# NEW TREATMENT STRATEGIES FOR DIABETES-RELATED COGNITIVE DECLINE IN GLOBAL HEALTHCARE

**Vera Novak**[(a)]

[(a)]Dept. of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School

[(a)]vnovak@bidmc.harvard.edu

**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 and functional decline in older adults and dementia. Intranasal insulin (INI) therapy has emerged as a potential new treatment for T2DM-related cognitive decline. Insulin resistance and glycemic variability are potential mechanisms underlying T2DM-related brain damage. Wearable technologies now allow better monitoring of behaviors and glycemic levels over several days, and may be used in the future to deliver real time feedback and new therapies for T2DM complications.

Keywords: type 2 diabetes, intranasal insulin, glycemic variability, wearable technology

## 1. 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 (Xu et al., 2004), alters neurovascular coupling (Mogi and Horiuchi, 2011,Last et al., 2007,Novak and Hajjar, 2010,Novak et al., 2011,Tiehuis et al., 2008), and increases the risk for dementia and Alzheimer's disease(de Bresser et al., 2010a,de Bresser et al., 2010b,van den Berg et al., 2010). The long-term diabetes complications have a major impact on the high prevalence of cognitive impairment, depression, and disability in older adults. (Saczynski et al., 2008,Novak et al., 2011,Manor et al., 2012). Memory loss further deteriorates self-care and glycemic control and accelerates disease progression, worsening a vicious cycle of functional decline. Currently, there is no cure for DM-related cognitive impairment**.**

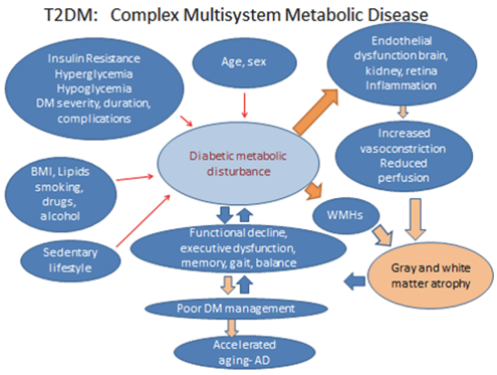



**Figure 1**: T2DM–a complex multi-organ disease

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 (**Figure2A**). In contrast, in a healthy person blood sugar levels remain tightly regulated during daily activities and during the sleep (**Figure2B**). As a result, even a strict glycemic control did not improve cognitive function in participants of the large clinical trials (Cukierman-Yaffe et al., 2009,Launer et al., 2011).

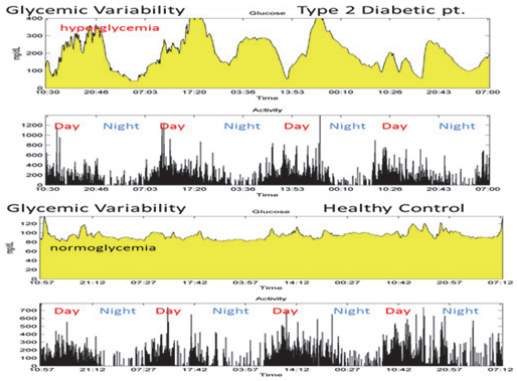



**Figure 2**: A. Glycemic variability in T2DM, B. Control

Insulin resistance, altered transport and insulin signaling in the brain may be a potential pathway for DM-related cognitive decline. 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. This need for new therapies is also important as cognitive impairment poses a significant barrier for self-care, increasing further the risk for diabetic complications, disability, and dementia in this age group.(Xu et al., 2004)(Reijmer et al., 2011)(Korf et al., 2006)

## 2. 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 amnestic 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).

