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The Negative Effects of Obesity and Poor Glycemic Control on Cognitive function: A Proposed Model for Possible Mechanisms

Michael L. Alosco, M.A. and John Gunstad, Ph.D.

Kent State University, Department of Psychology, Kent, Ohio, USA

Abstract

Obesity has reached epidemic proportions and is a contributor to many adverse health outcomes, including increased risk for dementia and adverse structural and functional brain changes. Milder forms of cognitive impairment in multiple domains can also be found in obese individuals of all ages that are believed to stem from brain abnormalities long prior to onset of neurological conditions such as dementia. However, the mechanisms for adverse brain changes and subsequent cognitive dysfunction in obesity are complex and poorly understood. This paper proposes a possible etiological model for obesity associated cognitive impairment with emphasis on the role of poor glycemic control and conditions like type 2 diabetes mellitus. Clinical implications associated with treatment of obesity in persons with cognitive deficits in addition to the cognitive promoting effects of weight loss surgery are also discussed.

Keywords

Obesity; type 2 diabetes mellitus; cognitive function; brain mechanisms; glycemic control

Introduction

Approximately 80 million American adults are obese [1] and it is estimated that obesity rates will exceed 44% within every state over the next 20 years [2]. This pattern is concerning as obesity is a source of societal and economic hardship and is projected to account for up to 18% of healthcare costs by the year 2030 [1]. Indeed, obesity is associated with increased risk of morbidity and mortality and many poor physical health outcomes, including hypertension and type 2 diabetes mellitus (T2DM) [3].

Rapidly growing evidence also shows that obesity is associated with poor neurocognitive outcomes. Specifically, obesity is linked with elevated risk for Alzheimer's disease (AD), vascular dementia, and abnormalities on neuroimaging [4,5]. Obesity is also associated with mild deficits on cognitive testing, including on tasks assessing global cognition, attention, executive function, and memory [6–8]. Such deficits are particularly pronounced in severely obese individuals [6]. While cognitive dysfunction is common in obese middle aged and older adults [6,7], obesity related cognitive deficits are not limited to specific age cohorts.

For instance, higher BMI is correlated with cognitive dysfunction in multiple domains in children, adolescent individuals, and young adults [8–10].

Higher BMI is also associated with reduced cognitive function in otherwise healthy adult samples [12–14]. Indeed, Gunstad et al. (2006) [15] found prominent memory deficits in obese young and middle-aged healthy adults. These findings in healthy samples suggest that the presence of adiposity alone may negatively impact neurocognitive function.

Despite these findings, the mechanisms of cognitive deficits in obesity are poorly understood. The purpose of this paper is to propose a possible etiological model for obesity associated cognitive impairment with emphasis on the role of T2DM and related conditions (e.g., impaired glucose tolerance prior to T2DM onset). We chose to focus on the role of T2DM because of its high prevalence in obese individuals and strong association with poor neurocognitive outcomes independent of obesity. As an example, T2DM has been shown to nearly double the risk of dementia among >6,000 elderly subjects [16].

Proposed Mechanisms for Cognitive Impairment in Obese Persons

Please see Figure 1 for the proposed model of possible mechanistic pathways for the negative effects of obesity on neurocognitive outcomes. It hypothesizes that obesity-related cognitive impairment results from the adverse effects of comorbid conditions and novel risk factors on brain structure and function.

Adverse Brain Changes

Extant evidence documents the adverse effects of obesity on the brain. Consequently, we propose that adverse brain changes in obese persons directly precede manifestations of cognitive deficits.

Cerebral Hypoperfusion. Obesity is independently associated with reduced cerebral perfusion and metabolic activity among healthy adults, including to brain regions critical for attention, reasoning, and executive function abilities [13,17]. Reduced cerebral perfusion is a significant contributor to the pathogenesis of dementia [18,19,20]. Altered cerebral hemodynamics is also directly linked with brain insult, including ischemic-related injuries (e.g., white matter hyperintensities) [21]. Indeed, recent work shows that higher BMI interacts with cerebral hypoperfusion in cardiovascular disease patients to exacerbate cognitive impairment, particularly in attention/executive function [6].

