

Type 2 Diabetes and Risk of Cognitive Impairment and Dementia

Rachel A. Whitmer, PhD

Corresponding author

Rachel A. Whitmer, PhD

Kaiser Permanente Division of Research, Epidemiology Etiology & Prevention, 2000 Broadway, Oakland, CA 94612, USA.

E-mail: Rachel.whitmer@kp.org

Current Neurology and Neuroscience Reports 2007, 7:373–380

Current Medicine Group LLC ISSN 1528-4042

Copyright © 2007 by Current Medicine Group LLC

Diabetes is a major public health burden. Even a modest effect of diabetes on cognitive function has significant public health implications. Several lines of mechanistic evidence implicate a role of insulin and glucose metabolism on risk of developing dementia, including Alzheimer's disease. Population-based studies have shown that those with type 2 diabetes mellitus have an increased risk of cognitive impairment, dementia, and neurodegeneration. There are many mechanisms through which diabetes could increase risk of dementia, including glycemia, insulin resistance, oxidative stress, advanced glycation endproducts, inflammatory cytokines, and microvascular and macrovascular disease. This paper presents a review of the evidence on diabetes and increased risk of dementia and cognitive impairment, a discussion of different possible mechanisms, and remaining gaps in our knowledge.

Introduction

Diabetes mellitus is a common disease, affecting approximately 5% of the population. Type 2 diabetes mellitus (non-insulin-dependent diabetes mellitus) accounts for 85% to 90% of patients with diabetes [1]. Patients with diabetes have a threefold risk for all cardiovascular diseases [2], and their relative risk of death from all causes is increased by 75% [3]. As early as 1976, diabetes mellitus was considered "a special kind of accelerated aging" because it increases an individual's susceptibility to degenerative disease, including kidney disease, retinopathy, hypertension, coronary artery disease, stroke, and atherosclerosis. Recently, evidence has accumulated to suggest that diabetes also plays a role in accelerated brain aging. Although it is known that diabetes may be associated with an increased risk of dementia, mechanisms and mitigating factors remain unclear. As worldwide

estimates suggest that type 2 diabetes will increase in prevalence to 300 million by the year 2025 [4,5], it is imperative that the effect of diabetes on dementia is well characterized. Complicating this scenario are estimates that suggest 6 million adults in the United States alone have undiagnosed diabetes or impaired fasting glucose [4,5]. Dementia affects 15% of those over the age of 65 years and up to 50% of those over the age of 85 years, and it is expected to increase more than 100% in incidence by the year 2050 [6]. If diabetes increases risk of dementia even mildly, the public health implications could be enormous.

Insulin and the Brain

Those with diabetes make insulin but either they do not produce enough or their bodies cannot effectively use the insulin that they make. Insulin and its receptors are present in many parts of the brain. Insulin receptors are most dense in the hippocampus, hypothalamus, olfactory bulbs, and limbic system, whereas insulin itself is in highest concentration in the olfactory bulb and hypothalamus [7]. Concentrations of insulin receptors in the brain are particularly high in neurons, with many insulin receptor proteins in both cell bodies and synapses [8]. Although it is known that insulin receptors and insulin itself are present in the brain, the exact physiologic purpose in the brain is unclear. Insulin and insulin receptors play a modulator role in synaptic transmission, and animal models have found insulin to be linked to feeding behavior as well as learning and memory [9]. In an experimental animal model, rats, after training in a water maze, had increased insulin mRNA levels in the hippocampus, as well as increased accumulation of insulin receptor proteins [8]. There is evidence that insulin plays a role in cerebral glucose utilization [7]. Insulin may also function as a neuromodulator directing the secretion and reuptake of neurotransmitters and affecting learning and memory [10,11]. It is thought that impairments in the insulin signaling pathway play a role in Alzheimer's disease (AD), type 2 diabetes, and aging overall [9,12,13].

Recently, attention has focused on the role of insulin degrading enzyme (IDE) in AD. IDE is a protease and is thought to play a role in degradation of amyloid beta [14]. Evidence has emerged that IDE regulates the metabolism

of both insulin and amyloid beta deposition [15], a major part of the AD process, which generates neurofibrillary plaques in an animal model. Therefore, malfunction of IDE could contribute to greater deposition of amyloid beta. Animal models incorporating knockout gene technology have shown that deletion of the homozygous *IDE* gene is associated with a greater extent of cerebral amyloid beta [16,17].