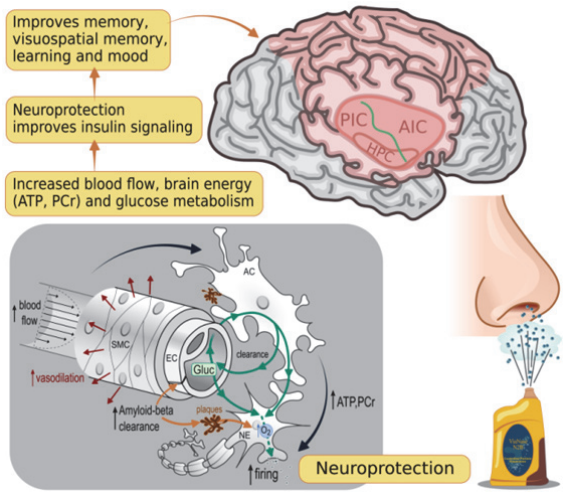



**Figure 3**: Conceptual design of intranasal insulin action and potential benefits on brain metabolism and function.

Central insulin plays a role as an important neuromodulator in key processes such as cognition (Shemesh et al., 2012, Freiherr et al., 2013), energy homeostasis, food intake, sympathetic activity, neuron-astrocyte signaling, synapse formation, and neuronal survival (Plum et al., 2005,Plum et al., 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 (Figlewicz, 2003,Figlewicz and Benoit, 2009,Stice et al., 2012). Insulin receptors (IRs) are expressed in numerous brain regions, namely in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, and hippocampus.(Hopkins and Williams, 1997,Albrecht et al., 1981)(Banks, 2004) Even wider IR distribution overlaps with expression of downstream proteins and isoforms in insulin-related pathways (Horsch and Kahn, 1999) (Banks, 2004). 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 (Hopkins and Williams, 1997),(Albrecht et al., 1981),(Cersosimo and DeFronzo, 2006),( Girouard and Iadecola, 2006) and the wall of small vessels (Abbott et al., 1999). We anticipate 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 (Lok et al., 2007) and neuronal activity in response to various stimuli (Amir and Shechter, 1987)(Cranston et al., 1998)(Kim et al., 2006)(Reger et al., 2006)(Muniyappa et al., 2007). 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 (Thorne et al., 2004)(Hanson and Frey, 2008)(Hallschmid et al., 2008). 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., 2013),(Morris and Burns, 2012),(Craft et al., 2012) (**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 CSF began to decline, but remained mildly elevated even 80 minutes after INI. (Born et al., 2002) INI administration 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 (Moses et al., 1983).

## 3. INTRANASALINSULIN 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,Craft, 2005b). These mild forms of insulin resistance may precede AD pathology for years (Freiherr et al., 2013), (Messier and Teutenberg, 2005). The risk of T2DM for dementia and AD in late life has been increasingly recognized (Xu et al., 2004)(Reijmer et al., 2011)(Korf et al., 2006) and impaired insulin signaling in the hippocampus and hypothalamus, as seen in both conditions, may provide a common link between DM and AD (Cedernaes et al., 2013). The evidence that INI could be a promising treatment for improving cognitive function is growing (Banks et al.,

2012),(Freiherr et al., 2013),(Cholerton et al., 2013), (Cholerton et al., 2012),(Park et al., 2000),(Reger et al., 2008a), (Reger et al., 2008b), (Schioth et al., 2012), (Watson et al., 2003). Clinical studies suggest that augmenting cerebral insulin improved performance in specific cognitive domains and memory in healthy young (Benedict et al., 2005)(Benedict et al., 2007c)(Benedict et al., 2007a) and older adults (Reger et al., 2006)(Reger et al., 2008a), patients with mild cognitive impairment and even AD patients (Reger et al., 2006)(Reger et al., 2008a) with both acute and chronic administration. In healthy men, INI also improved mood and regulated food intake (Hallschmid et al., 2008)(Benedict et al., 2008). 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., 2007d),(Benedict et al., 2007b). Patients with amnestic mild cognitive impairment (MCI) and mild-moderate AD were treated with 40 IU (Novolin® Novonordisk) 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 isoform (Reger et al., 2008d). 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., 2008c). The first clinical trial in 104 patients with amnestic 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 (Rotterdam study), as well as the high prevalence of insulin resistance syndrome in AD patients.(Craft and Watson, 2004), (Craft, 2005b),(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 (Figlewicz, 2003, Figlewicz and Benoit, 2009,Stice et al., 2012). 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 (Chapman et al., 2013).

### 3.1. INI Effects on Memory in Type 2 Diabetics

Our proof-of-concept (Novak et al., 2013,Zhang et al., 2014), randomized, double-blind, placebo-controlled intervention evaluated the effects of a single 40-IU dose of insulin (Novolin® Novonordisk) 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 was used to administer INI or sterile saline in 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.

*Brief Visuospatial Learning and Memory Test Revised (BVMT):* INI improved BVMT 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 improved performance on T2 (p=0.04) and Total Recall (paired t-test, p=0.05). *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).

#### 3.1.1. 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 DM group had lower baseline perfusion than controls (p=0.039). In the DM group, INI increased perfusion in the right insular cortex compared to placebo (p=0.0001) and to the control group (p=0.0003). BVMT 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., 2014). BVMT T3 and BVMT 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 BVMT 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. BVMT T2, T3 and Total Recall also correlated with vasodilatation in the anterior cerebral artery 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 DM group on INI, FAS scores were also associated with greater vasodilatation in the left (p=0.02) than in the right insular cortex ($R^2_{adj}$=0.26p=0.04).

