

Adipokines: a link between obesity and dementia?

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Being overweight or obese, as measured with body-mass index or central adiposity (waist circumference), and the trajectory of body-mass index over the life course have been associated with brain atrophy, white matter changes, disturbances of blood–brain barrier integrity, and risk of all-cause late-onset dementia and Alzheimer’s disease. This observation leads us to question what it is about body-mass index that is associated with health of the brain and dementia risk. If high body-mass index and central adiposity represent an increase in adipose tissue, then the endocrine function of adipose tissue, mediated by adipose tissue hormones and adipokines, could be a clue to mechanisms that underlie the association with dementia and Alzheimer’s disease. Hundreds of adipokines have been identified, creating a complexity that is a challenge to simplify. Nonetheless, adipokines are being investigated in association with clinical dementia outcomes, and with imaging-based measures of brain volume, structure, and function in human beings and in preclinical models of clinical dementia.

Introduction

Since 2003, when the first report was published of a risk association in women between Alzheimer’s disease and higher body-mass index (BMI), a common and simple measure of excess weight and obesity,¹ many epidemiological reports have related high midlife and late-life BMI to dementia.^{1–7} For example, people with high midlife BMI or central adiposity measures have a two times higher risk of dementia in later life.^{2,3,5,6} The levels of midlife adiposity that are associated with dementia or Alzheimer’s disease are in the overweight and obese ranges, based on the traditional anthropometric cutpoints for BMI, waist circumference, and waist-to-hip ratio (WHR) used to denote risk for cardiovascular disease and overall mortality (panel 1). After midlife, a decrease in BMI tends to occur, such that people who have clinical dementia have lower BMI or bodyweight than those who do not.^{8,9} This reverse epidemiological finding has been a topic of debate.¹⁰ The higher midlife adiposity that is associated with higher dementia risk could be attributable to vascular mechanisms, whereas the decline in BMI and bodyweight could be reflective of neurodegeneration and interruption of homeostatic feedback mechanisms in later life.¹⁰ But what does BMI, waist circumference, or WHR measure that translates to differences in dementia risk? One answer to this challenging question is the quantity and secretory capacity of peripheral white adipose tissue (WAT).

WAT is an endocrine tissue that secretes hundreds of cell-signalling molecules known as adipokines. The endocrine function of adipose tissue might provide clues to the mechanisms linking adipose tissue to the major neurodegenerative and vascular diseases of ageing—cognitive impairments and dementia. Other potential factors associated with adipose tissue and the risk for dementia include low physical activity, dietary constituents (nutrients and non-nutrients), eating patterns, health and disease status, and genetic background, but discussion of these factors is beyond the scope of this Review.¹¹

In this Review, we define and discuss the potential role of the adipokines that have shown associations with dementia in human observational and clinical studies.

We discuss examples of adipokines identified from preclinical models and characteristics of obesity that could be important for the brain and dementia (figure 1). The hypotheses described are related to selected adipokines, and their potential association with vascular events and neurodegeneration. This is not a comprehensive review of the literature, but provides an overview of how certain adipokines could be associated with the risk of late-onset dementia. In view of the evolving published work and the paucity of data for associations between adipokines and dementia and dementia-related brain outcomes, we also discuss the limitations of the current data.

Adipose tissue and adipokines

WAT is a complex tissue consisting of multiple cell types with multiple cellular phenotypes that depend on cell composition and location.¹² WAT consists of a stromal layer and a mature adipocyte layer. The stromal layer consists of adipose-derived stem cells or pre-adipocytes,

Lancet Neurol 2014; 13: 913–23

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Panel 1: Anthropometric measures and corresponding cutpoints of overweight and obesity in adults

Body-mass index (BMI)

- Calculated as weight in kilograms per height in metres squared (kg/m^2)
- $1 \text{ kg}/\text{m}^2$ =one unit of BMI
- $<18.5 \text{ kg}/\text{m}^2$ =underweight
- $18.5\text{--}24.9 \text{ kg}/\text{m}^2$ =healthy
- $25.0\text{--}29.9 \text{ kg}/\text{m}^2$ =preobese or overweight
- $\geq 30 \text{ kg}/\text{m}^2$ =obese
- $\geq 40 \text{ kg}/\text{m}^2$ =class III obesity

Central (abdominal) obesity

- Waist circumference calculated in centimetres or inches
- Men $\leq 102 \text{ cm}$ (≤ 40 inches)=healthy
- Women $\leq 88 \text{ cm}$ (≤ 35 inches)=healthy

