Diabetes-Related Cognitive Decline, a Global Health Issue, and New Treatments Approaches

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ABSTRACT
The epidemic of type 2 diabetes (T2DM) is spreading around the globe and challenging the unprecedented success of health sciences in increasing longevity. T2DM has been linked to accelerated brain aging, functional decline in older adults and dementia. Brain insulin resistance and glycemic variability are potential mechanisms underlying T2DM-related brain damage and cognitive decline. Intranasal insulin therapy has emerged as a potential new treatment for T2DM-related cognitive impairment. Wearable technologies now allow better monitoring of behaviors and glycemic levels over several days and deliver real time feedback that can be used to improve self-management and lead to new prevention strategies and therapies for T2DM complications.

KEYWORDS
Glycemic Variability, Intranasal Insulin, Type 2 Diabetes, Wearable Technology

INTRODUCTION
Healthcare sciences have achieved an unprecedented success in continuing increase in longevity, decrease of birth death rates and diminishing or eliminating the impact of many infectious diseases. Large health inequalities between countries around the globe shape differences in lifespan from < 50 to > 80 years of age. At the same time, non-communicable diseases, and in particular diabetes, hypertension and cardiovascular diseases have become the most common causes of death. Over the last twenty years, the obesity epidemic has been sweeping across the globe, and many countries face a dilemma of fighting both hunger and obesity at the same time. Type 2 diabetes mellitus (T2DM) is a complex metabolic disease that affects multiple organ systems and interactions among them (Figure 1). T2DM accelerates brain aging (Mogi & Horiuchi, 2011; Xu, Qiu, Wahlin, Winblad, & Fratiglioni, 2004), alters neurovascular coupling (Cerosimo & DeFronzo, 2006; Chung et al., 2015; Tielhius et al., 2008), and increases the risk for dementia and Alzheimer’s disease (de Bresser et al., 2010; van den Berg et al., 2010). Long-term impact of T2DM on cerebral vasculature further contributes to high prevalence of cognitive impairment, depression, and disability in older adults (Saczyński et al., 2008). Memory loss further deteriorates self-care and glycemic control and accelerates disease progression, worsening a vicious cycle of functional decline. Most recent research emphasized the role

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of brain insulin in neurotrophic signaling, neuromodulation, nutrient homeostasis and metabolism. A new concept of brain insulin resistance has emerged, as potential pathways for altered transport and signaling within the brain, as well as between the brain and the periphery, as a potential mechanism underlying DM-related cognitive decline.

Currently, there is no cure for DM-related cognitive impairment. Therefore, there is an urgent need to develop new therapies to target insulin delivery to the brain to treat cognitive impairment in older diabetic adults. In this paper we review the pathophysiology of insulin action within the brain, as well as evidence for intranasal insulin therapy for treatment of cognitive impairment. This need for new therapies is also important as cognitive impairment poses a significant barrier for self-care, further increasing the risk for diabetic complications, disability, and dementia in this age group (Xu et al., 2004). First, we discuss results of the recent trials using intranasal insulin delivery that have shown promise in delivering insulin directly to the brain and potentially enhancing its pleiotrophic effects on neuromodulation, functional connectivity, food intake and ultimately functional outcomes (Benedict, Hallschmid, Schultes et al., 2007; Craft et al., 2012; Novak et al., 2014; Reger et al., 2008; Zhang et al., 2014).

Second, we discuss and further emphasize contributions of environmental factors and social activities to the spread of obesity and T2DM, and the role of social networking and social contagion theory in T2DM epidemic (Christakis & Fowler, 2007).

Complexity of T2DM treatment lies in continuous effects on multiple systems and various time points. In T2DM, glucose levels fluctuate over various timescales, from minutes to days, exposing the organs (including the brain) to adverse effects of prolonged hyperglycemia (elevated blood sugar levels) and hypoglycemia (low blood sugar levels) during the day and night (Figure 2A). In contrast,
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