### 3.1.2. INI Improved Functional Connectivity of Hippocampus with Resting State Networks

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., 2014). The DM subjects on 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).

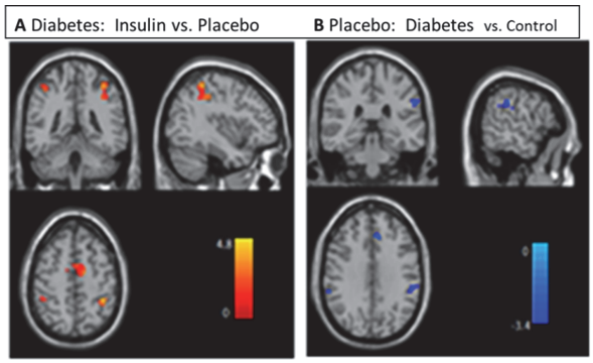



**Figure 4**: A. Diabetes group on INI had better functional connectivity between hippocampus and default mode network. B. On placebo DM group had worse connectivity than controls.

On placebo, DM group had lower connectivity as compared to controls ($p=0.02$) but connectivity on INI was similar. In DM 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.

## 4. 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 (Lurbe et al., 2008),(Wild et al., 2004). Obesity is a "social phenomenon" that spreads along the social networks, and obese peers increase probability for their friends to become obese, e.g. up to 100% for male friends, 40% in siblings, and 37% in souses(Christakis and Fowler, 2007). Interestingly, social contagion phenomenon has been also observed for other health-related behaviors (Christakis and Fowler, 2013), such as drinking alcohol (Christakis, 2004). 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 (Christakis and Fowler, 2008).

The major challenge is that the increase of obesity and T2DM in children and younger adults still affects even countries that previously had very low rates of obesity and cardiovascular complications. At the same time the media impact on behavior in younger generation 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 reinforcing the positive behaviors such as activity and healthy eating via web care (Christakis and Fowler, 2013),(Christakis, 2008)

The younger generation is at greater risk of developing T2DMs complications, because the perception of its risks is lower than in older generation, and therefore younger people are less likely to receive more aggressive treatments that are needed for long-term health preservation. At the same time the 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, however the perception of severity of its complications is declining. A phenotype of slow gait speed, depression and cognitive impairment has thus emerged that 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,(Novak et al., 2006)(Novak et al., 2009)(Last et al., 2007)(Hu et al., 2008) and poor balance in older age (Manor and Li, 2009),(Manor et al., 2012). DM affects verbal learning, executive function, and memory,(Morra et al., 2013),(Hajjar et al., 2009) and thus poses a barrier to self-care in DM patients (Kuo et al., 2005)(Munshi et al., 2006). Furthermore, cardiovascular risk (Albert et al., 1988),(Munshi et al., 2006),(Kuo et al., 2007),(Kuo et al., 2006) and genetic(Zade et al., 2013) and lifestyle factors (Levine et al., 1997,Rudolph et al., 2006) may contribute or lead to 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 (Leritz et al., 2011)(Kuo et al., 2004). 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.

### 4.1. The Self-Management and Mobile Technology

Look AHEAD long term clinical trial (Espeland et al., 2009) has shown that behavioral interventions are effective for short-term improvement of health status, but sustainability of healthy behaviors and prevention of long-germ complications still remains a challenge (Espeland et al., 2009),(Unick et al., 2011). Therefore, there is a need to bring novel non-traditional approaches

to reinforce healthy behaviors in people of all ages and improve prevention and management of cardiovascular risk factors that lead to T2DM and its complications.

Recent advancements of wearable technologies and web-based sites offer the new opportunity for self-monitoring of behaviors (e.g. gait, activity, sleep etc.), and have been effective in recording daily/weekly activities. However, accurate monitoring of food intake, food composition, metabolic rate and balance still remains a challenge. New sensors can be weaved into fabrics (smart textile technology), clothing or even directly printed on human skin (Zheng et al., 2014), (Jadad et al., 2015),(Alam and Ben, 2014) thus allowing pervasive yet unobtrusive health monitoring and telemonitoring (Hung et al., 2004) for prolonged tiem periods. The feasibility of wearable technology applications is growing (Choi et al., 2013),(Barnard and Shea, 2004),(Buttussi and 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 the healthcare worker's time, would be more cost effective, could reach larger population and would not require one-to-one contact.

The major challenge that remains in T2DM management is development of a closed loop system capable of real time monitoring of multiple physiological variables (e.g. activity, glucose, nutrients intake) and delivering treatments either behavioral notifications, feedback reinforcement or medications in a real time. Even better set-up would be preemptive 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.

