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Complications of Obesity

Cognitive dysfunction associated with metabolic syndrome

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Summary

Metabolic syndrome which includes visceral obesity, elevated triglycerides, elevated fasting blood sugar, high blood pressure and a decrease in high-density lipoprotein cholesterol levels comprises the most common chronic physical illnesses in modern society. Components of the metabolic syndrome play a role in the pathogenesis of a plethora of medical illnesses. Evidence has emerged highlighting the detrimental effects of metabolic syndrome and its constituent features on the cognitive aspects of neurological function. The precise mechanisms underlying this association are not known but a combination of neuroanatomical changes and neuroendocrine consequences of somatic dysregulation may be relevant. As the population ages and the prevalence of metabolic syndrome increases, it is important that this clinically relevant association be recognized.

Keywords: Cognition, obesity, metabolic syndrome.

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Introduction

Cognitive function refers to the acquisition, processing, integration, storage and retrieval of information. Cognitive functions are frequently divided into perception, attention, memory and executive function, with executive function including higher order planning and decision-making. Each of these general categories includes several subtypes of function: memory for example is commonly divided into working memory (holding information in mind for a short period while it is used), implicit or habit memory (memory for skills) and declarative memory (which itself is often further subdivided but includes memory for facts and events). These distinctions are not merely descriptive but reflect distinct neuroanatomical circuits that subsume different aspects of memory and cognition more generally.

Associations between neuroendocrine dysfunction and poor cognitive performance are commonly recognized. Hyperthyroidism and hypothyroidism, Cushing's disease, Addison's disease and other endocrinological disturbances routinely result in significant cognitive problems, often in the absence of other frank neurological symptoms such as motor or sensory symptoms. More recently it has been recognized that other, more prevalent forms of neuroendocrine disturbance such as that associated with type 2 diabetes, hypercholesterolemia and hypertension may also exert a negative effect on cognitive performance (1). Most striking perhaps, is the correlation between atherosclerosis and an increased risk of Alzheimer's disease (AD) and vascular dementia (2), but while dementia represents an extreme case of impaired cognitive function, there is emerging evidence for an association between subtle cognitive dysfunction and the endocrine disturbances associated with metabolic syndrome and its constituent features.

Below we review the evidence supporting an association between the various components of metabolic syndrome and cognition, highlighting the proposed mechanisms linking metabolic dysregulation with cognitive dysfunction. It is worth noting that studies differ in the degree of cognitive impairment examined. Some have focused on the

association between metabolic function and frank dementia, following standard clinical and research definitions of dementia. Others focus on mild cognitive impairment, which is generally accepted to mean measurable deficits in memory performance but intact performance in other cognitive domains and little impairment in daily function. Finally some studies refer to cognitive dysfunction when the group of interest has statistically significant deficits in performance compared with healthy controls. Although for most patients the associations between aspects of metabolic syndrome and cognitive changes will not be as striking as for illnesses such as thyroid disease or Cushings, for people living and working in a highly technological, information based society, even small declines in cognitive performance may have significant functional implications. Furthermore, on a population-based level, the epidemic-like increases in rates of obesity and metabolic syndrome among young and middle aged adults means that even relatively subtle consequences of these disorders may exert substantial impact on overall levels of societal health and function.

Obesity

Obesity has emerged as a common medical illness that confers risk for many other medical conditions (3,4) and it is increasingly recognized to confer risk for a decline in cognitive performance as well, an association that appears to be independent of other comorbid medical conditions. A prospective analysis of over 10 000 participants in a 27-year longitudinal population-based study concluded that obesity increased the risk of dementia even after adjustment for the prevalence of diabetes and cardiovascular disease (5). This study found that obese people (body mass index [BMI] >30) had a 74% increased risk of dementia while overweight people (BMI 25–30) had a 35% greater risk of dementia compared with normal weight individuals (5). These findings were replicated in a population-based study that determined abdominal obesity was associated with cognitive dysfunction as defined by scores obtained on a mini-mental state exam developed for the assessment of cognitive functioning in individuals over 65 years, even after adjustment for age (6) A population-based study of women aged 70–88 years meeting diagnostic criteria for dementia (7,8) also yielded similar results. This study followed women over an 18-year time period and found that women who developed dementia had higher BMIs at age 70, 75 and 79 years compared with non-demented women. The degree of cognitive deficit was age dependent with cognition declining with increasing age (9,10), but it is unknown whether this reflects cognitive changes inherent in the ageing process or whether age was a proxy for disease duration.