Waist-to-hip ratio

- Men <0.90 =healthy
- Women <0.80 =healthy

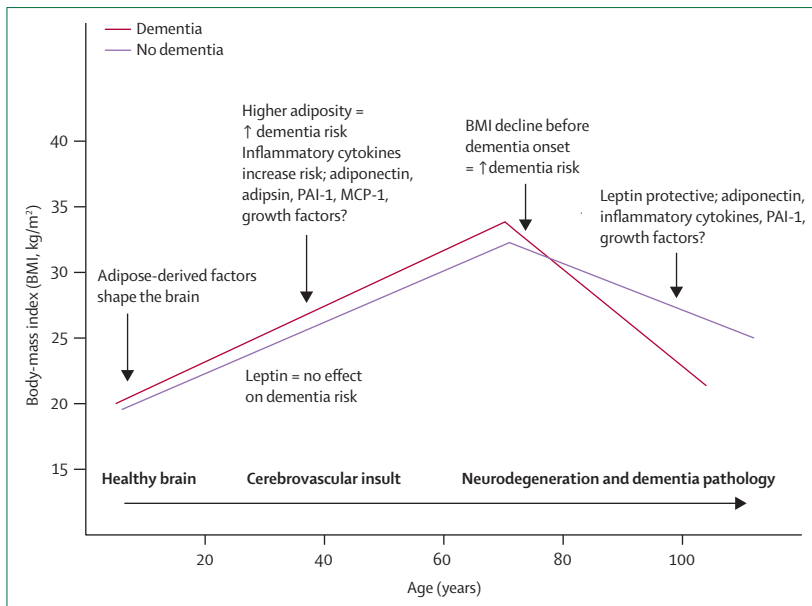


Figure 1: Possible life course trajectory of BMI in association with dementia

MCP-1=monocyte chemoattractant protein-1. PAI-1=plasminogen activator inhibitor-1. Reviewed adipokines regulate: energy balance and metabolism; thrombosis and hypertension; inflammation.

fibroblasts, blood vessels, and nerve cells. Adipose-derived stem cells are self-renewing and can differentiate along several mesenchymal lineages into adipocytes, osteoblasts, myocytes, chondrocytes, endothelial cells, cardiomyocytes, and even neuronal-like cells.¹³ The mature adipocyte layer consists of fully differentiated adipocytes.¹⁴

Adipokines include hundreds of polypeptides secreted by the different cells of WAT, which are sometimes referred to as the adipose secretome or adipokinome.¹⁵ In the periphery, adipokine release is fat depot-specific, consistent with differences in adipocyte morphology and the local milieu.^{13,16,17} More adipokines are released from visceral than from subcutaneous WAT. Additionally, brown, epicardial, and pancreatic adipose tissue seem to have unique adipokine profiles.^{18–20} Since the amount of visceral adipose tissue is associated with high waist circumference or WHR,^{21–23} rather unsophisticated methods to determine body adiposity, such as anthropometric measures, have been used to pinpoint mechanisms of action. Similarly, BMI grossly reflects total adipose tissue depots during adulthood, and is a relatively good correlate irrespective of changing body composition with ageing.²⁴

The word adipokine or adipocytokine means adipose (adipo-), cell (-cyto-), and movement (-kinos). The term adipokine originally referred to immunomodulatory cytokines secreted by adipose tissue. However, the popular use of this term has expanded to include compounds that are technically not cytokines. Adipokine instead refers to cytokines, acute phase reactants, growth factors and other inflammatory mediators, adipose tissue hormones such as leptin, and other chemical messengers.^{10,25,26} Adipokines

have autocrine, paracrine, and endocrine mechanisms of action,²⁷ and many adipokines affect processes in both the periphery and CNS.

Leptin, adiponectin, and interleukin 6 are three of the best known examples of adipokines that have an association with dementia. In 2011, experiments with isolated human adipocytes, serum, and adipose tissue biopsy samples from lean and obese individuals, identified 347 protein components (including 44 never before reported) of the adipokinome.¹⁵ However, more than 700 adipose tissue-derived proteins have been reported in response to specific chronic or acute stimuli or at rest.¹⁵

Although the CNS has the highest lipid content in the human body after adipose tissue, lipid in the CNS does not exist as adipose tissue, but as layers of myelin sheaths containing fatty acids that surround the axons of the brain and spinal cord.²⁸ CNS-derived adipokines are instead produced in various brain regions by many non-adipocyte cell types²⁹ and nuclei, such as the arcuate nucleus in the hypothalamus, for specific purposes such as regulation of feeding behaviour.

Because the neurodegenerative and vascular processes reported in dementia affect several brain regions and nuclei,³⁰ the action of adipokines could be altered during neurodegenerative and vascular events and might even feedback to contribute to neurodegeneration, although this has not been proven. Much remains to be discovered about the relative source—ie, brain versus periphery—and mechanistic actions of these adipokines in each compartment.

Adipokine release can be dysregulated both in obesity and in ageing, possibly because of disease or potentially impaired function. The terms inflamm-ageing³¹ and adiposopathy have been used to describe dysregulated adipose tissue. Adiposopathy describes excessive hypertrophy of adipocytes^{32,33} that leads to the dysregulated paracrine and endocrine adipose tissue activity associated with cardiovascular disease. These alterations in adipose tissue function and changes in structure also contribute to the syndromes reported in ageing, which encompass physical (eg, weight loss, sarcopenia) and functional (eg, diminished activities of daily living) frailty in the periphery and impaired cognitive function.³⁴

Panel 2 lists the adipokines most studied in human beings. These molecules can be grouped according to primary function, as shown; however, each can possess more than one function, and these functions do overlap. For example, leptin, adiponectin, resistin, plasminogen activator inhibitor-1 (PAI-1), hepatocyte growth factor (HGF), and nerve growth factor (NGF) are involved in dysregulation of nutrient utilisation as well as inflammation, endothelial dysfunction, hypertension, and atherogenesis.³⁶ Additionally, adipose and non-adipose hormones (eg, leptin and insulin) interact to augment the actions of each other.³⁷ Insulin interacts directly with hypothalamic nuclei, and both leptin and

insulin are mediators in insulin resistance, as shown by observations that pro-opiomelanocortin (POMC) neurons in the hypothalamus express both leptin and insulin receptors and regulate energy balance and glucose homeostasis.³⁸ Experimental mouse models lacking both leptin and insulin receptors in POMC neurons display systemic insulin resistance. Thus, direct action of both insulin and leptin on POMC neurons seems to be required to maintain normal glucose homeostasis.³⁸