### 4.2. Conclusions

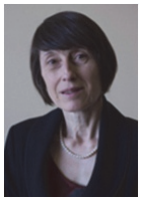
The utilization of wearable technologies, however, has not yet been adopted by the traditional systems, and there is great need for education of a younger generation that is not sparred from the risks of life-style related diseases and is facing a longer diseased life or even a shorter lifespan (Lurbe et al., 2008). At the same time, there is a need for better understanding of the impact of availability, sharing and potential misuse of health-related are information, mass data collection and a proper use of smart technology (Barnard and 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 technology and sensors.

Therefore, non-traditional approaches based on wearable technologies combined with artificial intelligence that could provide real time feedbacks about behavior modifications would allow the design and implementation of new strategies and and novel paradigms to further improve well-being of younger as well as older population of diabetic people and those at risk for diabetes.


### ACKNOWLEDGMENTS

V.N. has received grants from the NIH–National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (5R21-DK-084463-02 and 1R01 DK103902-01A1) and National Institutes on Aging (NIA)(1 R01DK103902) related to this study. V.N. receive salary from these grants. The author wish to thank Katharina Dormanns, PhD candidate Brain Trust Research Group, BlueFern Supercomputing Unit (University of Canterbury) for her design of figures.


### AUTHORS BIOGRAPHY



Vera Novak MD PhD is Director of the Syncope and Falls in the Elderly (SAFE) program, Associate Professor of Neurology at Harvard Medical School and Adjunct Professor of Mathematics at North Carolina State University. Her interests are to study the effects of life style disorders (obesity, diabetes) on well-being of older adults, recognizing the path by which diabetes accelerates brain aging and a path toward dementia. She leads the MemAID (Memory Advancement by Intranasal Insulin in Type 2 Diabetes) RCT trial sponsored by NIH-NIDDK.

RERERENCES


Abbott M A, Wells D G, Fallo J R. The Insulin Receptor Tyrosine Kinase Substrate p58/53 and the Insulin Receptor Are Components of CNS Synapses. Journal of Neuroscience 1999; 19: 7300-7308.

Alam M M, Ben H E. Surveying wearable human assistive technology for life and safety critical applications: standards, challenges and opportunities. Sensors (Basel) 2014; 14(5): 9153-9209.

Albert M S, Heller H S, Milberg W. Changes in naming ability with age. Psychol Aging 1988; 3(2): 173-178.

Albrecht J, Wroblewska B, Mossakowski M J. The binding of insulin to cerebral capillaries and astrocytes of the rat. Neurochemical Research 1981; 7: 489-494.

Amir S, Shechter Y. Centrally mediated hypoglycemic effect of insulin: apparent involvement of specific insulin receptors. Brain Res 1987; 418(1): 152-156.

Banks W A. The source of cerebral insulin. Eur J Pharmacol 2004; 490: 5-12.

Banks W A, Owen J B, Erickson M A. Insulin in the brain: there and back again. Pharmacol Ther 2012; 136(1): 82-93.

Barnard R, Shea J T. How wearable technologies will impact the future of health care. Stud Health Technol Inform 2004; 108: 49-55.

Benedict C, Dodt C, Hallschmid M, Lepiorz M, Fehm H L, Born J, Kern W. Immediate but not long-term intranasal administration of insulin raises blood pressure in human beings. Metabolism 2005; 54(10): 1356-1361.

Benedict C, Hallschmid M, Schmitz K, Schultes B, Ratter F, Fehm H L, Born J, Kern W. Intranasal insulin improves memory in humans: superiority of insulin aspart. Neuropsychopharmacology 2007a; 32(1): 239-243.

Benedict C, Hallschmid M, Schmitz K, Schultes B, Ratter F, Fehm H L, Born J, Kern W. Intranasal insulin improves memory in humans: superiority of insulin aspart. Neuropsychopharmacology 2007b; 32(1): 239-243.

Benedict C, Hallschmid M, Schultes B, Born J, Kern W. Intranasal insulin to improve memory function in humans. Neuroendocrinology 2007c; 86(2): 136-142.

Benedict C, Hallschmid M, Schultes B, Born J, Kern W. Intranasal insulin to improve memory function in humans. Neuroendocrinology 2007d; 86(2): 136-142.

Benedict C, Kern W, Schultes B, Born J, Hallschmid M. Differential sensitivity of men and women to anorexigenic and memory-improving effects of intranasal insulin. J Clin Endocrinol Metab 2008; 93(4): 1339-1344.

Born J, Lange T, Kern W, McGregor G P, Bickel U, Fehm H L. Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci 2002; 5(6): 514-516.