Adiposity has a direct effect on neuronal degradation (5). Studies using rodent models of obesity report that obese animals have impaired performance on spatial memory tasks (11) and poor long-term potentiation of neurones in the hippocampus (12). Obesity is also associated with subclinical inflammatory status, a condition linked to dementia (13) and cognitive decline (14–19).

Although the association between obesity and poor cognitive function is prominent in the elderly, middle-aged obese adults may have a greater degree of brain atrophy compared with age-matched, non-obese people (20). This finding suggests that non-elderly obese people may experience subtle cognitive dysfunction and may be at greater risk of progression to significant cognitive impairment (20).

Proposed mechanisms mediating the association between cognitive dysfunction and obesity

The pathways through which obesity negatively affects cognition are not well-described. Several studies report that change in weight is associated with alterations in cognitive performance (21–23). These findings have primarily emerged from studies with dieting subjects and the results are conflicting. Some report that subjects may have reduced reaction times (21,22), poorer performance in vigilance tests, or poorer immediate recall of words (22) with dieting. Other investigators found that dieters in fact have better word recall performance (21) or that dieting has nearly no impact on cognition (23). The discrepancies among reports may reflect differences in the amount of weight lost, the level of dietary restriction and weight at baseline. In overweight women, being on a prescribed diet has minimal effect on cognitive performance and may even enhance some aspects of memory (23). In weight loss studies in which normal-weight women lost further weight, working memory and tests of executive function were negatively affected (24).

Restriction of food or nutrition can have an impact on central nervous system function via reduced glucose levels in the brain (24); studies report positive effects on cognitive performance with glucose administration (25), and negative effects of long-term fasting due to eating disorders (26). However, there is no relation between lowered glucose levels as a result of missing a meal and cognitive performance, suggesting that cognitive changes are more complicated than simply as a result of transient, mild hypoglycemia (27). There is also evidence from rodent and human studies that adrenaline release and its effect on glucose is an important contributor to the process by which memory formation is regulated (28). With the release of adrenaline, a rise in circulating glucose levels occurs which in turn contributes to neuronal processes responsible for memory formation. The change in cognitive performance after administration of