We review eight adipokines or classes of adipokines, grouped according to primary function. First, we discuss the adipokines that have been reported in epidemiological studies in association with dementia (table); second, we present a selection of adipokines that could be associated with brain pathology or dementia because of their biological roles or associations with brain processes. Although the evidence we present here suggests that adipokines might be a link between obesity and dementia, there is no known pharmacological intervention targeting adipokines or other potential links between adipose tissue and cognitive impairment or dementia.

Energy balance and metabolism

Leptin

Leptin is a 16 kDa protein hormone^{51–53} that is primarily secreted by adipose tissue and positively correlated with BMI.^{54,55} Correlations of about $r=0.7$ between BMI and blood leptin concentrations are recorded in adults, even in those with obesity syndromes.⁵⁶

Peripheral leptin enters the CNS and CSF and interacts with specific areas of the brain such as the hypothalamus and hippocampus.^{57,58} However, apart from leptin transport into the CSF and other brain regions, several studies indicate that human and rodent brains also produce leptin (eg, hypothalamus, cortex, cerebellum).^{59–63} Leptin transport across the blood–brain barrier occurs via a mechanism involving leptin receptor A and a second, as yet uncharacterised, transport mechanism.⁶⁴

Leptin regulates food intake and energy expenditure, improves insulin sensitivity, facilitates lipolysis, and inhibits lipogenesis.^{65,66} Additionally, leptin has a permissive role in neuroendocrine immune function.⁶⁷ Leptin is the most studied adipokine associated with brain structure and function, and has several effects on brain development⁶⁸ and potentially on brain health in relation to cognition and ageing. Leptin affects hypothalamic function, and learning and memory processes controlled by the hippocampus.^{68–71} Experimental data show that leptin and other adipokines interact directly with hypothalamic nuclei, such as the arcuate nucleus, and regulate energy expenditure and food intake through production of orexigenic (NPY, agrp) and anorectic (aMSH) peptides.^{72,73} Additionally, leptin seems to facilitate presynaptic and postsynaptic transmitter release and sensitivity, respectively, in hippocampal

CA1 neurons,⁷⁰ which translates into improved performance in relation to spatial learning and memory function. In mice, leptin might also shape the hypothalamus in the earliest stages of development and thus enhance cognition.⁶⁸ In-vitro leptin reduces β -secretase activity, increases APOE-dependent amyloid β (A β) uptake, and affects A β turnover via lipolytic mechanisms in experimental models.⁷¹

Human population studies suggest that high leptin concentrations and high BMI are associated with low dementia risk in late life when measured within 10 years of clinical dementia diagnosis (table).^{40,68} Long-term follow-up and cross-sectional studies show no association between leptin and dementia. Since leptin concentrations are higher in adults who do not develop dementia during

Panel 2: Adipokines that could have relevance for Alzheimer's disease³⁵

Energy balance and metabolism

- Adiponectin
- Adipsin (complement factor D)
- Apelin
- Chemerin
- Dipeptidyl peptidase-4 (adenosine deaminase complexing protein-2 or CD26)
- Leptin
- Lipocalin
- Omentin
- Resistin
- Retinol binding protein-4
- Vaspin
- Visfatin (pre-B-cell enhancing factor)

Inflammation

- Interleukin 6
- Interleukin 1
- Interleukin 10
- Interleukin 8
- MCP-1
- TNF α

Thrombosis and hypertension

- Serum amyloid A
- C-reactive protein
- PAI-1, total, active
- Proteins of the renin angiotensin system

Growth factors

- Nerve growth factor
- Hepatocyte growth factor

Brown fat

- Fibroblast growth factor 21
- Interleukin 6
- Insulin-like growth factor 1

MCP-1=monocyte chemoattractant protein-1. TNF α =tumour necrosis factor α . PAI-1=plasminogen activator inhibitor-1.

the prodromal phase (roughly 10 years) than in those who develop dementia, the potential of leptin as a cognitive enhancer when given at the early stages of cognitive impairment or dementia has been proposed.⁷⁴ In view of the strong correlation between leptin concentrations and BMI in relation to dementia, there is

scope for leptin to have an independent role in the health of the ageing brain, although further study is needed.

