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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 (Cersosimo & DeFronzo, 2006; Chung et al., 2015; Tiehuis 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 (Saczynski 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 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, in a healthy person, blood sugar levels remain tightly regulated during daily activities and during sleep (Figure 2B). As a result of these glycemic excursions, even a strict glycemic control did not improve cognitive function in participants of the large clinical trials (Cukierman-Yaffe et al., 2009).

Therefore, we propose to enhance the T2DM care with new wearable self-monitoring systems that would provide a real time closed loop feedback to adjust treatment in a real time, dependent on tissue glycemia, physical activity and metabolism and to diminish glycemic and metabolic excursions and also propose a wider use of social media to promote healthy behaviors and lifestyle.

The array of new methodologies that has recently emerged has shown promise using new treatment strategies to tackle the dilemma of T2DM epidemic by targeting the brain and

central homeostasis regulation using intranasal insulin administration (Cukierman-Yaffe et al., 2009; de la Monte, 2012; Freiherr et al., 2013; Shemesh, Rudich, Harman-Boehm et al., 2012) using wearable technologies to improve self-monitoring (Barnard & Shea, 2004), and social media and web-based technologies to address socio-economic aspects of T2DM (Zhou et al., 2014) and enforce spread of healthy behaviors (Unick et al., 2011). However, these promising approaches still need further development and long-term validation the population level.

INSULIN A KEY MODULATOR IN THE BRAIN

Insulin has emerged as a key neurotrophic factor in the central nervous system and as a promising therapeutic for treatment of amnesic cognitive impairment and Alzheimer's disease (AD) (Figure 3). Insulin's role in the brain is different from its actions in the periphery (Lioutas et al., 2015).

Central insulin plays a role as an important neuromodulator in key processes such as cognition (Freiherr et al., 2013; Shemesh et al., 2012), energy homeostasis, food intake, sympathetic activity, neuron-astrocyte signaling, synapse formation, and neuronal survival (Plum, Belgardt, & Brüning, 2006). Furthermore, insulin has been shown to reinforce signaling in the brain-reward dopamine-mediated limbic system and modulate behavioral responses to natural food and other reward stimuli (de la Monte, 2012; Freiherr et al., 2013; Shemesh et al., 2012).

Insulin receptors (IRs) are expressed in numerous brain regions, namely in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, and hippocampus (Plum et al., 2006). Even wider IR distribution overlaps with the expression of downstream proteins and isoforms in insulin-related pathways (Plum et al., 2006). Insulin also contributes to cortical blood flow regulation, as evidenced by the presence of IRs within the neurovascular unit, e.g., in neurons, astrocytes, and capillaries and the walls of small vessels (Cersosimo & DeFronzo, 2006). We hypothesized that cerebral insulin may directly modulate neuron-astrocyte signaling through neurovascular coupling and autonomic control of vascular tone and thus enable better regulation of local and regional perfusion and neuronal activity in response to various stimuli. Intranasal insulin (INI) enters the brain, where it rapidly propagates through perivascular channels and binds to the receptors in the limbic system and memory networks including the hippocampus, hypothalamus, and insular cortex (Schilling et al., 2014). INI increases blood flow and energy metabolism and improves functional connectivity in these regions. More efficient neuronal signaling within memory networks improves visuospatial memory, learning, and other cognitive functions associated with these areas. It may also improve mood, regulate feeding behavior, and increase amyloid-beta clearance (Craft et al., 2012; Reger et al., 2008) (Figure 3). Ten minutes after INI administration (dose 40 IU), insulin began to rise and peaked at 30 to 45 minutes as compared to placebo (insulin 1091 ± 219.8 vs. placebo 603.2 ± 34.6 AUC (pmol/lxmin), $p = 0.02$), with no change in serum levels (insulin 3410 ± 276.8 vs. placebo 3410 ± 106.1 AUC (pmol/lxmin), $p = 0.22$). After that, insulin in the CSF began to decline, but remained mildly elevated even 80 minutes after INI (Born et al., 2002). INI administration is safe, without triggering hypoglycemia, but INI does

not effectively control hyperglycemia because it results only in about 1–2% bioavailability in the serum as compared to the intravenous route.

