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Obesity as a Risk Factor for Poor Neurocognitive Outcomes in Older Adults with Heart Failure

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Abstract

Heart failure (HF) has reached epidemic proportions and is a significant contributor to poor outcomes. HF is an established risk factor for Alzheimer's disease, vascular dementia, and abnormalities on neuroimaging. Moreover, up to 80% of HF patients also exhibit milder impairments on cognitive tests assessing attention, executive function, memory, and language. The mechanisms of cognitive impairment in HF are not entirely clear and involve a combination of physiological processes that negatively impact the brain. Cerebral hypoperfusion and common comorbid conditions in HF are among the most commonly proposed contributors to poor neurocognitive outcomes in this population. Obesity is another likely risk factor for adverse brain changes and cognitive impairment in HF, as it is a known contributor to neurocognitive outcomes in healthy and patient samples. This paper reviews the literature on HF and cognitive function and introduces obesity as a significant risk factor for poor neurocognitive outcomes in this population.

Keywords

Obesity; Heart Failure; Cognitive Function; Risk Factors; Brain

Heart failure (HF) affects nearly 6 million Americans and prevalence rates are expected to rapidly increase given the growing population of individuals with its risk factors such as obesity, hypertension, and type 2 diabetes mellitus [1]. With nearly 600,000 new cases of HF diagnosed each year, it is projected there will be a 25% increase in the prevalence of HF by 2030 [1]. This pattern is unfortunate, as HF is associated with a number of poor outcomes, including recurrent hospital readmissions, elevated rates of mortality [1,2], poor quality of life, and reduced functional independence [3].

Growing evidence also links HF with poor neurocognitive outcomes, including elevated risk for Alzheimer's disease, vascular dementia, and abnormalities on neuroimaging (e.g., Alzheimer's disease (AD)) [4-6]. Subtle impairments in cognitive function are also found in up to 75% of HF patients [7] with frequent deficits observed on tasks of attention, executive function, memory, psychomotor speed, and language [7,8]. However, the cognitive domains

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affected in HF also appear to be heterogeneous and observed deficits likely vary as a function of brain regions damaged secondary to a range of demographic, clinical, and HF-specific factors. For example, a recent study found a sample of HF patients to exhibit three distinct cognitive profiles, including cognitively intact, impaired memory, and global cognitive impairments [9]. Prospective studies show HF patients exhibit progressive decline in global cognitive function, attention/executive function, and memory [10-12]. In contrast to these findings, there is also evidence for improvement and/or stability in cognitive function over time in HF [13]. These inconsistencies suggest that the exact pattern of cognitive decline and impairment in HF may be more variable than commonly believed and likely influenced by the presence of various medical conditions.

Cognitive impairment has an adverse outcome on clinical outcomes in HF, including elevated rates of hospital readmissions and mortality in this population [14]. A possible explanation for these findings may involve the adverse impact of cognitive dysfunction on treatment adherence. Up to 19% and 53% of HF patients have been shown to be non-adherent to critical treatment recommendations such as following medication and exercise regimens, respectively [15,16]. Indeed, HF patients with poorer cognitive function demonstrate lower self-care maintenance and management [17]. For instance, recent work in HF shows decreased attention/executive function is a significant predictor of mortality [18], reduced functional status, and non-adherence to medication regimens and maintaining doctor's appointments [19,20]. This is troubling, as treatment non-adherence been linked with increased recurrent hospital readmissions and mortality risk in HF [21].

Etiology of Cognitive Impairment in HF

The exact mechanisms for cognitive impairment in HF are not entirely clear and likely involve a combination of processes that negatively impact the structural and functional integrity of the brain. Reduced cerebral blood flow is believed to be the most prominent contributor to poor neurocognitive outcomes in this population [22,23]. However, growing evidence also suggests common medical and clinical comorbidities that accompany HF (e.g., hypertension, diabetes, sleep apnea, depression, physical inactivity) contribute to adverse brain changes and cognitive dysfunction in HF [24].