Adiponectin

Adiponectin (ACRP30) exists as complex multimeric isoforms comprised of high-molecular-weight

	N	Age (years)*	Observation time (years)	Study type	Results
Leptin					
Prospective Population Study in Gothenburg, Sweden ³⁹	1462	38–60	24	Long	No association of midlife leptin with late-onset dementia in women (multivariate adjusted HR 1.01, 95% CI 0.98–1.03, p=0.620)
Framingham Heart Study, USA ⁴⁰	785 (no dementia)	79 (SD 5)	8.3	Long	Higher leptin levels associated with lower risk of incident dementia and AD in multivariable models (HR per 1 SD log leptin, 0.68, 95% CI 0.54–0.87, for all-cause dementia; HR per 1 SD log leptin, 0.60, 95% CI 0.46–0.79, for AD). A 1 SD elevation in plasma leptin concentration was associated with higher total cerebral brain volume (p=0.005)
Study of Osteoporotic Fractures ⁴¹	579 (no dementia)	82.6	5	Long	Among women with BMI <25 kg/m ² , a 1 SD difference in log leptin (0.91 ng/mL) was associated with 32% lower odds of dementia/MCI (OR 0.68, 95% CI=0.46–0.99) compared with those with BMI ≥25 kg/m ²
Health ABC Study, USA ⁴²	2871	73.7	4	Long	Elders in the high leptin group (32.3 ng/mL [SD 8.0 ng/mL], range 22.8–54.7 ng/mL) had lower likelihood of cognitive decline (OR 0.66, 95% CI 0.48–0.91) than did those in the lowest leptin group (2.3 ng/mL [SD 1.0 ng/mL], range 0–3.7 ng/mL). Middle leptin group: mean leptin 10.9 ng/mL (SD 5.2 ng/mL), range 3.7–22.8 ng/mL
Case-control study, Japan ⁴³	60 (20 VaD, 40 age-matched controls)	79	0	XS	Average leptin concentrations not different between VaD and controls (5.2 [SE 0.9] vs 4.5 [0.6] ng/mL, p=0.548)
Adiponectin					
Framingham Heart Study ⁴⁴	826	Median 76	13	Long	Total adiponectin concentrations associated with increased all-cause dementia risk (HR 1.29, 95% CI 1.00–1.66, p=0.054) and AD (HR 1.33, 95% CI 1.00–1.76, p=0.050) in women; baseline adiponectin > median at higher risk for all-cause dementia (HR 1.63, 95% CI 1.03–2.56, p=0.04) and AD (HR 1.87, 95% CI 1.13–3.10, p=0.01)
Rochester Epidemiology Project, USA ⁴⁵	890 (no dementia)	Median 80	0	XS	Total adiponectin not related to MCI in a case-control study; average concentration for MCI 14.4 (range 9.8–19.6) mg/L vs no MCI 14.5 (range 9.8–19.6) mg/L, p=0.97
Case-control study, Japan ⁴³	60 (20 VaD, 40 age-matched controls)	79	0	XS	Average total adiponectin levels not different between VaD and controls (14 [SE 2] vs 12 [1] µg/mL, p=0.387)
Clinical case series, Japan ⁴⁶	28 controls, 18 MCI, 27 AD	74.7	0	XS	Higher plasma adiponectin in MCI and AD compared with controls (p<0.05), and higher CSF adiponectin in MCI compared with controls (p<0.05)
Clinical case series of MCI and AD, Brazil ⁴⁷	157 (41 AD, 65 MCI, 51 controls)	71	0	XS	Lower total adiponectin concentration in those with MCI and AD (p=0.001); adiponectin did not predict progression of MCI to AD
Interleukins					
Framingham Heart Study ⁴⁸	691	79	7	Long	Compared with the lowest tertile, individuals in the top two tertiles of PBMC production of interleukin 1 were at higher risk for AD: for tertile 2, HR 2.84, 95% CI 1.09–7.43, p=0.03; for tertile 3, HR 2.61, 95% CI 0.96–7.07, p=0.06
Health ABC Study ⁴⁹	665 high inflammation, 1967 low inflammation	73.5	4	Long	Among those with metabolic syndrome, high inflammation defined as higher than the median for both CRP (≥2.0 mg/L) and interleukin 6 (≥2.0 pg/mL) was associated with risk of developing cognitive impairment (RR 1.66, 95% CI 1.19–2.32)
Rochester Epidemiology Project, USA ⁴⁵	890 (no dementia)	Median 80	0	XS	Total interleukin 6 not related to MCI in a case-control study; average concentration for MCI 4.8 (2.5, 14.0) vs 4.0 (2.4, 11.0) pg/mL, p=0.35
Dutch family study ⁵⁰	206 children of parents with AD, 200 children of parents with no AD	50.3	0	XS	Middle-aged children of late-onset AD cases had higher mean production capacity of interleukin 1β (13 091 [380] vs 10 548 [580] pg/mL, p<0.001), higher ratio of interleukin 1β to interleukin 1RA production capacity (1.38 [0.06] vs 1.10 [0.05], p<0.001), and higher mean production capacity of interleukin 6 (96 031 [2809] vs 88 226 [2827], p=0.04), measured after stimulation with 10 ng/mL lipopolysaccharide
Case-control study, Japan ⁴³	60 (20 VaD, 40 age-matched controls)	79	0	XS	Average interleukin-6 concentrations suggested higher in VaD vs controls (7.5 [SE 1.7] vs 4.6 [0.7] pg/mL, p=0.078)
PAI-1					
Case-control study, Japan ⁴³	60 (20 VaD, 40 age-matched controls)	79	0	XS	Average PAI-1 concentrations suggested higher among VaD vs controls (26 [SE 5] vs 18 [2] ng/mL, p=0.064)

Long=longitudinal. HR=hazard ratio. AD=Alzheimer's disease. BMI=body-mass index. MCI=mild cognitive impairment. OR=odds ratio. VaD=vascular dementia. XS=cross-sectional. PBMC=peripheral blood mononucleated cells. CRP=C-reactive protein. RR=relative risk. PAI-1=plasminogen activator inhibitor-1. *Age values are mean values, unless indicated otherwise.