INTRANASAL INSULIN IMPROVES COGNITION IN CLINICAL STUDIES

The insulin resistance syndrome, characterized by chronic peripheral insulin elevations, reduced insulin activity, and reduced brain insulin levels, is associated with age-related memory impairment and AD (Craft, 2005a, 2005b). These mild forms of insulin resistance may precede AD pathology for years (Freiherr et al., 2013b; Messier & Teutenberg, 2005). The risk of T2DM for dementia and AD in late life has been increasingly recognized (Xu et al., 2004) and impaired insulin signaling in the hippocampus and hypothalamus, as seen in both conditions, may provide a common link between DM and AD. The evidence that INI could be a promising treatment for improving cognitive function is growing (Freiherr et al., 2013; Reger et al., 2008). Clinical studies suggest that augmenting cerebral insulin improved performance in specific cognitive domains and memory in healthy young people, patients with mild cognitive impairment and even AD patients (Reger et al., 2008) with both acute and chronic administration. In healthy men, INI also improved mood and regulated food intake (Benedict et al., 2007). In healthy people, INI administration of rapid-acting insulin (40 IU q.i.d.) for 8 weeks improved long-term declarative memory more than regular insulin, and both insulins were better than placebo. No systemic side effects were observed, and serum glucose and insulin levels did not change (Benedict et al., 2007). Patients with amnesic mild cognitive impairment (MCI) and mild-moderate AD were treated with 40 IU (Novolin® NovoNordisk, Bagsvaerd Denmark) for 3 weeks. The INI-treated group retained more verbal information and showed greater improvement of attention and functional status than the placebo-treated group. The INI-treated group also had increased short form of β -amyloid peptide 40, without effects on the longer isoforms (Reger et al., 2008). Acute INI administration improved verbal memory in memory-impaired ApoE4-adults, with best performance at 20 IU; but no improvement was seen at 60 IU. In contrast, memory-impaired ApoE4+ adults showed a decline in verbal memory (Reger et al., 2008). The first clinical trial in 104 patients with amnesic MCI or mild-moderate AD over a 4-month period has shown that INI 20 IU (10 IU b.i.d.) (Novolin®) improved delayed memory, and both 20 IU and 40 IU (20 IU b.i.d.) doses preserved caregiver-rated functional ability and general cognitive function. Cognitive performance was better with the 20 IU (10 IU b.i.d.) dose in this population (Craft et al., 2012). These findings are clinically relevant because of the high prevalence of dementia in DM patients, as well as the high prevalence of insulin resistance syndrome in AD patients (de la Monte, 2012; Freiherr et al., 2013). Functional MRI studies that showed increased activity in the brain–reward dopamine–mediated limbic system further support these findings (Zhang et al., 2015). These data suggest that intranasal administration of insulin is a safe and feasible approach to improve central insulin levels. In addition, INI could be a promising method for the treatment of disorders with an etiology that may involve disturbances in brain insulin signaling, such as AD, obesity, and T2DM.

INI Effects on Memory in Type 2 Diabetics

Only a few studies have evaluated the effect of INI in the memory and cognition of patients with type 2 DM. Our proof-of-concept (Novak et al., 2014; H. Zhang et al., 2015),

randomized, double-blind, placebo-controlled intervention evaluated the effects of a single 40-IU dose of insulin (Novolin® NovoNordisk, Bagsvaerd Denmark) on vasoreactivity and cognition in 15 type 2 DM patients (60.1±9.9 years old, HbA1c 7.4 ±1.4%, DM duration 11.3±4.7years, 7 F), and 14 age- and sex-matched healthy controls (62.0±7.9 years old, 10 F). A ViaNase device (Kurve Technology, Inc., Seattle, WA) was used to administer INI or sterile saline in a random order with cross-over assignment on Day 2 or Day 3. Perfusion MRI using 3-D CASL at 3 Tesla and cognitive test were done < 2 hr after INI administration.