Treatment of type 2 diabetes with insulin aims to normalize blood glucose levels, thus protecting the brain and other tissues from hyperglycemia. However, insulin treatment can also directly impact the brain. Insulin has neuromodulatory effects, and defects in insulin action both in the periphery and the brain are thought to contribute to the pathogenesis of AD [18]. Peripheral insulin can cross the blood-brain barrier, and one study has shown that insulin infusions in humans result in increases of amyloid beta in the cerebral spinal fluid [19,20]. Case-control studies of those with and without AD show that cerebrospinal fluid levels of insulin were decreased in those with moderate or severe AD versus those with mild AD [21]. In this same study, plasma insulin levels were increased in those with severe AD, whereas plasma insulin levels were only slightly increased in those with mild AD compared with controls. Some researchers have proposed that the reduction in cerebrospinal fluid/plasma insulin ratios in patients with AD is a consequence of deficient insulin uptake and signaling in the brain, whereas increased plasma insulin levels are a compensatory mechanism [22]. Consequently, some have labeled AD as an “insulin-resistant brain state” [13].

Treatment of type 2 diabetes with insulin affects cerebral insulin levels and insulin-mediated signaling. Epidemiologic evidence from cohort studies shows that patients with type 2 diabetes who are treated with insulin are at a greater risk for dementia and AD than those who are not treated with insulin [23,24]. Although these findings could be due to the severity of type 2 diabetes, it may also indicate a possible role of insulin treatment on neurodegeneration. Future studies should assess whether insulin treatment affects the brain, or if it is simply a surrogate indicator of more severe diabetes.

Glucose and the Brain

Several lines of research indicate that there are parallel biochemical abnormalities between glucose hypometabolism in AD and in type 2 diabetes. Advanced glycation endproducts (AGE) are sugar-derived protein modifications that cross link “long-lived” proteins; among them are amyloid-beta plaques and neurofibrillary tangles, which are characteristic hallmarks of AD. AGEs are considered to be markers of protein aging. AGEs are present in those with type 2 diabetes due to insulin resistance, which reduces the ability of the glucose transport system to effectively transport glucose into the cells of the liver

and muscle, resulting in a high concentration of AGEs. Higher levels of plasma glucose cause AGE formation in diabetic patients [25]. Accumulation of AGE in those with AD is thought to be due to accelerated oxidation of glycated proteins [26]. Amyloid-beta plaques, proteins present in AD, are a precursor for the formation of AGEs. AGE formation has several metabolic sequelae including oxidative stress, glucose hypometabolism, and impaired cell function. AGEs impair neuronal functioning through a variety of mechanisms including apoptosis, calcium influx, oxidative stress, and inhibition of oxidative phosphorylation [25]. AGEs can affect neuronal function [26] by modifying functionally important proteins. In tissues most affected by diabetic complications, AGEs are present in highest concentrations, resulting in structural changes in cell membranes and intracellular components [26–28].

Diabetes and the Brain: AD-related Neuropathology

Although it is established that diabetic patients are at an increased risk for stroke, less is known about the other effects of diabetes on neurodegeneration. Previous studies have shown diabetes to be associated with white matter lesions or lacunae, and cerebral atrophy. Given that diabetic patients have increased glycation, and that AD plaques and neurofibrillary tangles have glycated proteins, it is plausible to suspect that diabetic patients may have an increased prevalence of AD-associated brain lesions. Some studies have examined whether diabetic patients have increased AD-associated neuropathology [29]. One small postmortem case control study ($n = 61$) did not find that those with diabetes were more likely to have a greater amount and degree of senile plaques and neurofibrillary degeneration. Another larger postmortem study ($n = 216$) by Peila et al. [30] found that diabetic patients, and particularly diabetic patients with the apolipoprotein E (APOE)- $\epsilon 4$ allele, a genetic risk factor for AD, had increased hippocampal neuritic plaques, neurofibrillary tangles in the cortex and hippocampus, and a higher risk of cerebral amyloid angiopathy. This finding was not attenuated with adjustment for age, education, stroke, coronary heart disease, atherosclerosis, blood pressure, or cholesterol. Recent work involving a cohort of more than 1000 people has shown that diabetic patients have greater cortical atrophy, independent of hypertension, total cholesterol, smoking status, body mass index, coronary heart disease, and sociodemographics [31].

