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Obesity and Alzheimer's Disease: A Link Between Body Weight and Cognitive Function in Old Age

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Obesity is now a global health hazard. It not only predisposes to an array of risk factors leading to increased morbidity and mortality amongst adults but it also has a major negative impact on children's health. The deleterious effects of obesity on cardiovascular system have now been well acknowledged. It causes insulin resistance that in turn leads to diabetes, hypertension and cardiovascular abnormalities. The vascular effects of obesity may have a role in the development of a rapidly growing disease of late life, Alzheimer's disease. The precise mechanisms of the association between adiposity and impairment of cognitive performance remain to be elucidated. However, negative impact of obesity on cognitive function may be, at least in part, due to vascular defects, impaired insulin metabolism and signaling pathway or a defect in glucose transport mechanisms in brain. This review examines the available data regarding the impact of obesity on cognitive function.

Keywords: obesity; cognitive function; old age; Alzheimer's disease

Obesity: A Health Problem

Obesity, defined by accumulation of excess adipose tissue has now become a worldwide epidemic. In fact, in 1997 the World Health Organization (WHO) stated that "*obesity should now be regarded as one of the greatest neglected public health problems of our time* ...." A numerous studies have indicated obesity per se as an independent cardiovascular risk factor, as well as predisposing to type 2 diabetes, induction of insulin resistance, hypertension, and dyslipidaemia.[1,2]

The origins of adult obesity stems from childhood lifestyle behavior with numerous longitudinal studies indicating a positive correlation between high body weight and obese adults.[3-5] Although certain proportions of cardiovascular disorders are attributed to the secondary complications of obesity (eg, hypertension, atherosclerosis, type 2 diabetes, and aging), a direct deleterious effect of obesity on the cardiovascular system is now clearly evident. For example, patients with morbid obesity have higher rates of sudden unexpected cardiac-related death,[6] implicating the importance of obesity as an independent risk factor for cardiovascular dysfunction, both at arterial and at cardiac myocyte levels.

There is no comprehensive information on the role of obesity on vascular morphology and function. However, almost all animal and clinical studies examining vascular function in obesity have shown some degree of vascular abnormalities that occur at both endothelial and smooth muscle levels.[7-10] Therefore, it is plausible to hypothesis that increased vascular disease at the level of the brain may in turn affect memory function. Obesity results in insulin resistance.[4,5,8,9] Insulin has a significant role on modulation of synaptic plasticity and learning memory.[11] Insulin receptors and insulin-sensitive glucose transporters are densely expressed in the medial temporal region of the brain that supports memory formation,[12] indicating that insulin may have a role in maintaining normal cognitive function. Hence, abnormalities in the insulin signaling pathway may contribute to impairment of memory function, similar to those seen in patients with

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Alzheimer's disease (AD). In fact animal studies have shown that intranasal administration of insulin improves cognitive behavior in mice[13] perhaps by modulating neuronal communication within the brain.

Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disease that is mainly diagnosed by its clinical features. The clinical characteristics of AD involve progressive impairment of cognitive function, impaired orientation, impaired attention, language disturbance (aphasia), difficulty in recognizing or identifying objects (agnosia), disturbance in executive functioning, and impaired motor activity (apraxia). Histopathologically, development of what is known as senile plaques and neurofibrillary tangles and deposits of aggregated amyloid β (Aβ) in neuritic plaques and cerebral vessels are characteristic hallmarks of AD.[14] The association between apolipoprotein E4 (ApoE4) alleles and cognitive dysfunction has also been extensively indicated.[15,16] Overweight participants exhibit an inverse association with ApoE4 and associated with decreased non-ApoE4 AD onset age. Pathogenic mechanisms associated with diabetes and overweight are enriched in AD cases without an ApoE4 allele.[17]

Obesity and Cognitive Function

Emerging reports from various clinical studies support the idea of negative correlation between adiposity per se and cognitive function. From published literature, it appears that deterioration of cognitive and motor function accelerates with increasing total body fat irrespective of body fat distribution pattern. In fact, a cohort study of obese women has shown that irrespective of body fat distribution, overall body weight is associated with derangement of motor function.[18] Similar observations from the Framingham heart study have also reported a marked impairment of cognitive function in patients with obese compared with nonobese counterparts.[19] These reports indicate an inverse correlation between higher body weight and memory function in adult human participants.