Brain Abnormalities

Cerebral Blood Flow in Heart Failure—Brief changes in cerebral blood flow are maintained in healthy individuals as a result of the body's autoregulatory mechanisms. These mechanisms become compromised in the presence of chronic hypoperfusion that results from HF and older age [25]. Cerebral hypoperfusion and resulting ischemia have been proposed to be the most significant contributor to brain changes and poor neurocognitive outcomes in patients with HF [23,25]. Supporting the contribution of such mechanisms is past work showing reduced cerebral blood flow is prevalent in HF (e.g., up to 31% of HF patients), correlated with the severity of HF, and linked with neurocognitive consequences and structural brain damage in HF and other cardiovascular disease populations [26-28]. Moreover, improvements in cerebral blood flow have been shown to lead to better outcomes, including cognitive function [26,29,30].

Consistent with this pattern, cerebral blood flow reductions in HF patients are associated with degree of cognitive impairment [27]. Furthermore, vast evidence links cardiac dysfunction—a significant contributor to reduced cerebral perfusion in HF [31]—with reduced cognitive test performance and abnormal neuroimaging [22,25]. HF patients have also been found to exhibit a pattern of cerebral blood flow deficits similar to those observed in patients with AD, including reduced cerebral blood flow of the pre-cuneus and posterior cingulate gyrus [32].

Neuroimaging in Heart Failure—Adverse structural and functional brain changes are known to negatively affect cognitive test performance in cardiac and cognitively impaired populations [33]. Indeed, extant evidence documents total and regional brain atrophy and white matter hyperintensities (WMH) in older adults with HF relative to healthy controls [6,34]. Demyelination of the brain and subsequent functional cerebral damage is also evident in HF patients. Kumar and colleagues (2011)[34] found reduced axonal integrity of limbic, motor, hedonic, and cardiovascular regulatory pathways in HF patients, including the basal forebrain, hypothalamic and limbic projections through the medial forebrain bundle and raphe magnus projections to the medulla and cerebellum. This study also found damage to many pathways directly implicated in cognitive function (e.g., limbic, basal-ganglia, thalamic, internal capsule, and the corpus callosum).

Fewer studies have simultaneously examined structural and functional brain imaging with cognitive function in HF patients. Serber and colleagues (2008) [35] found that HF patients demonstrating poorer performance on tasks of executive function also displayed corresponding brain tissue abnormalities of the frontal cortex. Consistent with this pattern, medial temporal lobe atrophy and deep white matter hyperintensities have been linked with reduced performance on neuropsychological tests assessing memory, executive functions, and global cognitive function [6,36].

Medical and Clinical Comorbidities

Hypertension—Hypertension is the most common medical comorbidity among HF patients and is likely an important contributor to cognitive impairment in this population. Nearly 75% of HF patients have hypertension prior to a HF diagnosis [1] and prospective studies have shown that hypertension is significantly associated with incident risk of Alzheimer's disease and cognitive decline independent of HF[37,38]. Hypertension is also independently associated with lower regional gray matter volume [39] and increased WMH [40]. Not surprisingly, HF patients with hypertension exhibit greater reductions on neuropsychological tasks of attention, executive function, and psychomotor function than HF patients without such history [41]. Hypertension may produce additive deficits in cognitive function through further disruptions of the cerebral vasculature [42].

Type-2 Diabetes Mellitus—As many as 31% of HF patients have comorbid type 2 diabetes mellitus (T2DM) [43]. Patients with T2DM are at increased risk for cognitive impairment independent of HF [44] and as many as 18% of community-residing diabetic older adults exhibit cognitive impairment and probable dementia [45]. Specific cognitive deficits in diabetic older adults are noted in attention, executive function, and processing

speed [46]. The effects of T2DM on cognitive function have recently been observed in HF patients. Specifically, Alosco et al. (2012) [47] found HF patients with a diagnostic history of T2DM demonstrated worse deficits in attention, executive function, and motor function relative to patients without a history of T2DM. T2DM may accelerate cognitive decline in HF patients through its adverse effects on the structural integrity of the brain, including WMH and total brain volume atrophy.

Obstructive Sleep Apnea—Obstructive sleep apnea (OSA) is also common in HF; up to 37% of HF patients have a concomitant diagnosis of OSA [48]. Persons with OSA are at increased risk for neurological changes, including dementia and mild cognitive impairment [49]. Patients with OSA also exhibit neuropsychological impairments in attention/vigilance, executive functioning, memory, constructional abilities, and psychomotor function [50]. Recent evidence suggests that OSA produces additive impairments in cognitive function among HF patients. Specifically, Knecht and colleagues (2012) showed that OSA in HF exacerbates cognitive deficits in attention [51].