Buttussi F, Chittaro L. MOPET: a context-aware and user-adaptive wearable system for fitness training. Artif Intell Med 2008; 42(2): 153-163.

Cedernaes J, Chapman C D, Brunner Y, Schioth H B, Freiherr J, Benedict C. Intranasal insulin targeting to brain and cerebrospinal fluid (CSF): A review of its clinical effects and mechanisms. Respiratory Drug Delivery 2013; 60-67.

Cersosimo E, DeFronzo R A. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. Diabetes Metab Res Rev 2006; 22(6): 423-436.

Chapman C D, Frey W H, Craft S, Danielyan L, Hallschmid M, Schioth H B, Benedict C. Intranasal treatment of central nervous system dysfunction in humans. Pharm Res 2013; 30(10): 2475-2484.

Choi C, Ko B H, Lee T, Park G, Shin K. Exercise amount calculation using a wearable half-cell potential sensor for mobile aerobic exercise management. Conf Proc IEEE Eng Med Biol Soc 2013; 2013: 2878-2881.

Cholerton B, Baker L D, Craft S. Insulin, cognition, and dementia. Eur J Pharmacol 2013.

Cholerton B, Baker L D, Trittschuh E H, Crane P K, Larson E B, Arbuckle M, Saucedo H H, McCurry S M, Bowen J D, McCormick W C, Craft S. Insulin and sex interactions in older adults with mild cognitive impairment. J Alzheimers Dis 2012; 31(2): 401-410.

Christakis N A. Social networks and collateral health effects. BMJ 2004; 329(7459): 184-185.

Christakis N A. Health care in a web. BMJ 2008; 336(7659): 1468.

Christakis N A, Fowler J H. The spread of obesity in a large social network over 32 years. N Engl J Med 2007; 357(4): 370-379.

Christakis N A, Fowler J H. The collective dynamics of smoking in a large social network. N Engl J Med 2008; 358(21): 2249-2258.

Christakis N A, Fowler J H. Social contagion theory: examining dynamic social networks and human behavior. Stat Med 2013; 32(4): 556-577.

Craft S. Insulin resistance and cognitive impairment: a view through the prism of epidemiology. Arch Neurol 2005a; 62(7): 1043-1044.

Craft S. Insulin resistance syndrome and Alzheimer's disease: age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiol Aging 2005b; 26 Suppl 1: 65-69.

Craft S, Baker L D, Montine T J, Minoshima S, Watson G S, Claxton A, Arbuckle M, Callaghan M, Tsai E, Plymate S R, Green P S, Leverenz J, Cross D, Gerton B. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012; 69(1): 29-38.

Craft S, Cholerton B, Baker L D. Insulin and Alzheimer's disease: untangling the web. J Alzheimers Dis 2013; 33 Suppl 1: S263-S275.

Craft S, Watson G S. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004; 3(3): 169-178.

Cranston I, Marsden P, Matyka K, Evans M, Lomas J, Sonksen P, Maisey M, Amiel S A. Regional differences in cerebral blood flow and glucose utilization in diabetic man: the effect of insulin. J Cereb Blood Flow Metab 1998; 18: 130-140.

Cukierman-Yaffe T, Gerstein H C, Williamson J D, Lazar R M, Lovato L, Miller M E, Coker L H, Murray A, Sullivan M D, Marcovina S M, Launer L J. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. Diabetes Care 2009; 32(2): 221-226.

de Bresser J, Reijmer Y D, van den B E, Breedijk M A, kappelle L J, Viergever M A, Biessels G J. Microvascular determinants of cognitive decline and brain volume change in elderly patients with type 2 diabetes. Dement Geriatr Cogn Disord 2010a; 30(5): 381-386.

de Bresser J, Tiehuis A M, van den Berg E, Reijmer Y D, Jongen C, kappelle L J, Mali W P, Viergever M A, Biessels G J. Progression of cerebral atrophy and white matter hyperintensities in patients with type 2 diabetes. Diabetes Care 2010b; 33(6): 1309-1314.

de la Monte S M. Contributions of brain insulin resistance and deficiency in amyloid-related neurodegeneration in Alzheimer's disease. Drugs 2012; 72(1): 49-66.

Espeland M A, Bray G A, Neiberg R, Rejeski W J, Knowler W C, Lang W, Cheskin L J, Williamson D, Lewis C B, Wing R. Describing patterns of weight changes using principal components analysis: results from the Action for Health in Diabetes (Look AHEAD) research group. Ann Epidemiol 2009; 19(10): 701-710.

Figlewicz D P. Insulin, food intake, and reward. Semin Clin Neuropsychiatry 2003; 8(2): 82-93.