In a prospective study of 2798 adults without dementia, over an average follow-up period of 5.4 year, 480 people were diagnosed with incident of dementia of which 245 with AD (no vascular dementia [VD]) and 213 with VD (with or without AD). An increased risk of dementia was found for obese (BMI >30) versus normal weight (BMI 20-25) participants with midlife (age 50 years) obesity. Interestingly, this study reported reversal of risk estimates in assessments of late-life (>65 years of age) BMI. Underweight persons (BMI <20) had an increased risk of dementia, whereas being overweight (BMI >25-30) was not associated and being obese reduced the risk of dementia compared with those with normal BMI.[20] A similar finding is also reported in another large scale study. In a population-based prospective cohort study of 1836 with a mean age of >71 years at base line who were followed up for further 7 years reported that the higher baseline BMI was significantly associated with a reduced risk of AD. More importantly, slower rate of decline in BMI was associated with a reduced risk of dementia,[21] indicating protective effects of higher late life adiposity in retaining cognitive function. Furthermore, another prospective study of 10 136 participants (40-45 years of age) examining association between midlife BMI and dementia over an average of 36 years follow-up reported that obese participants (BMI ≥30) at midlife had more than 3-fold increase in risk of AD compared to those with a normal BMI (>18.5-<25) at midlife. What is important to note is that the increase in AD risk was significant even after adjustments for age, education, race, sex, marital status, smoking, hyperlipidaemia, hypertension, diabetes, ischemic heart disease, and stroke. The risk of VD was also increased by 5-fold, while those overweight at midlife (BMI ≥25 and <30) had a 2-fold increase in risk of AD and VD.[22] These data strongly implicate midlife BMI as a marker for prediction of AD and VD in later life. Moreover, it strongly suggests that obesity per se has significant negative impact on cognitive function irrespective of secondary complications of obesity. Data from the above studies suggest a "bimodal" effect of total adiposity on cognitive function in later life—a negative effect if the participant is obese at midlife and a positive effect if the participant is obese in later life. Interestingly, in a study of healthy adults (20-82 years), BMI was also inversely related to performance on all cognitive tests such that overweight and obese adults (BMI > 25) exhibited poorer executive function test performance than normal weight adults (BMI = 18.5-24.9).[23] This study may suggest that obesity-induced cognitive impairment can set in at an early age if total adiposity is increased. A similar retrospective study with 18 year follow-up on women with dementia reported higher BMI for participants with AD compared with non-AD participants with similar age. In fact for every 1.0 increase in BMI at age 70 years, AD risk increased by 36%,[24] further highlighting the

importance of overall adiposity on cognitive function at any given age.

Noninvasive studies using magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopic indicate higher BMI is strongly correlated with lower concentrations of *N*-acetylaspartate (spectroscopic marker of neuronal viability) in frontal, parietal, and temporal white matter as well as lower *N*-acetylaspartate levels in frontal gray matter. There were also lower concentrations of choline-containing metabolites (associated with membrane metabolism) in frontal white matter.[25] Furthermore, these differences were irrespective of age or sex, stressing negative impact of increased BMI per se on central nervous system (CNS) neuronal viability. Moreover, these results suggest that higher BMI at midlife (midlife 40-50 years of age) is associated with neuronal and/or myelin abnormalities, which may in turn reflect accelerated aging and subsequently the development of age-related cognitive impairment. Furthermore, in older adult participants without significant neurological or psychiatric history, plasma levels of Aβ were correlated directly with adiposity and inversely with cognitive function[26,27] suggestive of role of obesity in deposition of Aβ and ultimately deterioration of cognitive function.