Table: Selection of epidemiological studies that associate blood adipokine concentrations with clinical dementia, Alzheimer's disease, or cognitive impairment

hexamers and trimers.⁷⁵ Adiponectin modulates inflammatory responses, energy expenditure in the CNS and periphery, central food intake, and several metabolic processes, including glucose regulation and fatty acid catabolism in the periphery. It is an effective insulin sensitiser, and circulating concentrations are inversely correlated with insulin resistance, metabolic syndrome, obesity, type 2 diabetes, and cardiovascular diseases.⁷⁶ High-molecular-weight adiponectin or the ratio of high-molecular-weight adiponectin to total adiponectin might be better indicators of insulin sensitivity than total adiponectin in obesity, diabetes, and cardiovascular disease.⁷⁵ Adiponectin is produced solely by adipose tissue. However, trimeric and low-molecular-weight adiponectins are detectable in the CSF of human beings and rodents.^{73,77,78} In a study of human beings, the ratio of CSF to serum adiponectin was 1000 times lower than that seen in rodents.⁷⁹ In combination with the lack of high-molecular-weight adiponectin measured in CSF, this finding could imply that only smaller forms of adiponectin cross the blood–brain barrier.^{64,77,78} Thus, the origin of brain adiponectin has yet to be ascertained.

The peripheral effects of adiponectin are mediated mainly by two receptors, AdipoR1 and AdipoR2.⁸⁰ Expression of these receptors is reported in adipose tissue, brain, ovaries, endometrium, and placenta.⁸¹ AdipoR1 and AdipoR2 are widely found throughout the CNS in brain microvessels, hippocampus, hypothalamus, and brainstem in human and rodent models.^{63,77,79,82,83}

The Prospective Study of Women in Gothenburg, Sweden, shows late-life (age ≥ 70 years) correlations of $r = -0.29$ between BMI and blood high-molecular-weight adiponectin concentrations. Similar correlations are reported in midlife for women with or at risk for HIV infection (Gustafson DR, unpublished). The inverse association of adiponectin with BMI in adults might lead one to expect that high adiponectin concentrations are associated with prevalent dementia and Alzheimer's disease, since individuals with dementia tend to lose weight before a clinical diagnosis and subsequently weigh less than do those without a dementia diagnosis.^{8,84}

Of the studies summarised in the table, conclusions are mixed. Adiponectin is suggested to be a visceral adiposity marker^{85,86} and only moderately correlated with BMI (eg, compared with leptin), and blood–brain barrier transport mechanisms are unclear. Thus, blood concentrations might not provide an adequate indication of the potential interaction between adiponectin and the brain.⁸⁷ Studies evaluating adiponectin in association with dementia have reported total adiponectin concentrations. Isolation of high-molecular-weight adiponectin from the smaller adiponectin fragments can present problems in the laboratory, with high inter-assay and intra-assay variability,⁷⁵ making laboratory assay difficult.

Adipsin (complement factor D)

Plasma adipsin is inversely correlated with age and positively associated with BMI, WHR, and excess weight and obesity.⁸⁸ Observational studies in human beings have not shown an association between adipsin and dementia. However, adipsin is increased in animal models of γ -secretase inhibitor-mediated gastrointestinal toxicity characterised by cell population changes in the ileum of rats, which are indicative of Notch signalling disruption.⁸⁹ γ -secretase inhibition raises adipsin secretion from ileum crypt cells only (measured by higher concentrations of faecal adipsin), but not from adipose tissue.⁸⁹

Thrombosis and hypertension

PAI-1

In human beings, PAI-1 is increased in plasma of obese children, adolescents, and adults,^{90–93} mainly as a result of increased adipocyte secretion. PAI-1 affects vascular health by inhibiting fibrinolysis⁹⁴ through inhibition of tissue-type plasminogen activator and urokinase plasminogen activator.^{94,95} Furthermore, excess adipose tissue, especially due to central obesity in adults, is associated with decreased fibrinolysis, possibly as a result of increased PAI-1.⁹⁶ Despite the association of peripheral PAI-1 with obesity, peripheral PAI-1 might not be capable of affecting brain processes, since no transport mechanism for PAI-1 across the blood–brain barrier has been discovered. In mice, PAI-1 produced within the brain by microglia and astrocytes can regulate apoptosis, survival of neurites, and migration of microglia.^{97–100} Moreover, in-vitro studies show that PAI-1 contributes to the survival of neurites, axons, and dendrites.¹⁰⁰

Several studies have investigated interactions between PAI-1 and tissue-type plasminogen activator in the brain, but the data are not clear. Tissue-type plasminogen activator is produced by endothelial cells, mediates fibrinolysis, and crosses the blood–brain barrier intact.¹⁰ Since PAI-1 inhibits tissue type-plasminogen activator, the role of endogenous tissue-type plasminogen activator in the brain might be protective in the ageing and dementia processes, through mechanisms such as clot dissolution^{101–103} or amyloid degradation.¹⁰⁴ Additionally, brain amyloid induces tissue-type plasminogen activator formation, thus increasing plasmin concentrations, which can lead to $A\beta_{42}$ degradation.¹⁰⁵ However, in the brain, tissue-type plasminogen activator could be neurotoxic, lead to tau hyperphosphorylation, destabilise microtubules, mediate amyloid toxicity, and shift apoptosis in a stressed brain, such as that noted in strokes without clot formation.¹⁰⁵ The only study identified on PAI-1 and vascular dementia (table) showed higher tissue-type plasminogen activator mRNA expression in tissue from Alzheimer's disease brains than in control brains.¹⁰⁶

