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Diabetes, Obesity and the Brain: New Developments in Biobehavioral Medicine

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Abstract

Diabetes and obesity, two major public health concerns, are associated with increased risk for problems in multiple organ systems, including the central nervous system. The adverse effects of diabetes and obesity on cognitive functioning are increasingly well recognized. This special issue of *Psychosomatic Medicine* features the latest research linking diabetes, obesity and brain structure, function and metabolism and follows a special meeting on this topic organized by the American Psychosomatic Society in October 2013. Evidence for the increased prevalence of diabetes and obesity is reviewed as it relates to cognitive decline. These papers indicate that the age of onset of Type 1 diabetes may be relevant to future cognitive function and that disease duration of Type 2 diabetes as well as sociocultural factors are related to cognitive decline during the aging process. The hypothalamus and other neural circuits, notably the dopaminergic system that underlies feeding and reward-related aspects of food intake, are among the key factors involved in obesity. Research on the associations between obesity and cognitive function is described using the positive effects of weight reduction following bariatric surgery or behavioral methods. This issue concludes with a conceptual framework for linking obesity and diabetes with accelerated cognitive decline as related to the aging process. The collection of papers highlights the importance of using a lifespan perspective to understand the influence of both Type 1 and Type 2 diabetes on brain metabolism, function and structure. Moreover, these studies show that distressing environmental circumstances can adversely influence neurocognitive processes in obesity and diabetes.

Diabetes and obesity are major public health burdens that increase risk for numerous adverse health outcomes (1). Obesity rates have increased dramatically since 1980 with prevalence rates in some populations exceeding 34% (2). Diabetes rates also have increased substantially, coincident with the obesity epidemic. Currently, 9.3% of the total U.S. population, equivalent to approximately 29.1 million Americans, has diabetes, the vast majority (> 95%) of which is type 2 diabetes (3). Prevalence increases markedly with age; nearly 26% of adults over the age of 65 have diabetes. Recent estimates suggest that diagnosed cases of diabetes cost the economy \$245 billion annually (4) and it can be reasonably assumed that these costs will only increase given the increase in the proportion of the population who are over 65 (5). In addition to the economic and public health burdens associated with obesity and diabetes, a growing literature documents the adverse impact that both diabetes and obesity have on the brain, both in terms of structure and function. Diabetes is associated with an increased risk of cognitive impairment (6) both during childhood and

adolescent development and later in life when age-related degenerative processes in the brain emerge (7). These data have led to the conceptualization of diabetes as a form of accelerated aging (8). Additionally, diabetes increases the risk for both Alzheimer's disease and vascular dementia (9), diseases that impose substantial burden on patients, caregivers, and society.

Given the increasing burden of diabetes and obesity, and their multifactorial effects on cognition and health, the *American Psychosomatic Society* hosted a symposium on the topic of "Diabetes, Obesity and the Brain" (on October 11, 2013). This special issue of *Psychosomatic Medicine* focuses on the themes related to the meeting and presents novel research and state-of-the-art reviews of advances in our understanding of the impact of diabetes and obesity on the brain, as well as conceptual frameworks to guide future investigations.

The goal of diabetes treatment is maintaining blood sugar levels around a relatively constant and "healthy" range. However, the hyper- and hypo-glycemia associated with the disease have deleterious effects on numerous organ systems. In the opening paper of this special issue (10), Dr. Elizabeth Seaquist provides a selective review of investigations on the pathophysiology of glycemia extremes, their effects on cognition, and neuroimaging-based research on how cerebral metabolism, structure and function mediate these relationships.

Type 1 diabetes results from destruction of the pancreatic beta cells and typically has an onset during childhood or adolescence. As a result of advances in treatment regimens, individuals with type 1 diabetes are now living significantly longer (11), but how type 1 diabetes interacts with the aging brain is unknown. To investigate the relationships between age at diagnosis and brain connectivity, Ryan et al. (12) used resting state functional MRI. They found that later age of disease diagnosis was associated with lower functional brain connectivity in several intrinsic connectivity networks. However, this relationship was moderated by age of the participant: the age of diagnosis effects were strongest for oldest participants, but less so for younger participants. Although the differences in connectivity were not related to cognition, these findings highlight the need to expand our understanding of the effects of aging on brain function and cognitive function in diabetic populations.

Type 2 diabetes has been associated with accelerated cognitive decline. One domain of cognitive function that consistently is decreased in persons with Type 2 diabetes is executive functioning. Vincent and Hall provide a meta-analysis of studies investigating executive functioning impairments and find that type 2 diabetes is associated with a mild to moderate decrement in executive functioning (13). Notably, this relationship was moderated by disease duration: the decrements were stronger in individuals with *shorter* disease duration. The authors hypothesize that this relationship may result from better treatments for glycemic control that extend to cognitive benefits in those with longer disease duration. Given the need for intact executive functioning in treatment adherence (14), further investigations of mediators and moderators that could attenuate this effect are warranted.