Depression—An estimated 42% of HF patients have clinically significant levels of depression [52]. In addition to being associated with more frequent hospitalizations and cardiac events [53], depression is a significant risk factor for cognitive impairment in patients with HF [54]. Garcia and colleagues (2011) [54] showed that increased depressive symptomatology is associated with reduced cognitive function across multiple domains in HF, including attention, executive function, psychomotor sped, and language. These findings are consistent with evidence that shows structural injury of emotional regions of the brain [34].

Reduced Physical Activity—A recent accelerometer based study showed that HF patients on average exhibit 587 minutes of sedentary time and only .31 minutes of vigorous activity per day [55]. Previous work has also shown that nearly half of persons with HF do not engage in regular exercise [56], and limited physical activity is the most common self-care failure in this population [57]. Reduced physical activity is an important contributor to cognitive impairment in HF. For instance, lower daily step count in older adults with HF has been associated with reduced cognitive function [55]. Consistent with this finding, recent work also links reduced cardiovascular fitness with cognitive dysfunction in persons with HF [58] and such deficits have been observed to improve following exercise training programs [59].

Obesity as a Risk Factor for Cognitive Impairment in Heart Failure

Obesity is another likely contributor to cognitive impairment in HF. Obesity is associated with a 2-fold increased risk for HF [60] and more than 40% of persons with HF exhibit a body mass index (BMI) consistent with obesity [61]. Although obese HF persons exhibit additive deficits in psychosocial functioning (e.g., reduced quality of life and depressive symptomatology) [62], its effects on cognitive function in this population have yet to be fully investigated. The purpose of the subsequent discussion is to introduce obesity as a risk factor for cognitive impairment in HF by highlighting the existing literature on obesity and neurocognitive outcomes.

Obesity and Cognitive Decline

Mid-life obesity has been linked with a 3-fold increased risk for Alzheimer's disease [63] and 5X greater risk for vascular dementia [64]. A meta-analysis study also showed that higher BMI increased AD risk by as much as 80% [65]. The link between obesity and AD risk does not appear to be fully accounted for by increased risk of vascular medical comorbidities. For instance, past work demonstrates that obesity is associated with increased dementia risk even after accounting for hypertension, diabetes, cardiac disease, stroke, and hyperlipidemia [66].

Obese persons also frequently exhibit reduced performance on neuropsychological testing prior to the onset of dementia. Multiple indices of obesity (e.g., BMI, waist to hip ratio (WHR), waist circumference) have been independently linked with reduced performance on measures of global cognitive function, learning, memory, and language abilities [67]. Relative to normative data, up to 24% of bariatric surgical patients also exhibit impaired performance on tests of learning, 22.9% on memory recognition tasks, and 7.3% on tasks of executive function [68].

Deficits on tests of attention, executive dysfunction, and psychomotor slowing are most prominent in obese persons; these functions are mediated by the frontal lobe and its connections with subcortical structures [69,70]. Medical and demographic adjusted analyses have shown that relative to their non-obese peers, obese persons are nearly at a 4-fold increased risk for reduced performance on tasks of executive function and psychomotor speed [71].

Past work has sought to examine the independent effect of obesity on cognitive function by utilizing otherwise healthy samples. These samples are derived from large-scale studies that exclude participants with medical or psychiatric conditions that influence cognition, including history of traumatic brain injury, neurologic disorder, and medical conditions (e.g., hypertension, diabetes, cardiac disease, thyroid disease, sleep apnea) [72].Results from these studies have revealed that higher BMI is associated with reduced cognitive test performance in obese persons, including on measures of attention, psychomotor speed, memory, and executive function [72,73].

