF-1 inhibits the expression of neprilysin and increases the cleavage of amyloid precursor proteins [122, 158]. Also, HIF-1 exerts a neuroprotective effect against the development of AD via suppression of oxidative stress and neuroinflammation induced by Aβ toxicity [123]. Indeed, HIF-1 prevents metabolic derangement and mitochondrial dysfunction triggered by chronic hypoxia in AD. Besides, HIF-1 promotes cerebral circulation by regulating the expression of neuronal erythropoietin receptors [159]. Erythropoietin inhibits the generation and aggregation of neuronal Aβ [159]. Thus, HIF-1 hydroxylase inhibitors could be effective in the management of AD.

These findings revealed that the increase of HIF-1 in patients with VO could be protective against the development of AD.

Taken together, different inflammatory signaling pathways are activated in VO that all have a negative impact on the cognitive function and progression of AD except HIF-1 which has beneficial and neuroprotective effects in mitigating the progression of AD.

Sirtuin1 Pathway

Sirtuin1 (SIRT-1) also known as NAD-dependent deacetylase sirtuin-1, is a protein that in humans encoded by the SIRT1 gene [160]. SIRT-1 is an enzyme located primarily in the cell nucleus that deacetylates transcription factors that contribute to cellular regulation. The SIRT family comprises seven NAD^+-dependent deacetylases which control the overall health of organisms through the regulation of pleiotropic metabolic pathways [160, 161]. SIRT-1 is an important modulator of adipose tissue metabolism and its expression is higher in lean than obese subjects [162]. Of note, SIRT-1 inactivation is involved in lipid metabolism and VO [163]. SIRT1 and SIRT2 modulate the differentiation of human adipose stem cells [162]. Reduced expression of SIRT1 and SIRT2 may enhance the differentiation capacity of visceral adipose stem cells in human obesity, fostering VAT expansion [163]. SIRT1levels in adipose-derived stem cells are consistent with protective effects against VO and inflammation and suggest a transcriptional mechanism through which acute hypoxia up-regulates SIRT1in the visceral adipose-derived stem cells of obese patients [124]. SIRT-1 is critical to neuron proliferation and SIRT-1 inactivation is associated with defective Aβ clearance and AD. SIRT-1 is involved with the prevention of oxidative stress, inflammatory changes, leptin resistance and adiponectin levels [45, 125]. SIRT-1 is responsible for the transcriptional regulation of various transcription factors and signaling pathways including MAPK, mTOR, HIF-1, NF-κB and NLRP3 [164]. These findings suggest that the downregulation of SIRT-1 in VO may induce the development of AD. Therefore, SIRT-1 could be a potential link between VO and AD, and targeting this pathway may mitigate VO-induced AD. It has been observed that SIRT1 protects against memory loss through mechanisms that involve oxidative stress, Aβ toxicity, neurofibrillary degeneration, vascular injury, mitochondrial dysfunction, and neuronal loss. In addition, SIRT1 relies upon other avenues that can include trophic factors, such as erythropoietin, and signaling pathways, such as Wnt1 inducible signaling pathway protein 1 (WISP1/CCN4).

Yet, SIRT1 can have detrimental effects as well that involve tumorigenesis and blockade of stem cell differentiation and maturation that can limit reparative processes for cognitive loss. Further investigations with SIRT1should be able to capitalize upon these novel targets for dementia and cognitive loss [165, 166]. Poor et al. [107] showed that metformin improves cognitive function in AD through the activation of the SIRT1 pathway. As well, resveratrol has antioxidant, anti-inflammatory, and neuroprotective properties and can decrease the toxicity and aggregation of Aβ peptides in the hippocampus of AD patients, promote neurogenesis, and prevent hippocampal damage [167]. In addition, the antioxidant activity of resveratrol plays an important role in neuronal differentiation through the activation of the SIRT1 pathway. SIRT1 plays a vital role in the growth and differentiation of neurons and prevents the apoptotic death of these neurons by deacetylating and repressing p53 activity; however, the exact mechanisms remain unclear. Resveratrol also has anti-inflammatory effects as it suppresses M1 microglia activation, which is involved in the initiation of neurodegeneration, and promotes T helper 2 (Th2) response by increasing anti-inflammatory cytokines and SIRT1 expression [167]. A recent study conducted by Sousa et al. [126] illustrated that monoterpenes as SIRT1 activators could be effective potential therapeutic treatments against aging and aging-related disorders including AD. SIRT1 expression and activity reduce with aging, and increasing its activity extends the life span in various mammals, and improves many age-related diseases. Consequently, many natural and synthetic SIRT1 activators and inhibitors have been developed. Known SIRT1 activators of natural origin are mainly polyphenols. Nonetheless, various classes of non-polyphenolic monoterpenoids have been identified as inducers of SIRT1 expression and/or activity [126]. Besides, SIRT1 activators attenuate ED and systemic complications induced by obesity [168]. Therefore, SIRT1 activators could be effective against obesity-mediated complications and the development of AD.