Histological examination of autopsied brain has indicated frequent Alzheimer-type neurological changes in hippocampal structure of morbidly obese participants. Obese (BMI > 45) patients >65 years showed higher levels of Aβ (4G8), τ (AT8), or Aβ PP protein deposits in brain compared with none-obese participants. More interestingly, these indices in some cases were comparable to those seen in patients with established AD. Furthermore, the differences in τ and Aβ PP expression were significantly higher in obese non-AD patients than non-obese non-AD controls.[28] What is important to note is that Alzheimer-type neuropathological changes in morbidly obese elderly individuals but not younger obese patients were observed without any clinical history of cognitive impairment. Contrary to human studies, animal histopathological studies were equivocal failing to show a clear association between diet-induced obesity and development of AD. High-fat diet feeding of animal model of obesity and type II diabetes mellitus (C57BL/6 mice) doubled mean body weight, caused type II diabetes mellitus, and marginally reduced mean brain weight. Moreover, these effects were associated with significantly increased levels of τ, insulin-like growth factor (IGF)-I receptor, insulin receptor substrate-1 (IRS-1), IRS-4, ubiquitin, glial fibrillary acidic protein, and 4-hydroxynonenol, and decreased expression of β-actin. High-fat diet feeding also caused brain insulin resistance manifested by reduced BMAX (baseline standard expected to yield the highest possible bound response) for insulin receptor binding and modestly increased brain insulin gene expression. Despite such alteration in above indices high-fat diet-fed mouse brains did not exhibit AD histopathology, increases in amyloid-β or phospho-τ, or impairments in IGF signaling or acetylcholine homeostasis.[29] Therefore, in animal models, although diet-induced obesity and subsequent development of type II diabetes causes brain atrophy, it does not produce characteristics histological changes seen in AD. A similar increased atrophic change has also been reported in obese human compared with lean counterparts. Overweight and obese women present with increased temporal but not frontal, parietal, or occipital atrophy compared with lean controls.[30] Therefore, it is plausible to consider obesity and overall adiposity as an important independent factor in the genesis and progression of cognitive impairment. This hypothesis is further strengthened by an important animal study where addition of sucrose-sweetened water to normal rodent diet daily intake of animal model of AD induced obesity, glucose intolerance, hyperinsulinaemia, and hypercholesterolaemia. What is significant in this study to note is that these metabolic changes were associated with increased exacerbation of memory impairment and a 2- to 3-fold rise in insoluble Aβ protein levels and its deposition in the brain of these animals compared with nonobese transgenic AD mice.[31] This study provides direct evidence that obesity not only induces cognitive decline but it in fact can exacerbate memory impairment in those who already show sign of cognitive dysfunction.

Summary

Obesity characterized by excess adipose tissue is a risk factor for the development of type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease. There are now growing evidences linking obesity and metabolic abnormalities to development and progression of cognitive impairment. This hypothesis has a major impact on the future health care of any given society. Increased prevalence of obesity as well as reduced age of onset of obesity in the population may lead to much higher incidence and prevalence of diseases such as AD, which are normally considered an old age disease. Both retrospective and animal studies have clearly outlined a strong association between obesity and cognitive

dysfunction such that higher total adiposity means higher risk of developing memory impairment. Moreover, weight increase may accelerate progression of memory impairment. The exact mechanisms of obesity related memory loss are not fully elucidated, yet however, obesity-induced insulin resistance, vascular dysfunction, and protein deposition in the brain have all been implicated in worsening of cognitive function. Nonetheless, observations so far suggest the presence of a bimodal relationship between obesity and cognitive function. It is important that a causation link between obesity and impairment of cognitive function be understood clearly as it would help us be prepared in tackling the massive influx of future patients with cognitive impairments.

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