Obesity and Neuroimaging Findings

Extant evidence also supports the deleterious effects of obesity on the brain. At autopsy, obese patients exhibit higher levels of AD markers relative to controls, including tau and amyloid beta protein expression [74]. Increased BMI among AD and mild cognitively impaired individuals is also associated with decreased volume of the hippocampus, frontal, temporal, parietal, and occipital lobes [75]. In addition, relative to their normal weight peers, obese persons demonstrate greater total and regional brain atrophy [76] and increased WMH [77]. Among healthy samples, Gunstad and colleagues (2008) found that healthy obese adults demonstrated smaller whole brain volume and total gray matter volume than the normal and overweight comparison groups [78].

Obese individuals also exhibit deteriorating axonal integrity and white matter disease [77]. In fact, past work using proton magnetic resonance spectroscopy shows elevated BMI is

associated with myelin damage of the frontal lobe [79] and decreased white matter microstructural integrity, including insult to the midbrain and brainstem tracts [80]. Stanek et al. (2011) also revealed greater BMI was linked with reduced factional ansioptry in the splenium, genu, and fornix among a sample of healthy adults [81]. Future studies are needed to examine functional neuroimaging in obesity as it corresponds to cognitive testing.

Mechanisms for Obesity's Neurocognitive Impact in Heart Failure

There are two distinct mechanisms that likely underlie the association between obesity and neurocognitive impairment: 1) Elevated vascular risk factors (e.g., cerebral hypoperfusion, hypertension, T2DM, OSA, lifestyle risk factors); and 2) Unique pathophysiological effects associated with adiposity that damage the brain.

Obesity and Cerebral Hypoperfusion

There is reason to believe that obesity may exacerbate cerebral hypoperfusion in HF. Past work demonstrates obesity is independently associated with reduced cerebral blood flow [65]. Cerebral hypoperfusion in obese individuals has been found in regions of the brain that mediate attention, reasoning, and executive function abilities (e.g., frontal lobe function)—deficits commonly observed in obesity [82]. Such physiological disturbances may be a result of common vascular abnormalities associated with obesity, including cardiac damage, reduced small vessel density, inflammation, arterial stiffness, decreased endothelial functioning, and/or impaired vasodilatoin [83,84].

Obesity and Comorbid Conditions in HF

Obesity likely exacerbates cognitive impairment in HF through increased risk for comorbid medical and clinical conditions. Specifically, obesity is associated with a 40X elevated risk for T2DM, 5X risk for hypertension, 6X risk for OSA, and depressive symptomatology [85-88]. Indeed, past work shows that obesity interacts with these factors to produce additive impairments in cognitive function [89,90]. The effects of these comorbid conditions on cognitive function in HF patients have been previously outlined.

The sedentary lifestyle that often accompanies obesity also likely exacerbates cognitive impairment in HF. As previously discussed, reduced physical activity is a significant contributor to reduced cognitive function in HF and greater levels of daily inactivity are associated with poorer cognitive function in older adults with HF [55]. This association likely stems from reduced physical fitness. Indeed, physical fitness refers to acquired health related attributes stemming from the act of physical activity that include cardiorespiratory endurance, muscular endurance, body composition, and/or flexibility [91]. It is suggested that reduced physical fitness is particularly sensitive to poor neurocogntiive outcomes [92], which is evident in obese individuals. For example, relative to weight status (e.g., normal versus obese), reduced cardiovascular fitness has been shown to be the most important contributor to all-cause mortality risk [93,94]. This is noteworthy, as not all obese individuals exhibit metabolic abnormalities and/or poor cardiovascular fitness and thus may not be at risk for poor outcomes, including cognitive impairment [95]. Although metabolically healthy/physically fit obese individuals are likely not found in HF populations,

it may be that obese patients with HF are more sedentary than their normal weight counterparts and subsequently at higher risk for cognitive impairment due to lower levels of physical fitness. Indeed, suggested to be independent of physical activity, sedentary behaviors have been linked with greater deficits in memory and executive functioning [96]. Similarly, sedentary middle-aged older adults have also been shown to exhibit smaller total brain volume and gray matter volume relative to physically active middle-aged adults [97]. Future work is much needed to clarify the extent of sedentary lifestyle behaviors in obese HF patients compared to non-obese patients with HF and associated risk for poor neurocognitive outcomes.

Novel Risk Factors for Neurocognitive Outcomes in Obese HF Patients

The association between obesity and adverse neurocognitive outcomes in healthy samples raises the possibility that obesity introduces several unique pathophysiological mechanisms.