Inflammation

Several adipokines, particularly interleukins, are associated with inflammatory processes and implicated

in dementia. Obesity is characterised by a chronic low inflammatory state, partly mediated by production of pro-inflammatory adipokines such as interleukin 1 and interleukin 6.^{29,107} Interleukin 6 is an immunoregulatory cytokine that activates a cell-surface signalling assembly composed of interleukin 6, interleukin 6RA, and the shared signalling receptor gp130, a common mechanism in inflammation.¹⁰⁸ Interleukin 6 crosses the blood–brain barrier by a saturable transport mechanism, entering both CSF and brain parenchyma. About 50% of interleukin 6 in the CSF and 16% in brain parenchyma is derived from peripherally secreted interleukin 6 in male mice.¹⁰⁹ Since there is excessive degradation of interleukin 6 in the brain, the effect of peripheral interleukin 6 in the CNS is unclear, but small amounts of intact interleukin 6 might be effective.¹¹⁰ Rodent studies show that interleukin 6 is produced in the brain by glial cells, astrocytes, and endothelial cells of the brain's microvessels.^{110–112} Additionally, amyloid deposition and other neuropathological events in dementia are associated with local inflammatory events in the brain and are characterised by interleukin release and the release of TNF α and other proinflammatory compounds.²⁹

The hippocampus is particularly vulnerable to the adverse effects of interleukin 6, which affect brain functions such as synaptic plasticity and neurogenesis in rodents.^{113–116} In the hypothalamus, interleukin 6 modifies leptin signalling and other anorexic signals in mice.¹¹⁷ Early-onset elevation of interleukin 6 caused by childhood and adolescent obesity, and its persistence in ageing obese adults, has been proposed to negatively affect brain functioning by inhibiting neurogenesis, decreasing synaptic plasticity, and subsequently disrupting learning and memory processes, particularly in the hippocampus, which increases the risk of cognitive deficits in obese individuals.⁴⁹ In middle-aged adults, high plasma interleukin-6 concentrations are associated with low hippocampal grey matter volume.¹¹⁸ Several different interleukins have been studied in association with dementia and mild cognitive impairment (table), and interleukin concentrations generally increase with mild cognitive impairment and dementia.

Circulating MCP-1 is another marker of systemic inflammation. Insulin induces substantial expression and secretion of MCP-1 in vitro in insulin-resistant adipocytes and in vivo in insulin-resistant obese mice (*ob/ob*).¹¹⁹ *MCP1* (*CCL2*) functionally resembles other genes, such as *PAI1* (*SERPINE1*), that are sensitive to insulin in insulin-resistant states. *MCP1* is overexpressed in obesity and belongs to the family of genes that continue to respond to exogenous insulin in insulin-resistant mice and adipocytes. Insulin-resistant mice remain sensitive to insulin in terms of *Serpine1* gene expression, possibly because glucose homeostasis and *Serpine1* gene expression are regulated by different insulin signalling pathways.¹²⁰ Consistent with this hypothesis, insulin signalling in murine liver in leptin-deficient states also

diverges along two pathways; the transcription factor *Srebp-1c* (*Srebf1*) is another gene that remains sensitive to insulin in these insulin-resistant mice.^{119,121} Similar selective insulin resistance has been described in human and rodent muscle.^{122,123}

Collectively, these findings raise the possibility that in metabolic insulin resistance accompanied by hyperinsulinaemia and obesity, the expression of certain insulin-responsive genes can dramatically increase in insulin target tissues. High concentrations of MCP-1 protein can induce adipocyte dedifferentiation and contribute to pathological states associated with hyperinsulinaemia and obesity, including type 2 diabetes. Increased MCP-1 mRNA in adipose tissue and MCP-1 protein in plasma are reported in genetically obese diabetic (*db/db*) mice and in wild-type mice with obesity induced by a high-fat diet.¹²⁴ Plasma MCP-1 is correlated with severity of traumatic brain injury (TBI) and an index of compromised axonal fibre integrity in the frontal cortex. MCP-1 is suggested as a marker of Alzheimer's disease risk in TBI.¹²⁵

Growth factors

Hepatocyte growth factor

HGF, also known as scatter factor and hepatopoietin A, is increased in obese adults and adolescents.¹²⁶ In-vitro secretion of HGF is greater from adipocytes removed from obese versus lean individuals.¹²⁷ HGF is a multifunctional trophic factor that binds to its receptor, MET, and activates a tyrosine kinase signalling cascade. Whereas HGF is produced by both neurons and non-neuronal cells, MET is highly expressed in neurons. During embryogenesis, HGF acts as a neural inducer, an interneuron motogen, axonal chemoattractant, angiogenic factor, and a neuroprotective survival factor.^{128,129} HGF production in adults is induced by ischaemic injury¹³⁰ and in Alzheimer's disease.¹³¹

HGF enhances long-term potentiation¹³² and improves memory deficits caused by ischaemia.¹³³ HGF mRNA is found in the brain. HGF-like immunoreactivity is seen in both the cerebral cortex and white matter. Confocal microscopy confirms that HGF is present in GFAP-positive astrocytes, LN3-positive microglial cells, and rare scattered cortical neurons.¹³¹ HGF is increased in the brains of patients with Alzheimer's disease compared with age-matched control brains as a function of the gliosis and microglial proliferation that is associated with Alzheimer's disease.¹³¹ HGF and other growth factors are also shown to accelerate neuroprotection, angiogenesis, and regeneration in the brain of rodents.¹³⁴ However, the role of central versus peripheral HGF is unclear.