These findings indicate that the SIRT1 pathway is highly dysregulated in obesity and this dysregulation contributes to the pathogenesis of AD. Therefore, SIRT1 activators could be effective in the mitigation of VO-induced AD.

Adipocytokines in Obesity and AD

Different types of adipocytokines are dysregulated in VO which affect the metabolic profile and brain functions. Interestingly, obese subjects have high circulating levels of IL-6, TNF-α, CRP and pro-inflammatory adipocytokines like leptin. Pro-inflammatory adipocytokines trigger chronic inflammation [53]. In contrast, the anti-inflammatory adiponectin plays a crucial role in the mitigation of VO-induced inflammation by inhibiting the expression of NF-κB and TNF-α [55]. In consonance, adiponectin serum level is reduced in obese subjects [59]. A prospective study involved 193 obese subjects showed that adiponectin serum level was low mainly in subjects with high VAI and VAT [59]. Therefore, the expression of leptin and adiponectin are dysregulated in VO leading to systemic inflammation and oxidative disorders. Bonda et al. [169] showed that dysregulation of leptin signaling is involved in AD. Notably, leptin receptors and concentration are increased in specific brain areas and CSF in AD patients. Leptin resistance in the hippocampus and dysregulation of leptin signaling are associated with the development of AD. There is a significant correlation between leptin levels in both CSF and the brain with the progression of AD [170]. It has been shown that leptin promotes the pathogenesis of AD. A prospective study involving 785 subjects showed that high circulating leptin was associated with a low risk for the development of AD [170]. Since leptin level highly fluctuates, and most of the measured leptin was performed in experimental and preclinical studies, a potentially positive correlation between high leptin and cognitive function in AD patients needs to be elucidated in clinical studies. It was suggested that high leptin in presymptomatic AD could be protective and attenuate the progression of AD. Notably, brain leptin level is correlated with the volume of gray matter and hippocampus, and can reverse neurocognitive deficits in humans with congenital leptin deficiency [171]. Different experimental studies reported that the administration of leptin can reduce the formation and aggregation of Aβ [172, 173].

Recent studies confirmed that leptin has neuroprotective against the progression of AD [174, 175]. Leptin improves neurogenesis and antioxidant potential with reduction in the expression of Aβ and tau phosphorylation in mice with experimental AD [174, 176]. Therefore, VO-induced leptin resistance may increase the risk for AD neuropathology through augmentation of neurotoxicity [175]. Thus, disruption of brain leptin signaling may induce the development of AD in mice [175]. These findings indicated that VO-induced leptin resistance could be a possible mechanism for the development of AD via disruption of brain leptin singling (Fig. 9).

Notably, adiponectin plays a crucial role in promoting cognitive function and amelioration the pathogenesis of AD. Adiponectin has a neuroprotective effect against the development of AD through anti-inflammatory and antioxidant effects [177]. A prospective study showed that adiponectin level was reduced in AD patients [178]. Decreasing brain adiponectin favors Aβ accumulation and associated neurodegenerative changes in mice [179]. Therefore, brain hypoadiponectinemia is implicated in the progression of neurodegeneration and AD via induction of brain IR and tau phosphorylation with subsequent propagation of neuroinflammation [178, 179]. Thus,