Figlewicz D P, Benoit S C. Insulin, leptin, and food reward: update 2008. Am J Physiol Regul Integr Comp Physiol 2009; 296(1): R9-R19.

Freiherr J, Hallschmid M, Frey W H, Brunner Y F, Chapman C D, Holscher C, Craft S, De Felice F G, Benedict C. Intranasal Insulin as a Treatment for Alzheimer's Disease: A Review of Basic Research and Clinical Evidence. CNS Drugs 2013; 7: 505-514.

Girouard H, Iadecola C. Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. J Appl Physiol 2006; 100(1): 328-335.

Hajjar I, Yang F, Sorond F, Jones R N, Milberg W, Cupples L A, Lipsitz L A. A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: relationship to blood pressure and other cardiovascular risks. J Gerontol A Biol Sci Med Sci 2009; 64(9): 994-1001.

Hallschmid M, Benedict C, Schultes B, Perras B, Fehm H L, Kern W, Born J. Towards the therapeutic use of intranasal neuropeptide administration in metabolic and cognitive disorders. Regul Pept 2008; 149: 79-83.

Hanson L R, Frey W H. Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease. BMC Neurosci 2008; 9 Suppl 3: S5.

Hopkins D F, Williams G. Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabet Med 1997; 14(12): 1044-1050.

Horsch D, Kahn C R. Region-specific mRNA expression of phosphatidylinositol 3-kinase regulatory isoforms in the central nervous system of C57BL/6J mice. J Comp Neurol 1999; 415(1): 105-120.

Hu K, Peng C K, Czosnyka M, Zhao P, Novak V. Nonlinear assessment of cerebral autoregulation from spontaneous blood pressure and cerebral blood flow fluctuations. Cardiovasc Eng 2008; 8(1): 60-71.

Hung K, Zhang Y T, Tai B. Wearable medical devices for tele-home healthcare. Conf Proc IEEE Eng Med Biol Soc 2004; 7: 5384-5387.

Jadad A R, Fandino M, Lennox R. Intelligent glasses, watches and vests...oh my! Rethinking the meaning of "harm" in the age of wearable technologies. JMIR Mhealth Uhealth 2015; 3(1): e6.

Kim J A, Montagnani M, Koh K K, Quon M J. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006; 113: 1888-1904.

Korf E S, White L R, Scheltens P, Launer L J. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study. Diabetes Care 2006; 29(10): 2268-2274.

Kuo H K, Jones R N, Milberg W P, Tennstedt S, Talbot L, Morris J N, Lipsitz L A. Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the advanced cognitive training for independent and

vital elderly cohort. J Am Geriatr Soc 2005; 53(7): 1154-1161.

Kuo H K, Jones R N, Milberg W P, Tennstedt S, Talbot L, Morris J N, Lipsitz L A. Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the Advanced Cognitive Training for Independent and Vital Elderly cohort. J Am Geriatr Soc 2006; 54(1): 97-103.

Kuo H K, Leveille S G, Yu Y H, Milberg W P. Cognitive function, habitual gait speed, and late-life disability in the National Health and Nutrition Examination Survey (NHANES) 1999-2002. Gerontology 2007; 53(2): 102-110.

Kuo H K, Sorond F, Iloputaife I, Gagnon M, Milberg W, Lipsitz L A. Effect of blood pressure on cognitive functions in elderly persons. J Gerontol A Biol Sci Med Sci 2004; 59(11): 1191-1194.

Last D, Alsop D C, Abduljalil A M, Marquis R P, de Bazelaire C, Hu K, Cavallerano J, Novak V. Global and regional effects of type 2 diabetes mellitus on brain tissue volumes and cerebral vasoreactivity . Diabetes Care 2007; 30: 1193-1199.

Launer L J, Miller M E, Williamson J D, Lazar R M, Gerstein H C, Murray A M, Sullivan M, Horowitz K R, Ding J, Marcovina S, Lovato L C, Lovato J, Margolis K L, O'Connor P, Lipkin E W, Hirsch J, Coker L, Maldjian J, Sunshine J L, Truwit C, Davatzikos C, Bryan R N. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol 2011; 10(11): 969-977.

Leritz E C, McGlinchey R E, Kellison I, Rudolph J L, Milberg W P. Cardiovascular Disease Risk Factors and Cognition in the Elderly. Curr Cardiovasc Risk Rep 2011; 5(5): 407-412.

Levine B, Stuss D T, Milberg W P. Effects of aging on conditional associative learning: process analyses and comparison with focal frontal lesions. Neuropsychology 1997; 11(3): 367-381.