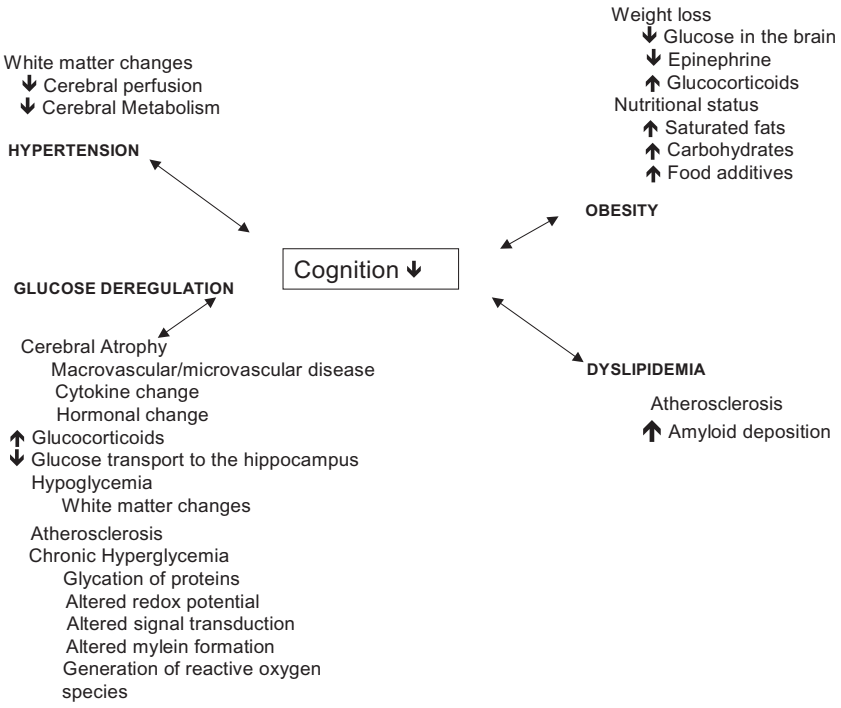

Figure 1 Mechanisms mediating the effects of metabolic syndrome on cognition.

glucose and other foods may depend on the level of sympathetic activation, glucocorticoid secretion and pancreatic β-cell function, rather than simple fuelling of neural activity. Functioning of these systems may be susceptible to dietary influences on neural membrane fluidity and vitamin-dependent cerebrovascular health (29).

Another link between obesity and cognition depends on the 'economics of obesity' (30). Environmental influences are a primary contributor to the obesity epidemic (31–33). Socioeconomic status (SES) may be an important mediating factor of the relations between glycemic control and cognitive function as SES is a strong correlate of obesity, abnormal glucose tolerance and cognition, with people from low SES being negatively impacted across all three modalities (34). Low SES is also associated with low consumption of fruits and vegetables and high consumption of fats (35). Nutritional status may have an impact on cognitive function, with weight gain acting as a surrogate marker for poor nutritional intake. The best evidence for links between nutrition and cognition are arguably in paediatric studies (36) with the effect of morbidity chronically poor nutrition on cognition in adults being less understood. Diets rich in carbohydrates or fats can affect cognitive function (29), as can eating patterns, additives and the pharmacological effects of certain foods, especially in children. In the Isle of Wight studies, the removal of foods with artificial colourings resulted in a decrease in hyperactivity (37) and further work is ongoing to assess classroom attention in response to diet (36). Both epidemiological data and animal studies indicate that ingestion of a diet rich in saturated fats may result in deficits in cognitive performance (38–40). (Fig. 1)

Glucose abnormalities and cognition

Cognitive dysfunction is a complication of diabetes (41). Prospective studies report that diabetes is associated with low cognitive test scores in middle-aged or older adults (42–44) and this risk extends to those with type 2 diabetes (45). Several studies link type two diabetes with risk for vascular dementia and AD through a variety of biological mechanisms (46–50) and there is some evidence that impaired glucose tolerance, a precursor to type 2 diabetes, may also be associated with cognitive deficits (51).

A prospective study of 7000 women with diabetes or impaired fasting glucose found that diabetic and pre-diabetic woman have impaired cognitive performance and a greater risk of developing cognitive impairment relative to normoglycemic subjects (1). The links between diabetes and cognition are supported by several cross-sectional studies. Among woman enrolled in the Nurses Health Study, those with diabetes scored lower on the Telephone Interview of Cognitive Status and on a composite measure of four cognitive tests, even after multivariate adjustment. In that study, longer duration of diabetes was associated with lower cognition scores (52). Similarly, both a Finnish study (53) and the Framingham study (54) reported an association between diabetes and impaired cognition. Conversely, prospective studies of diabetes have demonstrated that improvements in glucose tolerance were associated with improved cognitive function (25).

The association between glucose regulation and cognition has been consistently replicated and in some 25 studies, diabetes mellitus has been associated with adverse

cognitive changes involving psychomotor efficiency, attention, learning and memory, intelligence and executive function (10,55–58). Furthermore, among the non-diabetic normal middle age and elderly population, those with poor glucose regulation have poor memory performance and smaller head size-adjusted hippocampal volumes (59).