INI improved *Brief Visuospatial Learning and Memory Test – Revised (BVM-T-R)* performance in both groups. Controls on INI performed better than diabetics on either INI or placebo on immediate recall Trials 2–3 (T2, T3) [(least squares model adjusted for age $R^2_{adj} = 0.1$, $p = 0.03$), T3 ($R^2_{adj} = 0.14$, $p = 0.03$), and Total Recall. These effects remained significant after adjusting for education (T2: $R^2_{adj} = 0.1$, $p = 0.02$; T3: $R^2_{adj} = 0.1$, $p = 0.03$). INI also improved performance on T2 ($p = 0.04$) and Total Recall (paired t-test, $p = 0.05$). In the *Verbal Fluency Task (timed word generation using letters F, A, S)*, INI improved verbal fluency. Controls on INI performed better than diabetics on the FAS ($R^2_{adj} = 0.26$, $p = 0.0045$), switching ($R^2_{adj} = 0.2$, $p = 0.006$), and composite verbal fluency ($R^2_{adj} = 0.12$, $p = 0.02$).

The mechanisms by which INI improves memory and brain function in T2DM, have not been completely elucidated, and detailed mechanisms and pathways by which T2DM increases the risk for AD and other cognitive abnormalities require further studies (Freiherr et al., 2013).

Cognitive Performance Correlates with Regional Vasodilation

Regionally, perfusion changes on INI were observed in the middle cerebral artery (MCA) territory and insular cortex, integrative areas for learning, memory, and language. The T2DM group had lower baseline perfusion than controls ($p = 0.039$). In the T2DM group, INI increased perfusion in the right insular cortex compared to placebo ($p = 0.0001$) and to the control group ($p = 0.0003$). BVM-T and verbal fluency performances correlated to perfusion and vasodilatation within the MCA territory and the insular cortex, an area that regulates attention-related task performance (Novak et al., 2014b) BVM-T T3 and BVM-T Delayed Recall (MCA: $R^2_{adj} = 0.28$, $p = 0.04$; insula: $R^2_{adj} = 0.22$, $p = 0.04$). In diabetics, better visuospatial memory after INI correlated with vasodilatation in the MCA territory for BVM-T immediate recall (T2: $R^2_{adj} = 0.43$, $p = 0.01$; T3: $R^2_{adj} = 0.39$, $p = 0.035$), and Total Recall ($R^2_{adj} = 0.44$, $p = 0.0098$). These relationships were not observed after placebo administration. BVM-T T2, T3 and Total Recall also correlated with vasodilatation in the anterior cerebral artery (ACA) territory ($p = 0.05$ – 0.08). In controls on INI, FAS score ($R^2_{adj} = 0.39$, $p = 0.04$) and the composite verbal fluency score ($R^2_{adj} = 0.18$, $p = 0.045$) were associated with greater vasodilatation in the right insular cortex. In the T2DM group on INI, FAS scores were also associated with greater vasodilatation in the left ($p = 0.02$) than in the right insular cortex ($R^2_{adj} = 0.26$, $p = 0.04$) (H. Zhang et al., 2015).

Other studies have also demonstrated the prospectively an association between reduced regional vasodilation and cognitive decline (Chung et al., 2015) in patients with T2DM, but

not in controls. After 2 years of follow-up, T2DM participants demonstrated a diminished regional and global vasoreactivity, as well as worse performance on multiple cognitive tasks. In T2DM, a decline in a composite T score of executive function was associated with a decline in vasodilation in the frontal and parietal lobes independent of age, education, hematocrit and 24-h mean arterial pressure. In the T2DM group, the higher serum soluble intercellular and vascular adhesion molecules, higher cortisol, and higher C-reactive protein levels at baseline were associated with greater decreases in cerebral vasoreactivity and vasodilation, suggesting that DM-related inflammation may contribute to these effects.