Lioutas V A, Alfaro-Martinez F, Bedoya F, Chung C C, Pimentel D A, Novak V. Intranasal Insulin and Insulin-Like Growth Factor 1 as Neuroprotectants in Acute Ischemic Stroke. Transl Stroke Res 2015; 6(4): 264-275.

Lok J, Gupta P, Guo S, Kim W J, Whalen M J, van Leyen K, Lo E H. Cell–cell Signaling in the Neurovascular Unit. Neurochemical Research 2007; 32(12): 0364-3190.

Lurbe E, Torro I, Aguilar F, Alvarez J, Alcon J, Pascual J M, Redon J. Added impact of obesity and insulin resistance in nocturnal blood pressure elevation in children and adolescents. Hypertension 2008; 51(3): 635-641.

Manor B, Li L. Characteristics of functional gait among people with and without peripheral neuropathy. Gait Posture 2009; 30(2): 253-256.

Manor B, Newton E, Abduljalil A, Novak V. The relationship between brain volume and walking outcomes in older adults with and without diabetic peripheral neuropathy. Diabetes Care 2012; 35(9): 1907-1912.

Messier C, Teutenberg K. The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. Neural Plast 2005; 12(4): 311-328.

Mogi M, Horiuchi M. Neurovascular coupling in cognitive impairment associated with diabetes mellitus. Circ J 2011; 75(5): 1042-1048.

Morra L, Zade D, McGlinchey R E, Milberg W P. Normal aging and cognition: the unacknowledged contribution of cerebrovascular risk factors. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2013; 20(3): 271-297.

Morris J K, Burns J M. Insulin: an emerging treatment for Alzheimer's disease dementia? Curr Neurol Neurosci Rep 2012; 12(5): 520-527.

Moses A C, Gordon G S, Carey M C, Flier J S. Insulin administered intranasally as an insulin-bile salt aerosol. Effectiveness and reproducibility in normal and diabetic subjects. Diabetes 1983; 32(11): 1040-1047.

Muniyappa R, Montagnani M, Koh K K, Quon M J. Cardiovascular actions of insulin. Endocr Rev 2007; 28(5): 463-491.

Munshi M, Grande L, Hayes M, Ayres D, Suhl E, Capelson R, Lin S, Milberg W, Weinger K. Cognitive dysfunction is associated with poor diabetes control in older adults. Diabetes Care 2006; 29(8): 1794-1799.

Novak V, Haertle M, Zhao P, Hu K, Munshi M, Novak P, Abduljalil A, Alsop D. White matter hyperintensities and dynamics of postural control. Magnetic Resonance Imaging 2009; 27: 752-759.

Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nat Rev Cardiol 2010; 7(12): 686-698.

Novak V, Last D, Alsop D C, Abduljalil A M, Hu K, Lepicovsky L, Cavallerano J, Lipsitz L A. Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. Diabetes Care 2006; 29(7): 1529-1534.

Novak V, Milberg W, Hao Y, Munshi M, Novak P, Galica A, Manor B, Roberson P, Craft S, Abduljalil A. Enhancement of Vasoreactivity and Cognition by Intranasal Insulin in Type 2 Diabetes. Diabetes Care 2013.

Novak V, Milberg W, Hao Y, Munshi M, Novak P, Galica A, Manor B, Roberson P, Craft S, Abduljalil A. Enhancement of Vasoreactivity and Cognition by Intranasal Insulin in Type 2 Diabetes. Diabetes Care 2014; 3: 751-759.

Novak V, Zhao P, Manor B, Sejdic E, Alsop D, Abduljalil A, Roberson P K, Munshi M, Novak P. Adhesion molecules, altered vasoreactivity, and brain atrophy in type 2 diabetes. Diabetes Care 2011; 34(11): 2438-2441.

Park C R, Seeley R J, Craft S, Woods S C. Intracerebroventricular insulin enhances memory in a passive-avoidance task. Physiol Behav 2000; 68(4): 509-514.

Plum L, Belgardt B F, Bruning J C. Central insulin action in energy and glucose homeostasis. J Clin Invest 2006; 116(7): 1761-1766.

Plum L, Schubert M, Bruning J C. The role of insulin receptor signaling in the brain. Trends Endocrinol Metab 2005; 16(2): 59-65.

Reger M A, Watson G S, Frey W H, Baker L D, Cholerton B, Keeling M L, Belongia D A, Fishel M A, Plymate S R, Schellenberg G D, Cherrier M M, Craft S. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol Aging 2006; 27(3): 451-458.

Reger M A, Watson G S, Green P S, Baker L D, Cholerton B, Fishel M A, Plymate S R, Cherrier M M, Schellenberg G D, Frey Ii W H, Craft S. Intranasal Insulin Administration Dose-Dependently Modulates Verbal Memory and Plasma Amyloid-beta in Memory-Impaired Older Adults. J Alzheimers Dis 2008a; 13(3): 323-331.