Mechanisms mediating the association between cognitive dysfunction and impaired glucose regulation

The cognitive problems associated with diabetes have traditionally been attributed to atherosclerosis (60), as similar pathological changes are the end result of both diseases. Chronic hyperglycemia induces biological toxicity via glycation of proteins, altered redox potential, altered signal transduction and generation of reactive oxygen species (61). The resulting oxidative stress contributes to vascular/endothelial dysfunction and this microvascular damage may be an important determinant of the observed cognitive deficits. The fact that young people with diabetes have cognitive deficits prior to developing comorbid medical complications suggests that diabetes itself may have a direct role in contributing to memory impairment (59,62). Purported mechanisms to explain this include both the effects of hypoglycemia on the developing brain (63), as well as the effects of chronic hyperglycemia on myelin formation (64). Deficits in learning and memory also remain in non-diabetic individuals with insulin resistance after accounting for the possible effects of atherosclerosis (65).

Elevated glucocorticoid levels are also likely to be a mediating factor in diabetes-related cognitive decline. Cortisol levels and peripheral glucose regulation are linked. In a longitudinal study, cortisol levels predicted cognitive impairment in older men and women (66). Physiological increases in cortisol acutely inhibit insulin release and pharmacological increases in cortisol cause insulin resistance (67). Cortisol reduces the amount of insulin transported across the blood–brain barrier (68). Not all cognitive functions are equally affected by cortisol and impaired glucose regulation. Glycemic control most strongly predicts function on cognitive tasks that are dependent on the hippocampus and surrounding structures (69), regions that are particularly important for declarative memory. In animal studies, glucocorticoid exposure inhibits glucose transport into hippocampal neurones and glia (70), perhaps because the hippocampus is one of the brain areas with the greatest co-localization of cortisol and insulin receptors (71). The brain expresses a full range of glucose transporters, including GLUT1, GLUT2, GLUT3 and GLUT4 (72–74). Recent evidence points to the presence and regulation of insulin and/or glucose by a novel glucose transporter, GLUTx1(GLUT8), a receptor that is found in high concentration in the hippocampus (75).

Insulin resistance may also potentate the harmful effects of cortisol elevations on the brain. For example, when diabetic rats are stressed with a consequent elevation in cortisol levels, they develop extensive hippocampal damage in one-third of the time it takes non-diabetic animals to develop stress mediated damage (76). This suggests that the hippocampus is more vulnerable to the deleterious effects of high glucocorticoid levels when glucose regulation is impaired. The hippocampus is very responsive to local tissue glucose levels, and this brain structure also appears to be involved in peripheral glucose regulation. Cognitive tasks activate basal forebrain cholinergic function and concurrently decrease extracellular levels of glucose in the hippocampus (77,78). This combination of events appears likely to increase glucose mobilization peripherally, as local stimulation of muscarinic cholinergic receptors in the dentate gyrus (79,80) increases peripheral glucose levels. When the hippocampus is damaged, as in AD, there is abnormal glucose regulation, observed in glucose tolerance tests as an abnormal cortisol response (79). After the administration of a bolus of cortisol there is a failure to decrease hippocampal glucose utilization and a failure to increase peripheral glucose levels (81). These findings suggest that neural circuits involving the hippocampus play some role in sensing glucose levels and regulating the peripheral metabolic response.

The hippocampus is affected in type 1 diabetes (82) and hippocampal neurones show accelerated remodelling in streptozotocin-induced diabetes (76) that can be reversed by insulin replacement (76). The metabolic alterations in diabetes may also include down-regulation of insulin-like growth factor-1 (IGF-1 83), which occurs in the early stages of the disease in rat models at least. IGF-1 deficiency leads to neuro-axonal dystrophy in rats (13) while direct delivery of IGF-1 in diabetic rats reversed atrophy of myelinated axons in the sural nerve (84). Global cerebral atrophy has been observed In Laron Syndrome, an illness associated with the inability to generate IGF-1 in humans (85). Cerebral atrophy has also been identified in diabetic patients. In 1965, Reske-Nielsen described the concept of 'diabetic encephalopathy' as a complication of long-term diabetes mellitus (86). This theory inclusively identified deviations from normoglycemia, macrovascular and microvascular disease, and hormonal and cytokine changes as possible mechanisms of diabetes-associated cerebral atrophy.