Brain Structure and Function. Relative to controls, obese persons exhibit higher levels of AD-related pathology, including tau and amyloid beta protein expression [22]. Obesity has also been linked with smaller regional and total brain volume in neurological and healthy adult samples [23–25]. White matter hyperintensities (WMH) and axonal injury is also common in obese individuals [26], with a 1 kg/m² increase in BMI associated with a two fold increased risk of white matter lesions in elderly individuals [26,27]. Decreased fractional anisotropy of the splenium, genu, and fornix also correlates with BMI among samples of healthy adults [28–30]. Unfortunately, no study has examined the association between structural and functional brain integrity with cognitive test performance in obesity

and future studies are needed to clarify the impact of brain injury in obesity on cognitive function.

Contributors to Adverse Brain Changes

We propose that adverse brain changes and resulting cognitive deficits in obesity largely stem from the independent and interactive effects of multiple comorbid conditions, particularly T2DM. However, long prior to the diagnosis of these medical conditions, subclinical pathology (e.g., poor glycemic control) may contribute to adverse brain changes and cognitive deficits in obese persons. Alternatively, risk factors unique to adiposity may also play a key role and future studies are needed to confirm their effects on cognition.

Type 2 Diabetes Mellitus

It is estimated that by the year 2050 nearly one out of every three American adults could have diabetes [31]. This pattern may largely be attributed to the rapidly rising rates of obesity in the United States. Obesity is recognized as a primary cause of T2DM because of its effects on skeletal muscle insulin resistance and pancreatic beta cell failure [32,33]. Obesity is associated with a 40X relative risk for T2DM, making it one of the most common comorbidities in obese individuals [34,35]. Subclinical elevations in glucose is also prevalent in obese persons and can be found in approximately 33% of U.S. adults [36,37].

T2DM and Cognitive Function. The well-known effects of T2DM and pre-diabetes on the brain are theorized to play a major role in obesity associated cognitive impairments. T2DM has been suggested to be a significant contributor to the development of mild cognitive impairment (MCI) and accelerate progression from MCI to dementia [38].

Neuropsychological testing reveals that persons with T2DM most commonly exhibit deficits on tasks of verbal memory and processing speed [39]. Pre-diabetic individuals also perform poorly on formal cognitive testing and are at a two-fold increased risk for cognitive decline relative to individuals with normal fasting glucose levels [40]. Not surprisingly, when compared to obese controls, obese persons with T2DM demonstrate greater cognitive deficits including in memory and psychomotor speed [41].

T2DM and Adverse Brain Changes. T2DM and related conditions likely impact the brain to exacerbate cognitive deficits in obese persons. Most notably, T2DM is an established risk factor for stroke and brain infarcts [42]. However, T2DM is also linked with brain atrophy [43] in addition to greater postmortem AD neuropathology such as increased hippocampal neuritic plaques, neurofibrillary tangles in the cortex and hippocampus, and higher risk of cerebral amyloid angiopathy [44]. Persons with T2DM also exhibit functional brain impairments. For instance, diabetes is associated with neuronal injury and [45] negatively impacts cerebral circulation to contribute to the development of white matter hyperintensities [46]. Resting state fmri studies show that T2DM patients exhibit impaired neuronal activity in among many lobar structures, notably in middle temporal lobe regions, and these impairments predicted poor neurocognitive performances [47]. Taken together, obese individuals with T2DM are at significant risk for accelerated brain insult, including atrophy and impaired neuronal function among structures implicated in AD (e.g., hippocampus) [48,49].

Physiological Mechanisms of T2DM. The synergistic effects of T2DM and obesity on shared abnormal physiological processes likely produces additive effects on the brain and cognition. Specifically, macrovascular risk factors (e.g., hypertension, atherosclerosis, elevated cholesterol) and microvascular disease (e.g., endothelial dysfunction) are prevalent in both obese and T2DM patients and associated with cognitive impairment and development of AD [50,51]. Alternatively, inflammatory markers are also elevated in obese [52] and T2DM populations [51] and may produce additive brain and cognitive deficits in obese individuals with T2DM [51,53,54].