Genetic Factors

The fat mass and obesity associated gene (FTO) is universally associated with obesity [98]. Among healthy elderly, Ho and colleagues (2010) identified that carriers of the FTO risk allele demonstrate ~8% and 12% less brain volume in the frontal and occipital lobes, respectively, than non-carriers [99]. In addition, Benedict et al. (2011) found that risk allele carriers among overweight and obese elderly men demonstrated diminished verbal fluency compared to non-carriers, concluding that FTO modulates cognition depending upon an individual's body weight [100]. The impact of FTO on cognition may be even greater in the presence of APOE (ε)4 [101]. APOE (ε)4 influences lipid profiles and significantly increases cardiovascular disease risk by disrupting cholesterol transport and homeostasis [102]. Past work has shown APOE (ε)4 to interact with vascular factors (e.g., stroke, myocardial infarction, hypertension) to exacerbate cognitive decline and risk of subsequent Alzheimer's disease [103]. It is possible that the presence of FTO and APOE (ε)4 in obese HF persons may produce synergistic effects on cognitive function in addition to cardiovascular disease risk.

Biomarkers

Obesity is associated with altered levels of circulating biomarkers, including leptin, ghrelin, brain derived neurotrophic factor (BDNF), and amyloid beta. These adipokines have been correlated with body fat and play key roles in food intake and regulation of energy homeostasis [104-107]. In addition to their association with body weight, serum levels of these biomarkers have also been linked with neurocognitive outcomes and are suggested to have neurotrophic and/or neuroprotective roles [108,109]. For instance, leptin, ghrelin, BDNF, and amyloid beta have all been implicated in the pathogenesis of Alzheimer's disease [108-111]. Consistent with this pattern, abnormal adipokine levels have also been associated with reduced cognitive function across multiple domains, including global cognitive function, executive function, memory, language [112-114]. Future work is needed to examine the influence of adipokines on cognitive function in HF patients, particularly as it involves increased body weight.

Inflammation

One of the final proposed mechanisms obesity may increase risk for cognitive impairment in HF is through inflammatory processes. Inflammatory markers are elevated in HF and both interleukin-6 and C-reactive protein have recently been found to negatively correlate with global cognitive status in this population [115]. Similarly, increased inflamatory markers have been linked with accelerated cognitive decline among the elderly and cardiovascular disease populations [116]. Inflammation is also a hallmark of AD with evidence showing increased expression of inflammatory proteins in the brain of AD patients [117]. Overweight and obese adults also exhibit elevated levels of proinflammatory markers [118] and may exacerbate pre-existing inflammatory processes in HF patients.

Discussion

Obesity is a likely contributor to cognitive impairment in HF patients. Obesity is a common vascular risk factor and is found in more than 40% of HF patients. In addition to its association with increased risk for vascular factors that negatively impact cognitive function, obesity also likely introduces unique pathophysiological mechanisms to produce cognitive impairment in this population.

Recent work from our group recently examined the association between obesity and cognitive function in HF persons. Alosco and colleagues (2012) found that increased BMI was independently associated with reduced neuropsychological test performance on measures of attention/executive function and language [119]. We further showed that obesity interacted with cerebral perfusion to exacerbate cognitive impairment in HF. These findings begin to clarify the mechanisms linking obesity to adverse neurocognitive outcomes in HF, though generalizability is limited due to specific study methodology. Prospective studies utilizing PET imaging would help elucidate the contribution of BMI and cerebral perfusion to cognitive outcomes over time in older adults with HF.

If confirmed as a risk factor for cognitive impairment in HF, obesity is modifiable and obesity related cognitive deficits in this population may be reversible. Indeed, Gunstad and colleagues (2011) showed that 12-weeks after bariatric surgery, patients demonstrate cognitive improvement relative to pre-surgical baselines [68]. Consistent with this pattern, exercise interventions among obese persons have also been shown to benefit cognitive function, including improvements in global cognitive function, psychomotor speed, and executive function [120]. Prospective studies are needed to confirm obesity as an independent risk factor for cognitive impairment in HF and whether weight loss leads to improved neurocognitive outcomes in this population.

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