Hypoglycemic episodes are associated with cerebral atrophy or white matter lesions in type 1 diabetes (87). Repeated hypoglycemic episodes are associated with persistent cognitive impairment (88–90). Cognitive function deteriorates during hypoglycemia if the arterialized venous plasma glucose is reduced below a concentration of 2.7 mmol L^{-1} (91). Severe hypoglycemia may trigger the

release of excitatory amino acids such as glutamate and aspartate which trigger calcium influx, activation of proteases and structural damage. As hypoglycemia can also occur in type 2 diabetes these mechanisms may also be relevant for understanding cognitive performance in people with this illness as well (92). (Fig. 1)

Hypertension and cognition

Hypertension is an established risk factor for cerebrovascular illness. Prior to a major cerebrovascular event, however, hypertension exerts a subtle impact on the brain that is revealed by poor performance on tests of attention, learning and memory, executive functions, visuospatial skills, psychomotor abilities and perceptual skills. Hypertension is also predictive of cognitive decline (93–95) although the interval between the respective manifestations of hypertension and cognitive deterioration may vary from a few years to several decades (96). Anti-hypertensive treatment has a positive effect on cognitive function and quality of life (49,97) regardless of duration of illness.

Proposed mechanisms mediating the association between cognitive dysfunction and hypertension

Several longitudinal studies show an association between middle-age elevations in blood pressure and impaired cognition in later life (93,98–101). The mechanisms underlying these associations are unknown, but one association may be between long-standing hypertension and white matter lesions, which are frequently found on cerebral MRI scans of elderly people, particularly those with hypertension (102). The presence of cerebral white matter lesions is an important prognostic factor for the development of stroke, and also for cognitive impairment and dementia. Correlations between cerebral white matter lesions and elevated blood pressure provide indirect evidence that structural and functional changes in the brain over time may lead to lowered cognitive functioning when blood pressure control is poor or lacking. Subjects with large white matter hyperintensities exhibit disturbed cerebral perfusion, reduced cerebral metabolism (103–105), abnormalities of cerebral white matter (106) and cerebral atrophy (107). All of these have been implicated in the pathogenesis of cognitive deficits (108). Some authors have even suggested that the presence of white matter lesions in hypertensive patients should be considered an early marker of brain damage (109). (Fig. 1)

Dyslipidemia and cognition

Lipid abnormalities are associated with an increased risk for CVD and for cognitive impairment. Raised plasma concentrations of cholesterol have been implicated as a risk factor for AD (110–114), and low serum concentrations of high-density lipoprotein (HDL) cholesterol are associated with cognitive impairment and dementia (115). Elevated total and low density lipoprotein (LDL) cholesterol have been reported in very old patients with AD (116). These findings are supported by a meta-analysis which concluded that patients with probable or possible early stage AD had elevated total cholesterol values compared with a non-demented population (113).

Subsequent to this meta-analysis, high LDL and total cholesterol levels were statistically linked to lower scores on the most common tests assessing cognitive impairment in a cohort of postmenopausal women. Moreover, a reduction in the LDL cholesterol level during the 4-year period of this study was associated with lower odds of cognitive impairment (117). Although in this study the improved cognitive outcome following statin use further links cognitive deficits to lipid abnormalities, the results of other studies examining the association between statin use and dementia are inconclusive. Some studies conclude that statin use lowers the risk for dementia (118) while others suggest that this association is artifactual (119).