T2DM further introduces several unique mechanisms in obese persons to negatively impact neurocognitive function. Advanced glycation endproducts (AGE) are elevated in patients with T2DM and linked with microvascular complications [55,56], AD-related pathology, as well as impaired neuronal function, oxidative stress, and glucose hypometabolism [51,57]. Hyperinsulinemia is also a likely mechanism of poor neurocognitive outcomes in T2DM, including increased risk for AD. Insulin plays a key role in the brain with receptor sites located in the hippocampus and entorhinal cortex [58]— brain structures affected by AD [59]. Impaired insulin function accelerates cognitive decline [60] and affects amyloid beta clearance in the brain [61]. Chronic hyperglycemia in obese persons with T2DM may also accelerate cognitive decline via cerebral hypoperfusion [62] and its adverse effects on central glucose utilization [63,64]. Lastly, lipoprotein related proteins (LRP) are diminished in T2DM patients and are another possible mechanism for risk of AD in this population, particularly in light of its role in amyloid beta clearance [43, 65].

Impaired Glucose Tolerance

Obese persons commonly exhibit impairments in glycemic control before the onset of T2DM. Such abnormalities also likely contribute to cognitive dysfunction in obese persons. Recent work in non-diabetic elderly shows that increases in HbA1c predicts cognitive decline over time [66]. Other work also demonstrates the negative effects of glucose intolerance on neurocognitive outcomes, including increased risk for MCI and dementia in non-diabetic individuals [67]. Poor glycemic control further appears to adversely impact the integrity of the brain. For instance, high HbA1c levels have been linked with reduced hippocampal volume, and possibly vascular related brain pathology such as cerebral hypoperfusion [68,69]. Future work is needed to clarify the effects of poor glycemic control on the brain and cognitive function in obese individuals prior to the development of T2DM.

Other Medical and Clinical Comorbid Conditions

Obesity is associated with many other comorbid conditions that negatively impact neurocognitive function and increase risk for AD. Most notably, obese persons exhibit reduced cardiac function and present with conditions such as hypertension and sleep apnea. Obese individuals also demonstrate higher rates of sedentary behaviors, poorer physical fitness, and are at greater risk for psychological disorders such as depression [70,71]. A vast literature supports the negative effects of these medical comorbidities and clinical factors on reduced neurocognitive function and increased risk for AD and dementia related processes [72–74]. Past work shows that obesity interacts with many of these conditions such as hypertension and reduced physical fitness to exacerbate neurocognitive impairments [75,76].

Novel Risk Factors

The extant literature linking obesity with cognitive deficits in healthy samples suggests that the presence of adiposity may introduce unique mechanisms to adversely impact neurocognitive outcomes. Much attention has been paid to the role of genetic factors and biomarker concentrations in cognitive function among obese individuals. Specifically, the fat mass and obesity associated gene (*FTO*) is associated with obesity [77] and carriers of the *FTO* risk allele exhibit poorer neurocognitive outcomes [78]. APOE ε4 is also involved in lipid regulation and may interact with vascular risk factors to accelerate cognitive decline and risk of AD [79].

Obese individuals also exhibit elevated inflammatory markers [52] and abnormal concentrations of circulating biomarkers, including appetitive neurohormones (e.g., leptin, ghrelin), brain derived neurotrophic factor (BDNF), and amyloid beta [80–83]. Increased inflammatory markers accelerate cognitive decline in medical and elderly populations and are also a hallmark of AD, suggesting a possible role for inflammation in obesity associated cognitive deficits [84,85]. Similarly, adipokines and appetite hormones (e.g., ghrelin, leptin) have important neurotrophic and neuroprotective roles [86,87] and disturbed levels of these biomarkers may contribute to the pathogenesis of AD and reduced cognitive function [86–88]. Interestingly, weight loss surgery and behavioral weight loss interventions may correspond to better cognitive function via their effects on concentrations of many of these biomarkers, appetite hormones (e.g., leptin, ghrelin, amyloid beta) [89,90, 91], as well as insulin levels [92] and prospective studies should test this possibility.

Discussion

Obesity has reached epidemic proportions and is a significant contributor to poor health outcomes. Obesity is now also a recognized risk factor for reduced neurocognitive outcomes, including increased risk for dementia (e.g., AD and vascular dementia). Obese individuals of all ages also exhibit deficits on formal cognitive testing that may stem from the impact of obesity on the brain. The etiology of adverse brain changes and cognitive dysfunction in obese persons likely involves multiple physiological processes subsequent to the effects of medical and clinical comorbidities as well as excess adiposity.