INI Improved Functional Connectivity of Hippocampus with Resting State Networks

We have used resting state functional magnetic resonance imaging (fMRI) to examine the impact of acute INI administration on functional connectivity between hippocampus and structures within the resting default mode network (DMN). For network correlation analyses we used a voxel-based approach to examine connectivity of the hippocampal regions with regions within the resting state DMN (Zhang et al., 2015). The T2DM subjects treated with INI demonstrated increased connectivity of hippocampus regions with DMN regions (MPC: medial prefrontal cortex [3.7, peak t score]; IPC: inferior parietal cortex [3.9]; PCC: posterior cingulate cortex [3.2]) than those on placebo (Figure 4 A–B) ($p < 0.05$, voxel corrected).

On placebo, T2DM group had lower connectivity as compared to controls ($p = 0.02$) but connectivity on INI was similar. In T2DM subjects, functional connectivity between hippocampus and anterior cingulate cortex was associated with better Verbal Fluency Score. BVMT showed a positive trend toward association between hippocampus and right IPC. INI may modify functional connectivity among brain regions regulating memory and complex cognitive behaviors.

Cerebrovascular dynamics are also impaired in patients with other cardiovascular risk factors, possibly adding to the cognitive/vascular burden imposed by T2DM and impairing functional connectivity within the DMN areas.

TYPE 2 DM EPIDEMIC, PHENOTYPE, AND HEALTHCARE SYSTEMS

As the epidemic of T2DM spans around the globe and different age groups, it presents complex health issues and care delivery that challenge the traditional health care systems. The major challenge is the increase of obesity and T2DM in children (18% of children in the U.S. are obese) and younger adults increasing their risk for cardiovascular complications in young adulthood, that occurs even in the countries that previously had very low rates of obesity and cardiovascular complications.

Obesity is a “social phenomenon” that spreads along the social networks, and obese peers increase the probability of their friends to become obese, e.g. up to 100% for male friends, 40% in siblings, and 37% in spouses. Interestingly, the social contagion phenomenon has been also observed for other health-related behaviors, such as drinking alcohol (Christakis & Fowler, 2007). However, this social phenomenon may also support the spread of health-positive behaviors such as smoking cessation, and smokers are progressively found on the

periphery of the networks. The probability of smoking decreased by 67% for the spouse, 36% for a friend, and 25% for a sibling. At the same time the media impact on the behavior of younger generations is much stronger, and therefore there is a greater opportunity for influencing both positive (activity) and negative behavior (e.g. obesity, drinking) via social networks and media and this phenomenon could be perhaps expanded to reinforce positive behaviors such as activity and healthy eating via web care. The methodologies that would promote and instill spread of healthy eating and activity as still under investigation, and have not been tested at the population level.

Younger generations are at greater risk of developing T2DMs complications, because the perception of their risks is lower than for older people. Therefore, younger people are less likely to receive more aggressive treatments that are needed for long-term health preservation. At the same time, older people with T2DM are living longer, and surviving cardiovascular complications. As a result, the number of people with disability due to diabetes is on the rise. In contrast, perception of DM severity and of its complications is declining among younger diabetics, thus undermining the risk of long-term disease complications.

A phenotype of slow gait speed, depression and cognitive impairment that has emerged may be linked to abnormal vasoregulation. Altered regulation of perfusion during daily challenges may accelerate brain atrophy and correlate with slower gait speed, worse cognition and function (Chung et al., 2015; de Bresser et al., 2010) and poor balance in older age. DM affects verbal learning, executive function, and memory, and poses a barrier to self-care in older patients. Furthermore, cardiovascular risk (Cukierman-Yaffe et al., 2009), genetic and lifestyle factors may further contribute or accelerate cognitive decline in older adults. Cardiovascular risk factors increase exponentially with age, and are often overlooked as a source of cognitive changes attributed to “normal” aging. Therefore, there is a great need to reinforce the concept that long-term health-oriented behaviors are crucial for prevention of T2DM and its long-term complications.