Nerve growth factor

NGF is a neurotrophin secreted by adipose tissue. Basic studies have shown that NGF is associated with neuronal survival, differentiation of target neurons, and growth of nerve fibres and their guidance (tropism) towards the

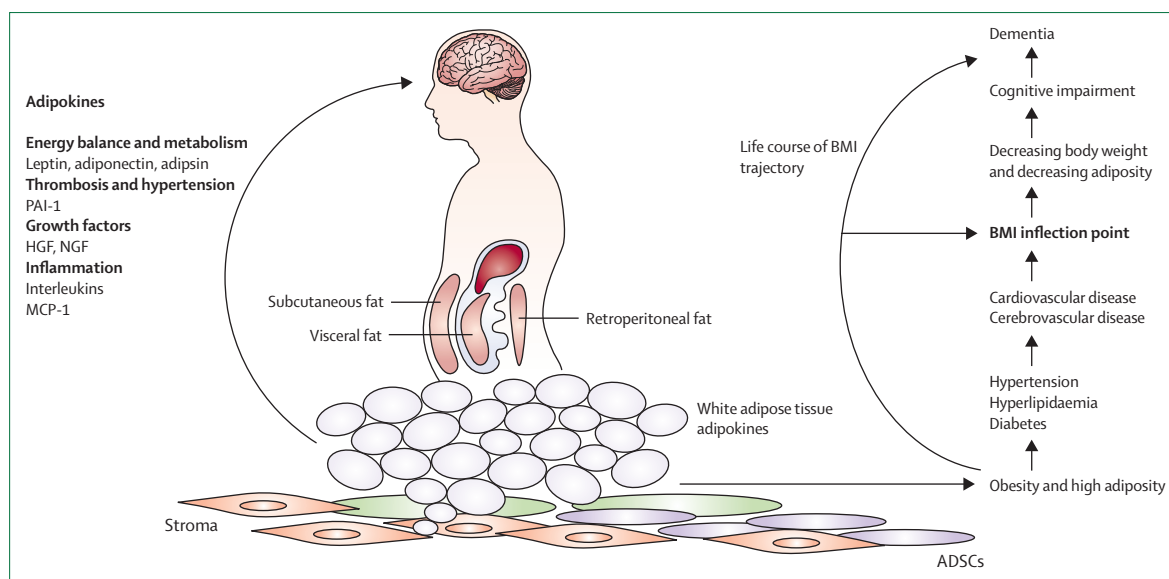


Figure 2: The trajectory of body-mass index over the life course by chronological age and potential roles of adipokines

PAI-1=plasminogen activator inhibitor-1. HGF=hepatocyte growth factor. NGF=nerve growth factor. MCP-1=monocyte chemoattractant protein-1. BMI=body-mass index. ADSC=adipose-derived stem cells.

source of production.¹³⁵ NGF inhibits the amyloidogenic processing of amyloid precursor protein (APP) in vitro,^{136,137} which could have application as a potential intervention for Alzheimer's disease. The source of this NGF could be central or peripheral, since NGF has been shown to cross the blood–brain barrier. Few studies have assessed circulating NGF with cognitive outcomes, although NGF repletion has been proposed as a potential intervention in Alzheimer's disease via protection of the cholinergic system.¹³⁸ Serum NGF has been suggested to be lower in those with Alzheimer's disease than in age-matched controls.¹³⁹ By contrast, CSF concentrations of NGF are reported to be higher in patients with Alzheimer's disease versus healthy controls.¹⁴⁰ NGF has also been proposed as a therapy for TBI,¹⁴¹ which is a risk factor for dementia.

In relation to adiposity, a study in China assessing the correlations between anthropometric indices and adipokines, showed that WHR was associated with circulating NGF ($r=0.48$), and leptin ($r=0.53$) concentrations. In this study, BMI and WHR were also correlated with mean HGF concentrations ($r=0.34$ and 0.51 , respectively) and PAI-1 concentrations ($r=0.42$ and 0.56 , respectively).¹⁴²

Conclusions and future directions

The association between adipokines and clinical dementia or cognitive impairment is largely unexplored, despite published epidemiological data supporting associations between adiposity, measured via anthropometry, and dementia and Alzheimer's disease.

There are several considerations or limitations when evaluating the adipokine–dementia link in published work. Adipokines are not secreted only from adipose

tissue. Although hundreds of adipokines—comprising the adipokineome—potentially reflect adipose tissue exposure, different adipokines could have different roles depending on mechanisms of action and tissues involved. In this case, adipokines could function as biomarkers for systems biology approaches or be good statistical markers of risk, but still be poor indicators of neurodegenerative or vascular mechanisms that are coupled to adipose tissue. Definitive estimates of dementia risk remain to be elucidated for any adipokine.