T2DM is one of the most common comorbid medical condition in obesity and obese persons with significant impairments in glucose tolerance may be at greatest risk for cognitive impairment and dementia. Indeed, T2DM is associated with abnormalities on neuroimaging, cognitive decline, AD, and interacts with BMI to exacerbate poor neurocognitive outcomes [42]. While it is plausible that tightly controlled glucose in obese individuals may attenuate cognitive impairment [93], the literature is not entirely consistent on this approach. For instance, past work has shown that better glycemic control is not related to improved cognitive function [94]. The exact reason for the discrepancy in these findings is unclear, but suggests other factors associated with T2DM (e.g., AGE) may contribute to cognitive dysfunction. Future work in obese individuals is much needed to determine other recently theorized mechanisms (e.g., epigenetics) [95] and medical and clinical factors by which T2DM may exacerbate cognitive deficits in obesity. Future work should also explore

whether sustained treatment of obesity and its accompanying medical conditions (e.g., T2DM) translates to improved cognitive function in obese individuals.

Cognitive impairment in obesity has significant clinical implications. Obese individuals are asked to adhere to complex treatment regimens to manage their many medical comorbidities and promote weight loss. Recent work shows that poorer cognitive function is strongly predictive of worse adherence behaviors among cardiovascular disease patients and persons with T2DM [96,97]. Interestingly, cognitive deficits in severely obese individuals undergoing bariatric surgery may interfere with adherence to post-operative treatment recommendations and result in decreased ability to lose or maintain weight loss [98]. Specific impairments in executive function seem most likely to preclude obese persons cognitive ability to plan ahead, multi-task self-care behaviors, organize medications, implement routine exercise regimens, monitor symptoms, among many other adherence behaviors. Poor adherence likely becomes particularly problematic in obese patients with T2DM, as cognitive impairment is exacerbated and the treatment regimens become more complicated. Future studies are needed to determine the benefits of cognitive screening in obese individuals to help determine those patients at greatest risk for treatment non-adherence, particularly among patients undergoing weight loss surgery.

Nonetheless, obesity is a modifiable risk factor and cognitive impairment in this population may be reversible. A growing literature shows that bariatric surgery is associated with improved acute and long-term cognitive function across several domains, particularly in memory abilities [7,99]. A likely mechanism for these findings involves resolution of medical comorbidities such as T2DM (See Figure 1). For example, bariatric surgery has been shown to improve glycemic control and result in long-term improvements and/or remission of T2DM and other metabolic risk factors [100]. In fact, recent attention has been paid to surgical intervention as an alternate treatment for T2DM versus lifestyle modifications [101]. Improvements in inflammation and circulating biomarkers after bariatric surgery may also lead to better cognitive outcomes [89,90]. Prospective studies are needed to clarify the mechanisms of improved cognitive function after weight loss surgery and whether surgical intervention can reduce the risk of cognitive decline and/or dementia in obese individuals. Although behavioral strategies (e.g., diet and exercise) are less successful for long-term weight loss, such interventions have been shown to improve cognitive function [102] and prospective studies should examine the neuroprotective effects of lifestyle modifications in obesity, particularly relative to weight loss surgery.

Conclusions

In brief summary, obese individuals are at risk for cognitive impairment via comorbid conditions and novel risk factors associated with adiposity. Clinicians working with obese individuals should be mindful of the possible presence of cognitive dysfunction and establish procedures for screening and/or referring for formal neuropsychological evaluation. Such screening methods may help to determine those patients at risk for reduced treatment adherence. Randomized control trials that follow obese individuals throughout the lifespan are needed to confirm the effects of obesity on the brain and identify the nature of cognitive decline in this population.

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Figure 1. Proposed Model for Mechanisms of Obesity Associated Cognitive Impairments

Note. The displayed medical, clinical comorbidities, and novel risk factors represent the most common factors in obese individuals. Weight loss may attenuate cognitive dysfunction in obesity via resolution of comorbid medical and clinical conditions, and improvements in novel risk factors stemming from substantial adiposity loss. Of note, while other genetic markers have been linked with obesity, only the *FTO* is displayed given evidence of it being one of the strongest genetic risk factors for obesity and its close link with cognitive outcomes. Altered biomarkers refers to disturbed levels of adipokines and appetite hormones such as leptin and ghrelin.