Animal models of induced diabetes suggest a direct neurodegenerative effect of diabetes. Most studies show results in the hippocampus, the major area associated with learning and memory. These results suggest that diabetes is associated 1) with changes in hippocampal synaptic plasticity that is related to the degree of hyperglycemia but is reversible by glycemic control [22,32,33]; 2) with molecular changes in hippocampal neurons, including

damage to presynaptic and postsynaptic structures [34]; and 3) in long-term diabetes, with decreased neuronal densities in the CA-1 region on the hippocampus [35]. The hippocampus is also the first structure to be affected by the neurodegeneration of AD. The evidence from animal models suggests actual roles that diabetes may have on the development of AD-associated pathology.

Type 2 Diabetes and Increased Risk of Dementia

Many population-based studies have found an association between type 2 diabetes and an increased risk of developing dementia [36–41]. Studies that have examined risk of subtypes of dementia (vascular vs AD) have reported mixed findings, with some showing the relative risk to be stronger with vascular dementia compared with AD [40–43], and some studies found a greater risk of developing AD [24,30,39,44–47]. In one study, the risk was stronger for type 2 diabetes patients who used insulin versus those who used oral hypoglycemic agents [44], although both groups had a higher risk of AD compared with nondiabetic patients. Although initially the association between type 2 diabetes and vascular dementia appeared to be more consistent than the relationship between type 2 diabetes and AD, recent work has shown more consistent evidence for diabetes and AD. As vascular disease is a common co-morbidity in diabetes, earlier studies may have classified AD cases as vascular dementia, and it may seem there is a low prevalence of diabetes among those with “pure” AD. Indeed, one earlier study reported that those with diabetes had a lower population prevalence of AD than those without diabetes [48]. Current evidence suggests the contrary—that those with diabetes are more likely to develop both vascular dementia and AD; however there are diagnostic difficulties in separating vascular dementia from AD *in vivo*. Evidence also suggests that APOE- ϵ 4, a genetic risk factor for AD, may impact risk of dementia more strongly among those with diabetes. Findings from three population studies show that those with both diabetes and APOE- ϵ 4 are at the greatest risk of AD [30,46,47] versus those without diabetes and without APOE- ϵ 4.

Is the Link Between Type 2 Diabetes and Dementia Macrovascular or Microvascular in Nature?

A large number of studies have shown that macrovascular risk factors, such as elevated total and low-density lipoprotein cholesterol, hypertension, and atherosclerosis, are associated with cognitive impairment and risk of dementia [49–56]. Moreover, there are also a large number of prospective studies showing that macrovascular risk factors, such as atherosclerosis, hyperlipidemia, and hypertension, are associated specifically with development of AD [57,58]. Some postulate that AD is a disease of vascular origin, with neurodegenerative consequences

[59]. There is also evidence supporting a role of microvascular disease, such as retinal microvascular abnormalities, on risk of cognitive impairment and dementia [60–62]. As diabetic patients are more likely to have atherosclerosis, stroke, hyperlipidemia, hypertension, and retinopathy, it is plausible that in diabetic patients both of these sets of risk factors play a role in the development of dementia, with a resultant increased incidence of dementia in diabetes. It is also plausible that the role of macrovascular and microvascular risk factors could vary depending upon the subtype of dementia (ie, vascular dementia or AD). To date, however there have not been studies carefully assessing the differential role of both sets of risk factors on subtypes of dementia (vascular and AD).

Diabetes alters cerebral microvascular structure in a number of ways. Findings from animal models suggest that in uncontrolled diabetes, there are focal changes in the thickness of vascular basement membranes and calcium deposits in the microvessels walls [63]. Several lines of evidence indicate that cerebral microvascular disease increases the risk of AD [64], and findings from pathology studies indicate that cerebral microcirculation and microvessels are affected in AD [65,66]. More specifically, AD involves cerebral arteriolar narrowing, endothelial cell dysfunction, capillary microaneurysms, and breakdown of the blood-brain barrier [66–68]. Although several studies have found associations between cerebrovascular risk factors and cognitive functioning [69,70], only one study has examined microvascular risk factors and cognitive functioning. In middle-aged adults, those with retinopathy, including microaneurysms and retinal hemorrhage, had significantly lower mean cognitive scores as well as a greater risk of cognitive impairment [60].