The Self-Management and Mobile Technology

The Look AHEAD clinical trial that evaluated the impact of behavioral interventions on cardiovascular morbidity and mortality over a decade, has shown that behavioral interventions achieved a short-term improvement of health status, but sustainability of healthy behaviors and prevention of long-term complications has remained a challenge (Unick et al., 2011). Therefore, there is a need to enrich healthcare with novel non-traditional approaches, such as social media, wearable technology (Barnard & Shea, 2004) and telemedicine (Zhou et al., 2014) to reinforce healthy behaviors in people of all ages, and thus improve prevention and management of risk factors that lead to T2DM and its complications. In the past decade, the use of digital media and wearable technologies has exponentially increased all over the world and it exerts a strong impact and influence on people's lives. Social media offer a popular, easy to access and cost-effective online platforms that can assist the formation of social supportive groups, information sharing groups and like-minded health oriented networks. Social media have been largely used today among people of all age groups, however the effects of social interaction on the spread of

healthy behaviors remain unknown. Their influence both positive or/and negative on health behaviors such as physical activity, weight management, food intake, alcohol and cigarettes use, etc. has not been studied in the large clinical trials. Recent studies have shown a positive effect of social media on physical activity (Joseph, Keller, Adams, & Ainsworth, 2015), and weight management (Willis et al., 2016). Online social networks, when combined with the health educator feedback promoting a weight loss, have shown a promising decline in body weight in 3 of the 5 recent studies (Willis et al., 2016). Text messaging and peer-to-peer interactions have demonstrated a reduced sedentary lifestyle, and an increased light and moderate-physical activity combined with greater participant satisfaction (Joseph et al., 2015). These studies (Jane, Foster, Hagger, & Pal, 2015) have limitations due to small sample size and short period of intervention, and clinical trials to study the long-term effects of online platforms remain needed. Therefore, the online networks and platforms may provide an important social support and educational tools that can be combined with health monitoring, web-based or wearable technologies for monitoring of physiologic variables and web-based feedback to reinforce a positive healthy behaviors and health improvement (Barnard & Shea, 2004). The most effective combination of these tools that would allow achieving a positive long-term and sustainable positive impact on health-related behaviors is yet to be determined. Long-term sustainable effects are essential to reduce cardiovascular risks, treat and prevent complications of life-style related diseases.

Wearable technologies and web-based sites also offer new opportunities for patients to be actively involved in their health management and to self-monitor behaviors (such as gait, physical activity, sleep etc.) on a daily/weekly basis. However, accurate monitoring of food intake, food composition, metabolic rate and balance still remains a challenge. New sensors can be weaved into fabrics or clothing (smart textile technology) or even directly printed on human skin thus allowing pervasive yet unobtrusive self-monitoring and telemonitoring for prolonged time periods. The feasibility of wearable technology applications is growing (Barnard & Shea, 2004; Buttussi & Chittaro, 2008) and some technologies are already achieving sustainable goals in combination with guided therapy (e.g. for weight loss, diabetes control etc.) that are comparable to the office visits and group therapy. In addition, these approaches would utilize only a fraction of a healthcare worker's time, would be more cost effective, could reach larger populations and has the potential to improve quality of life as well as psychological wellbeing of the subjects who use it all without requiring one-to-one contact. New wearable specifically self-monitoring devices with active biofeedback, combined with social media and health educators, have potential to become a new tool to achieve behavioral changes and offer a new domain for healthcare.

Large randomized control trials aimed at accurate glycemic control and decreasing hyperglycemia for prevention of cardiovascular complications (ACCORD (Action to Control Cardiovascular Risk in Diabetes) (Cukierman-Yaffe et al., 2009), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) And Diabetes Control and Complications Trial (DCCT)), and also reduction of hypoglycemic episodes (Dluhy & McMahon, 2008). However, these trials did not achieve improvement in cardiovascular complications (ACCORD) or cognitive outcomes despite of effective lowering of glycemic levels, because of higher number of hypoglycemic episodes.

In diabetic population, self-monitoring of blood glucose level has been used to facilitate glycemic control on a daily basis. The randomized Glucose Levels Awareness in diabetes Study (GLADIS), a 100 day randomized-control study in insulin treated T1 and T2DM subjects has shown that combining CGM with self-monitoring and feedback alarms has reduced the time spent outside glycemic target than self-monitoring alone or CGM without alarms (New, Ajjan, Pfeiffer, & Freckmann, 2015).