Reger M A, Watson G S, Green P S, Baker L D, Cholerton B, Fishel M A, Plymate S R, Cherrier M M, Schellenberg G D, Frey W H, Craft S. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. J Alzheimers Dis 2008b; 13(3): 323-331.

Reger M A, Watson G S, Green P S, Baker L D, Cholerton B, Fishel M A, Plymate S R, Cherrier M M, Schellenberg G D, Frey W H, Craft S. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. J Alzheimers Dis 2008c; 13(3): 323-331.

Reger M A, Watson G S, Green P S, Wilkinson C W, Baker L D, Cholerton B, Fishel M A, Plymate S R, Breitner J C, DeGroodt W, Mehta P, Craft S. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 2008d; 70(6): 440-448.

Reijmer Y D, van den Berg E., de Bresser J., Kessels R P, kappelle L J, Algra A, Biessels G J. Accelerated cognitive decline in patients with type 2 diabetes: MRI correlates and risk factors. Diabetes Metab Res Rev 2011; 27(2): 195-202.

Rudolph J L, Jones R N, Grande L J, Milberg W P, King E G, Lipsitz L A, Levkoff S E, Marcantonio E R. Impaired executive function is associated with delirium after coronary artery bypass graft surgery. J Am Geriatr Soc 2006; 54(6): 937-941.

Saczynski J S, Jonsdottir M K, Garcia M E, Jonsson P V, Peila R, Eiriksdottir G, Olafsdottir E, Harris T B, Gudnason V, Launer L J. Cognitive impairment: an increasingly important complication of type 2 diabetes: the age, gene/environment susceptibility--Reykjavik study. Am J Epidemiol 2008; 168(10): 1132-1139.

Schioth H B, Craft S, Brooks S J, Frey W H, Benedict C. Brain insulin signaling and Alzheimer's disease: current evidence and future directions. Mol Neurobiol 2012; 46(1): 4-10.

Shemesh E, Rudich A, Harman-Boehm I, Cukierman-Yaffe T. Effect of intranasal insulin on cognitive function: a systematic review. J Clin Endocrinol Metab 2012; 97(2): 366-376.

Stice E, Figlewicz D P, Gosnell B A, Levine A S, Pratt W E. The contribution of brain reward circuits to the obesity epidemic. Neurosci Biobehav Rev 2012.

Thorne R G, Pronk G J, Padmanabhan V, Frey W H 2. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience 2004; 127(2): 481-496.

Tiehuis A M, Vincken K L, van den Berg E, Hendrikse J, Manschot S M, Mali W P, kappelle L J, Biessels G J. Cerebral perfusion in relation to cognitive function and type 2 diabetes. Diabetologia 2008; 51(7): 1321-1326.

Unick J L, Beavers D, Jakicic J M, Kitabchi A E, Knowler W C, Wadden T A, Wing R R. Effectiveness of lifestyle interventions for individuals with severe obesity and type 2 diabetes: results from the Look AHEAD trial. Diabetes Care 2011; 34(10): 2152-2157.

van den Berg E, Reijmer Y D, de B J, Kessels R P, kappelle L J, Biessels G J. A 4 year follow-up study of cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia 2010; 53(1): 58-65.

Watson G S, Peskind E R, Asthana S, Purganan K, Wait C, Chapman D, Schwartz M W, Plymate S, Craft S. Insulin increases CSF Abeta42 levels in normal older adults. Neurology 2003; 60(12): 1899-1903.

Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004; 27(5): 1047-1053.

Xu W L, Qiu C X, Wahlin A, Winblad B, Fratiglioni L. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. Neurology 2004; 63: 1181-1186.

Zade D, Beiser A, McGlinchey R, Au R, Seshadri S, Palumbo C, Wolf P A, DeCarli C, Milberg W. Apolipoprotein epsilon 4 allele modifies waist-to-hip ratio effects on cognition and brain structure. J Stroke Cerebrovasc Dis 2013; 22(2): 119-125.

Zhang H, Hao Y, Manor B, Novak P, Milberg W, Zhang J, Fang J, Novak V. Intranasal insulin enhanced resting-state functional connectivity of hippocampal regions in type 2 diabetes. Diabetes 2014;(pii: DB_141000).

Zheng Y L, Ding X R, Poon C C, Lo B P, Zhang H, Zhou X L, Yang G Z, Zhao N, Zhang Y T. Unobtrusive sensing and wearable devices for health informatics. IEEE Trans Biomed Eng 2014; 61(5): 1538-1554.