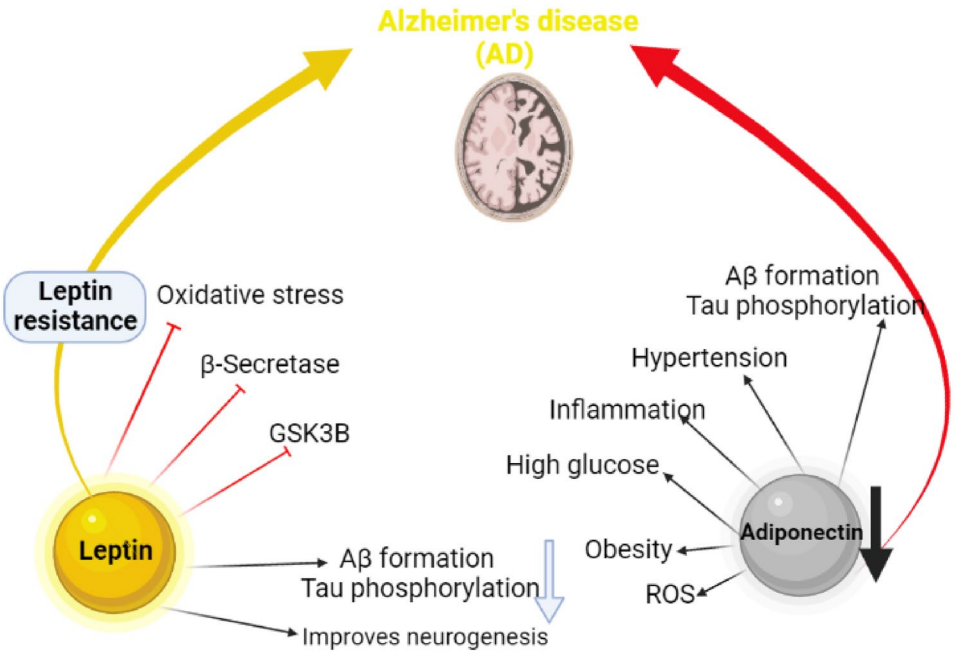


Fig. 9 Role of leptin and adiponectin in the pathogenesis of Alzheimer's disease (AD)

oxidative and inflammatory disorders induced by peripheral and central metabolic disorders may trigger a reduction of circulating adiponectin leading to the development of AD (Fig. 9). On the other hand, the anti-inflammatory adiponectin is highly reduced in VO leading to the development of IR and metabolic derangements [59]. Notably, increasing VAT in obese and overweight individuals is linked with a significant reduction of circulating adiponectin. A prospective study comprising 206 obese subjects who received a structured diet for weight control illustrated that weight loss is associated with increasing total adiponectin levels [59]. There is an inverse relationship between VAT and adiponectin expression. Besides, adiponectin is positively correlated with HDL and negatively correlated with pro-inflammatory cytokines [180, 181]. Thus, VO-induced reduction in circulating adiponectin promotes systemic inflammatory and metabolic changes which in turn reduce the expression of adiponectin and propagation of systemic complications. Reduction of adiponectin as in T2DM and VO increases free fatty acid levels, impairment of insulin signaling, and development of IR and hyperinsulinemia (Fig. 10).

Therefore, VO-mediated hypoadiponectinemia and leptin resistance may promote the progression of Aβ formation and tau phosphorylation with the development of AD.

Conclusion

AD is a common type of dementia, characterized by the deposition of Aβ plaques and TNTs in the brain. Remarkably, deposition of Aβ occurs prior to the pathology of cortical tau. Deposition of Aβ-induces tau-mediated neuronal and synaptic loss in AD, though tau neuropathology can progress independently of Aβ accumulation. The neuropathological changes in AD are related to the deposition of amyloid plaques and TNTs, the progression of neuroinflammation, neuronal mitochondrial dysfunction, autophagy dysfunction, and cholinergic synaptic dysfunction.