Cross-sectional studies of cholesterol lowering medications report a diminished risk for dementia with medication use, but this relation may not be robust (120). A pilot study examined 63 patients who already had a diagnosis of mild to moderate AD and were treated with either placebo or atorvastatin 80 mg day^{-1}. Atorvastatin reduced cholesterol levels as expected, and there was some beneficial reduction in the rate of cognitive and behavioural deterioration, although not all measures achieved statistical significance, again raising the issue of the clinical significance of this effect (121).

Mechanisms mediating the association between cognitive dysfunction and dyslipidemia

Autopsy studies have reported a correlation between elevated levels of cholesterol and amyloid deposition in the brain. A recent study examining autopsy cases of patients over 40 years of age found an association between cholesterolemia and the presence of amyloid deposition (subjects with or without amyloid deposition) as well as cholesterolemia and amyloid load (122). A study of the circle of Willis in a voluntary brain donation program examined 22 control cases and 18 AD cases, linking circle-of-Willis atherosclerotic lesions with AD lesions and dementia (123). Women with AD had a higher degree of pathologic severity and higher total cholesterol, LDL cholesterol and triglycerides than controls ($P < 0.01$). Among samples from patients with AD, there were positive correlations between brain Aβ n-42 levels and total serum cholesterol, LDL

cholesterol and apolipoprotein B-100 and a negative correlation with HDL cholesterol levels (124).

The mechanism underlying these post-mortem observations has been pursued in plaque-forming transgenic mouse models, where it has been reported that fat feeding increases brain plaque load and that hypocholesterolemic agents such as statins lower plaque burden (125,126). Sparks *et al.* determined that Watanabe rabbits on a 2% cholesterol diet developed increased levels of beta amyloid (Aβ) immunoreactivity in vesicles inside the neurones of their brains (127). In cultured neurones, simvastatin, atorvastatin and cyclodextrin, a compound used in the laboratory to deplete cellular cholesterol, lowered Aβ generation while activating the alternate, non-amyloidogenic α-secretase pathway for APP metabolism (128,129). The clinical significance of these preclinical studies is not known, but they do support the clinical findings suggesting that there may be an association between cholesterol levels and risk for cognitive deterioration. (Fig. 1)

Conclusion

People with physical illnesses frequently report problems in multiple cognitive domains. While the mechanisms contributing to cognitive dysfunction in this population remain to be elucidated, the likely combination of neuroanatomical changes and biochemical alterations secondary to dysregulation of various metabolic pathways create a clinically relevant problem. Many patients with one or a combination of obesity, diabetes, hypertension and dyslipidemia require optimal cognitive function to perform at high levels in their work places. While most patients with these illnesses would not meet criteria for dementia or even notable impairment on standard neuropsychological testing, subtle but persistent cognitive dysfunction may contribute to the morbidity experienced by those with metabolic syndrome or its constituent features.

Clinicians must be vigilant to this association and may need to consider further neuropsychological assessment in patients complaining of impaired cognitive performance and work-related disability. It would be easy to disregard such complaints but given the mounting evidence supporting a link between cognition and metabolic syndrome, these issues need to be addressed. It is also important to screen for and treat the component illnesses that confer a diagnosis of metabolic syndrome to prevent the detrimental effects these illnesses can have on cognition. The use of statins to control hyperlipidemia appears to improve cognition, as does the use of anti-hypertensive medication. The early diagnosis of diabetes to prevent the effects of chronic hyperglycemia and consistent regulation of glucose levels that prevent hypoglycemic episodes can also positively impact cognition. Investigators need to consider the inclusion of cognitive measures when examining treatment strategies for metabolic syndrome and related conditions to determine whether treatment of these illnesses has a positive impact on cognitive performance. A better understanding of the mechanisms through which changes in metabolic parameters exert an effect on cognitive performance will improve our understanding of the bi-directional relations between neuronal and somatic systems.

Conflict of Interest Statement

No conflict of interest was declared.

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