Many adipokines are not associated with anthropometric measures of excess weight and obesity, possibly because anthropometric measures do not give good estimates of the amount of adipose tissue during adulthood, adipose tissue is not a primary source of these particular adipokines, or adipokine release is not associated with the quantity of adipose tissue. Adipokine functions in the periphery are not necessarily similar to those in the brain (eg, PAI-1). This finding is challenging the understanding of adipokine actions in each compartment, and requires more research into their movement across the blood–brain barrier, and interactions with other adipokines. Furthermore, there are sex, race and ethnic differences in adult body composition and adipokine concentrations, and these differences do not correspond to differences in the occurrence of dementia.^{143,144} Factors that influence blood adipokine concentrations, such as medications, type of metabolic syndrome (eg, in type 2 diabetics, adults with HIV infection), amount of excess weight and obesity, are not well understood.

The trajectory of BMI over the life course suggested in figure 2,⁹ and variations in the relation of BMI to general

Search strategy and selection criteria

We searched PubMed with the terms “dementia”, “Alzheimer”, “adiposity”, “body-mass index (BMI)”, and the adipokines “leptin”, “adiponectin”, “plasminogen activator inhibitor-1 (PAI-1)”, “hepatocyte growth factor (HGF)”, “nerve growth factor (NGF)”, “adipsin (complement factor D)”, “monocyte chemotactic protein (MCP-1)”, and “interleukins” with no date restrictions. A comprehensive literature search was done for studies reporting on associations between adipokines and dementia with no date restrictions. We searched for studies of biological mechanisms published between Jan 1, 2010, and 31 Dec, 2013.

ageing, dementia, and mortality,¹⁴⁵ emphasise the importance of the age at which BMI measurements are taken and the proximity to the time of onset of clinical dementia (eg, midlife vs late-life). Although high adult BMI might increase risk for chronic neurodegenerative and vascular diseases of ageing, some studies show that the direction of the BMI–dementia relationship declines later in life.^{6,9} Perhaps high BMI and greater central adiposity are midlife markers of vascular risk that dominate the dementia risk equation, whereas declining or low BMI denotes predominant neurodegenerative events in recent life. This latter point is shown by data from the National Alzheimer Coordinating Center in the USA: in those with mild cognitive impairment, a high baseline BMI is associated with worse clinical dementia rating, but greater subsequent bodyweight decline is associated with faster clinical progression.⁸ However, not all observations show a similar trajectory. The Gothenburg Birth Cohort Studies showed that BMI increase is less before the inflection point indicated in figure 2, followed by a similar rate of BMI decline in those with and without dementia.⁹ This finding suggests that different biological mechanisms, perhaps mediated by adipokines, underlie the evolution of ageing and dementia, as well as heterogeneity in the dementia outcome reflecting both vascular and neurodegenerative processes in the brain.

Finally, survival bias could affect reported midlife and late-life obesity–dementia associations, since competing risk analyses tend to show that those who are overweight or obese die before the age at which they are at risk for dementia.^{4,146} However, this association could change as survival with multiple comorbidities, many associated with overweight and obesity, increases. These considerations can be best addressed, and limitations overcome, by additional research.

In summary, this Review focuses on adipokines associated with excess adiposity, a risk factor for late-onset dementia. We are unaware of published data for changes in adipokine concentrations over the life course. As more is known about the epidemiology and biological mechanisms linking adipokines and dementia, there will

be greater understanding of the inter-individual and intra-individual differences in adipokine metabolism; the dysregulation of metabolism that occurs with ageing, neurodegeneration, and dementia; and the differences in metabolism owing to differences in diet, physical activity, ethnic origin, and genetics. For example, whether changes in body composition due to physical activity interventions in elderly people improve the adipokine profile for the ageing brain is unknown. Considering the vast number of adipokines, one approach for exploration could be directed towards their cumulative role as classes of adipokines versus single adipokines. Additionally, therapeutic strategies related to the use of single or combined adipokines could be an avenue for exploration in the prevention of cognitive impairments and dementia, which has been suggested for leptin.⁷⁴

In view of the immense secretory capacity of adipose tissue, the often acute nature of the adipose secretome in response to various stimuli, and changing body composition with ageing, unravelling the effect of this organ over the life course remains a challenge. Adipokines as biomarkers could enhance the understanding of late-onset dementia risk over the life course, as well as the clinical progression of prodromal and manifest dementias. This information will allow the identification of populations at risk, and the design of better clinical trials to target vascular and metabolic risk associated with adipose tissue, both centrally and peripherally.

Contributors

DRG undertook literature searches, helped to design the figures and tables, and drafted the text. IACA and AJK undertook literature searches, helped to design the figures, and drafted parts of the text.

Declaration of interests

We declare no competing interests.

Acknowledgments

DRG is supported by the EU 7th framework LipiDiDiet project (FP7/2007-2015) under grant agreement number 211696; NIH/NIAID U01 318345; Swedish Research Council Diarienummer: 523-2005-8460; and the State University of New York Research Foundation. AJK is supported by the EU 7th framework LipiDiDiet project (FP7/2007-2015) under grant agreement number 211696. The funding sources had no role in the content of this Review.

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