Obesity is a medical condition due to excessive accumulation of body fat which adversely affects health. VO is commonly associated with low-grade inflammation due to higher expression of pro-inflammatory cytokines by adipose tissue. Development of VO is associated with augmentation of pro-inflammatory and proatherogenic mediators leading to ED, IR and atherosclerosis. VAT-induced oxidative stress triggers IR through the modulation of insulin receptors and insulin action. In addition, tissue hypoxia in obesity promotes tissue injury, production of adipocytokines and release of pro-inflammatory cytokines leading to an oxidative-inflammatory loop with induction of IR. Also, brain insulin signaling is involved in the pathogenesis of AD through AKT phosphorylation which induces AD pathology and lowers cognitive function. Of note, AD is developing due to Aβ accumulation via an amyloidogenic pathway with the formation of Aβ plaques. The processing and production of Aβ plaques affect neuronal activity through the interruption of synaptic activity and induction of cell death. Obesity and enlargement of VAT are associated with the deposition of Aβ. Obesity is regarded as an independent risk factor for the development of AD. These findings are consonant with VO increasing the risk of AD through the dysregulation of adipocytokines which affect the development of AD.

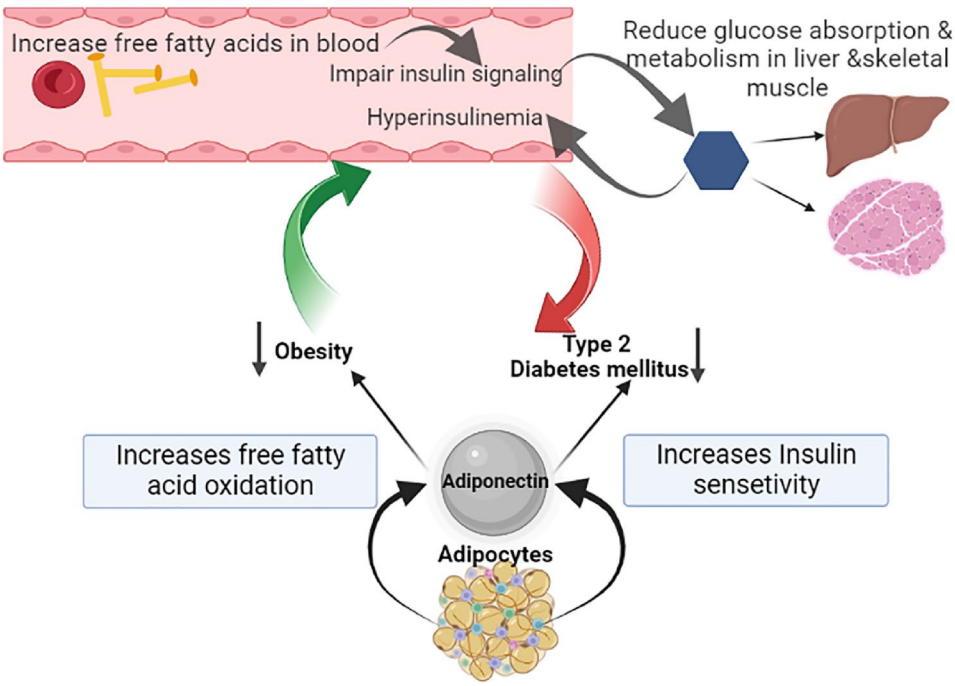


Fig. 10 Adiponectin and development of hyperinsulinemia

Activated NF-κB pathway in VO might be a potential link in the development of AD, so targeting of NF-κB pathway could be a possible therapeutic value in the management of AD. Likewise, the higher concentration of AGEs in VO could be implicated in the pathogenesis of AD. Thus, the reduction of the diet containing AGEs or weight loss may reduce the risk of VO-induced AD.

Different inflammatory signaling pathways are activated in VO that all have a negative impact on the cognitive function and progression of AD except HIF-1 which has beneficial and neuroprotective effects in mitigating the progression of AD. In addition, VO-mediated hypoadiponectinemia and leptin resistance may promote the progression of Aβ formation and tau phosphorylation with the development of AD.

Taken together, VO-induced AD is mainly mediated through the induction of oxidative stress, inflammatory changes, leptin resistance, and hypoadiponectinemia that collectively trigger Aβ formation and neuroinflammation. Thus, early recognition of VO by VAI with appropriate management could be a preventive measure against the development of AD in patients with VO. Large-scale prospective studies are warranted in this regard.

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