Type 2 Diabetes and Cognitive Functioning

A large number of cross-sectional studies have shown that diabetes impairs cognitive functioning. A review article summarizing 19 studies found that in 13 of these studies, type 2 diabetes subjects had significantly lower scores on at least one cognitive test, and effects were especially strong for verbal memory and complex information processing [71,72], suggesting a domain-specific effect of diabetes on cognition. Findings from cross-sectional studies do not account for the effects of diabetes treatment, co-morbid conditions, and socio-demographic differences between groups of subjects [73]. Nevertheless, all eight prospective studies conducted to date have found that diabetic patients are at a greater risk of cognitive impairment and have greater cognitive decline [74–80]. Moreover, one of these studies was conducted in middle-aged adults over a 6-year period. There is also evidence of a dose effect. Two of these studies found that those with “prediabetes” (ie, impaired fasting glucose) had cognitive decline intermediate to those with diabetes [75,80], another study found that duration of diabetes was associated with

cognitive decline in a dose-response fashion (which remained after adjustment for age and co-morbid diseases) [74], and another study found that diabetic patients on combination therapy had less decline than those on monotherapy [81]. One of the largest cohort studies to date (16,000 subjects) showed that in women, diabetes is associated with accelerated cognitive decline over 2 years; however, those patients taking oral hypoglycemic agents performed similarly to those without diabetes, suggesting that the medication ameliorated the effect of diabetes on cognitive decline [82].

Glucoregulation, Glycemic Control, and Cognitive Functioning

Impaired glucose tolerance is a metabolic condition intermediate between normal glucose homeostasis and diabetes. Those with impaired glucose tolerance have mildly elevated levels of glycemia after challenge with an oral glucose load but not levels diagnostic of type 2 diabetes [83]. The association between impaired glucose tolerance and cognitive function has been examined in healthy subjects. In two small separate studies, older nondemented, nondiabetic subjects were split into better or worse glucoregulation groups, according to a glucose recovery score. Those with worse glucoregulation performed significantly worse on a variety of cognitive tests compared with those with better regulation [84,85]. One study found that among younger healthy subjects without type 2 diabetes, glucose was a predictor of verbal episodic memory [86]. Extensive animal research involving glucoregulation and memory suggest that glucoregulation affects memory systems that are dependent on hippocampal function, whereas glucose has smaller non-domain-specific effects on general cognitive function [87]. Consistent with animal models, human studies have also found that glucose-modulated memory tasks may be generated from hippocampal functioning [87].

Two small studies using patient samples have examined glycemic control and cognitive functioning in a within-subjects design [88,89]. Both studies involved elderly type 2 diabetes patients and found that treatment with oral hypoglycemic drugs and improved glycemic control resulted in improved cognitive functioning when comparing pre- and post-test scores. This suggests that improved glycemic control may be beneficial to the brain by reducing the effect of chronic hyperglycemia. However, severe type 2 diabetes requires strict control of blood glucose levels, which can accentuate hyperinsulinemia.

Glycated Hemoglobin and Cognition

Although no studies have examined glycated hemoglobin (HbA_{1c}) with respect to risk of dementia, three small experimental studies and one population study have examined the association between HbA_{1c} and cogni-

tive functioning [90–92]. Higher levels of HbA_{1c} were negatively associated with cognitive performance on a number of tests, and other small trials have found that improved HbA_{1c} levels are associated with better cognitive performance. Gradman et al. [91] found that after 2 months of treatment with glipizide, patients experienced a decrease in HbA_{1c} and performed significantly better on tests of verbal memory. In a within-subject study design, Meneilly et al. [92] found improvement on cognitive tests after 6 months of treatment with oral hypoglycemics. Testa and Simpson [90] conducted a randomized, clinical, controlled double-blind trial of glycemic control in type 2 diabetic patients and found those in the treatment group had better subjective cognitive function. A larger population-based study found that lower levels of HbA_{1c} were associated with an increased risk of developing cognitive impairment in women both with and without diabetes [93••]. A recent study of over 200 elderly persons found that those with low levels of HbA_{1c} had a greater rate of cerebral atrophy over a 6-year period [94]. Whether effective glycemic control lowers the risk of dementia or slows progression to the onset of clinically recognized dementia remains unknown. More studies are needed that assess the role of chronic hyperglycemia on cognitive decline and risk of dementia in population-based cohorts.