There are marked racial and ethnic differences in the incidence rates of type 2 diabetes, and the increased risk for type 2 diabetes is amplified by differences in (low) socioeconomic

status (15). This issue features two articles on racial/ethnic groups that are at increased risk of type 2 diabetes. Dore et al. investigate how diabetes, race and socioeconomic status converge to influence cognitive function in a sample of African-American participants (16). Using a large epidemiological cohort, they find that African Americans who have diabetes *and* are living below 125% of the Federal poverty limit had diminished performance on measures of memory and attention relative to African-American participants with diabetes living above the poverty limit. Although the mechanisms for these associations are unclear, the authors highlight previous findings that individuals below the poverty limit typically have less access to medical care and increased distrust of the medical system. In addition, access and affordability of healthy foods could play a role in the observed findings. These findings highlight the complex social factors that affect the relationships between diabetes and cognition. Luchsinger et al. investigated the relationships between diabetes-related measures and cognition in a cohort of middle-aged (aged 55-64 years) Hispanic participants (17). Many studies that document associations between diabetes and impaired cognitive performance focus on elderly adults, but in this middle aged cohort the authors identified associations between diabetes and impaired memory and executive abilities. Notably, the decrements in executive functioning extend into individuals with pre-diabetes suggesting that the impact of higher glycemia may already have effects on cognitive processes early in the aging process. This cross-sectional study highlights the importance of integrating a sociocultural and lifespan approach to gain a more complete understanding of the relationships between diabetes and cognition.

Given the role of obesity in the natural history of type 2 diabetes, a significant amount of research is focused on understanding the complex interplay of factors that regulate feeding behavior. The hypothalamus has been the focus of the majority of research on the neural circuits underlying feeding (18), but other aspects of the brain reward circuitry – notably dopaminergic systems that influence the rewarding aspects of food – also become dysregulated in the obese state and in response to poor diet. Dr. Dianne Lattemann provides a review of these systems, and findings from a multitude of animal and human studies (19). This research highlights the intricacies of hormonal regulation of food intake, and integrates important information relating how environmental stressors can influence these circuits leading to increased intake of “comfort foods.”

In humans, neuroimaging has provided insights into the associations between obesity and brain structure and function. Kaur et al. report an association between visceral fat and cortical thickness in the posterior cingulate cortex (20). Contrary to their hypothesis, individuals with more visceral fat exhibited more cortical thickness in this region. Notably, the posterior cingulate cortex is the “hub” of the default mode network – a network of brain regions that co-activate in the absence of a task. Dysregulation of the default mode network is common in dementia and cognitive impairment, and the authors suggest that this thickening of the posterior cingulate may be an early marker for potential cognitive decline.

With the increase in obesity rates, medical comorbidities and associated costs, finding effective, lasting behavioral and medical interventions is of critical importance. Bariatric surgery has become increasingly common, with more than 340,000 surgeries performed worldwide in 2011 (21). Weight loss is not only associated with improvements in metabolic

status, but also tends to improve cognitive performance. In this issue, Haley et al. provide an overview of the state of research on the interventions for obesity and their effects on cognition (22). The authors highlight difficulties associated with different types of interventions, including adherence and efficacy.

The mechanisms underlying cognitive improvements that result from bariatric surgery are not yet understood. Obesity is associated with multiple comorbidities including sleep disturbances, hypertension, and increased levels of circulating inflammatory factors. Hawkins et al. test the hypothesis that the decrease in inflammatory markers that results from bariatric surgery may account for the improvement in cognitive outcomes that follow surgical weight loss (23). Using a prospective design, they find that performance in cognitive domains improved one-year post surgery, and inflammation decreased, as measured by high-sensitivity C-reactive protein. However, there were no statistically significant associations between improvements in cognition and high-sensitivity C-reactive protein. As the authors note, future studies will be needed to investigate other inflammatory markers as possible mediators, and a longer longitudinal timeline will be informative for determining if these gains in inflammatory markers confer reduced risk for other neurological problems such as Alzheimer's disease.

As is apparent in this special issue, the effects of diabetes and obesity on neural structure and function are multifactorial and complex. A commentary by Drs. Bischof and Park presents a conceptual framework linking obesity and diabetes with accelerated cognitive decline as related to the aging process (24). The Scaffolding Theory of Aging and Cognition model posits that the ability to maintain cognitive function during aging is dependent on the brain being able to adapt to degradation by utilizing compensatory “scaffolds.” However, brains that have undergone multiple insults – such as hyperglycemia, obesity and hypertension-related metabolic challenges – are burdened and less able to compensate. Notably, the model provides theoretically-based testable hypotheses for understanding the longitudinal changes that will be occurring in aging populations.

Clinical Perspectives and Future Directions

Obesity and diabetes are vexing clinical conditions that contribute to worse physical functioning, decreased quality of life, accelerated biological aging, and excess morbidity and mortality as well as higher health care costs. As highlighted by the research presented in this special issue, obesity and diabetes also clearly relate to altered brain metabolism, structure and function, which may be exacerbated during critical developmental periods or in persons living in disadvantaged or vulnerable environments. From a clinical perspective, the acute and chronic impacts of obesity and diabetes, while sobering, may present important opportunities for developing new interventions and enhancing patient education and disease management. For example, the rapid expansion of mobile technologies and innovations opens up possibilities for equipping individuals to manage these chronic conditions in more effective ways. Additionally, increased knowledge about the potential neurocognitive consequences of obesity and diabetes may provide additional impetus for behavior change, more careful monitoring of symptoms by patients and health care providers and early interventions to mitigate these effects.

The papers published in this issue highlight critical challenges for the adverse consequences of diabetes and obesity on brain structure and function, as well as some of the difficulties in finding effective and lasting interventions for prevention and treatment. Psychological factors, particularly stress and depression, are known to adversely affect diabetes (25, 26, 27) and may additionally contribute to the neurocognitive problems associated with obesity and diabetes. The socioeconomic and racial/ethnic disparities of these diseases, and the multiple biobehavioral pathways that become disrupted emphasize the need for a multidisciplinary approach to the understanding and prevention of obesity- and diabetes-related neurocognitive decline.

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