However, despite of meeting the standard for untrained individual use, these measurements are susceptible to errors from glucometers, test strips, environment, pharmacologic factors, glycemic excursions etc. Therefore, understanding and reducing blood sugar excursions using continuous glucose monitoring (CGM) has become a second target in diabetes control. CGM has an improved accuracy for monitoring of glucose levels over several days with frequent subcutaneous glucose sampling, and resulted in a better satisfaction with treatment (a key element in the management and compliance of chronic conditions such as diabetes). The subcutaneous sensor remains a major limitation to a wide use and compliance with these device, and new approaches e.g. fabric calibration) may allow to reduce the number of finger stick needed for calibration, prolong monitoring time and improve feasibility. Retrofitted and advanced algorithms have helped improve the accuracy of the CGM devices and utility for patients who need a strict glycemic control due a quick variation in the blood glucose level in a short period of time. However, a closed loop system providing longitudinal noninvasive assessments and real time feedback and feedforward loops with treatment on the implanted chip still remains a challenge. The cost effectiveness and accessibility to patients with diverse socio-demographic backgrounds, remains a concern especially for low income populations and countries.

Self-monitoring of glucose blood levels combined with educational& health care provider support (phone calls, text messages) has been shown more promising (Zhou et al., 2014) as compared to passive interventions. An optimal treatment for T2DM would be closed loop system capable of real time monitoring of multiple physiological variables (e.g. activity, food intake, environmental etc.) and delivering treatment with behavioral notifications, feedback reinforcement or medications in a real time that would be combined with traditional treatment regiments, medications, telemedicine, educators and supportive social media groups.

An even better set-up would be preventive modes that would predict glycemic fluctuations in real time and, through a closed loop system, maintain glycemic levels stable during daily activities, metabolic demands and challenges. Interesting possibilities and promising intranasal route as a new nose-to-brain delivery pathway, in combination with self-monitoring and social media reinforcement of healthy behaviors may enhance the traditional prevention and treatment options and approach in the next decade.

CONCLUSION

The global epidemic of T2DM and its complications threatens lives of people of all ages around the globe. Recognition of a syndrome of brain insulin resistance allows focus

physiological research on better understanding of insulin role in the brain and the mechanisms governing glucose and energy expenditure and their impact on brain health.

Intranasal route for delivery of insulin and other medications directly in the brain offers a new promise for prevention and treatment of T2Dm-related cognitive decline.

Wearable technologies now enable monitoring of behaviors and glycemic levels over several days, and social media provide platforms for peer-to-peer intervention and patient-provider interactions. The utilization of wearable technologies, however, has not yet been adopted by the traditional systems, and their role and cost-effectiveness needs to be validated in the large clinical trials. Prevention and education of a younger generation that is facing a longer diseased life or even a shorter lifespan, remains a challenge. While embracing new technologies, there is a need for better understanding of the impact of availability, sharing and potential misuse of healthcare-related information, mass data collection and a proper use of smart technologies (Barnard & Shea, 2004). There is a growing need for further development of telemedicine and “guided self-diagnostics and monitoring using smart devices” that is becoming more feasible based upon the advances and availability of mobile technologies and sensors. Therefore, a non-traditional approach based on wearable technologies combined with artificial intelligence that could provide real time feedback regarding behavior modifications would allow the design and implementation of new strategies and novel paradigms to further improve the well-being of younger and older populations of diabetic people and those at risk for diabetes.

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Diabetes Complex Metabolic Disease

Figure 1.
T2DM—a complex multi-organ disease

Blood Sugar Swings Correlate with Brain Damage

Figure 2.
Glycemic variability in T2DM subject (A) and control subject (B)

Intranasal insulin to improve cognition

Figure 3.
Conceptual design of intranasal insulin action and potential benefits on brain metabolism and function

Figure 4.

A. Diabetes group on INI had better functional connectivity between hippocampus and default mode network. B. On placebo DM group had worse connectivity than controls