Insulin and Cognition

The role of insulin in cognitive functioning and neurologic disease is complex. Given the role of insulin in the brain, disturbances in insulin and its receptors could negatively affect cognitive functioning. In fact, studies involving nondemented, nondiabetic elderly subjects have demonstrated that hyperinsulinemia is associated with accelerated cognitive decline [18,95], even after accounting for cardiovascular disease and glucose levels. Two population-based studies among elderly participants without dementia have been conducted. One study of elderly men in the Netherlands found that those with insulin levels in the upper quartile had lower scores on the Mini-Mental Status Exam [95]. Another Finnish population-based study found that among subjects with hypertension, those with hyperinsulinemia had impaired cognitive function [96]. In contrast to this association between hyperinsulinemia and impaired cognitive functioning, two experimental studies have shown opposite results. A small experimental study in younger, healthy male subjects involved administration of exogenous insulin, auditory evoked brain potentials, and cognitive functioning tests, including short-term memory word recall and selective attention [97]. This within-subject study design demonstrated that when normal subjects had high insulin they performed better on both cognitive measures (selective attention test and word recall) and had a slower negative shift in auditory evoked brain potentials over the frontal cortex. The second study involving administration of exogenous

insulin, while keeping blood glucose at fasting levels, demonstrated enhanced memory function in those subjects both with and without AD [98]. Inconsistencies between larger population-based studies and small experimental studies may be due to the difference between normal insulin levels and the acute benefit of increased insulin in an experimental setting versus long-term high levels of insulin, which may reflect insulin resistance and be more likely to cause long term damage.

It is unknown whether chronic hyperinsulinemia itself is a causal factor in cognitive decline or if it is reflective of a compensatory mechanism for reduced insulin uptake or insulin resistance in the brain. Findings from animal models suggest that insulin has a major role in feeding behavior, learning, and memory [8,9]. Moreover, a number of studies have found that insulin may modulate spatial memory. Animal experiments involving rats trained in a water maze have shown that insulin receptor mRNA is upregulated in the CA₁ region of the hippocampus, a region critical for spatial memory. Spatial training causes a series of changes in the insulin receptors of the hippocampus, including insulin receptor gene expression, protein translocation, and tyrosine phosphorylation. Another animal model involving induced diabetes via administration of streptozotocin, a compound that impairs production and secretion of insulin from beta cells in the pancreas, shows that there are severe deficits in spatial learning and memory on a water maze task [99,100]. Moreover, administration of insulin given at the onset of the induced diabetes prevented the spatial learning and memory impairment [101]. These findings are intriguing and perhaps future human research will involve brain imaging studies and insulin administration to determine if insulin in humans also impacts spatial memory. The role of insulin on cognitive functioning in those both with and without diabetes is an area of research that needs to be further understood.

Inflammatory Cytokines: A Factor Common to Both Diabetes and Dementia

Inflammatory markers, including C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), tumor necrosis factor (TNF)- α 1, and plasminogen activator inhibitor-1 (PAI-1), are elevated in patients with type 2 diabetes. Inflammation may be a consequence of having type 2 diabetes, but it could also contribute to the development of type 2 diabetes. Longitudinal studies have shown that inflammatory factors predict incident type 2 diabetes in adults. Festa et al. [102] found that PAI-1, CRP, and fibrinogen levels at baseline were associated with an increased risk of type 2 diabetes over a 5-year period. Work from the Cardiovascular Health Study found that CRP was associated with an increased risk of type 2 diabetes over a 3- to 4-year period [103]. Pradhan et al. [104] have found that elevated levels of IL-6 and CRP are associated with the development of ath-

erosclerosis and type 2 diabetes among individuals with no prior evidence of insulin resistance. There is also evidence that inflammation is associated with insulin resistance among those without diabetes. Festa et al. [105] found that CRP, fibrinogen, and leukocyte count are associated with insulin sensitivity, blood pressure, and body mass index in nondiabetic adults without coronary artery disease.

Although there have been several observational studies of anti-inflammatory agents and risk of dementia, there has been less work on the role of inflammatory agents and risk of dementia prospectively. In a cohort study of Japanese-American men, higher levels of CRP measured at mid-life were associated with an increased risk of incident dementia, vascular dementia, and AD [106]. Another study using a cross-sectional design has found that among centenarians, those with dementia and atherosclerosis have higher levels of plasma TNF, IL-6, and CRP.

Although the evidence for the role of inflammation within neurologic disease is well documented, the role of inflammation on cognitive functioning among nondemented elderly people is less understood. A handful of animal studies have demonstrated an association between inflammatory markers and cognitive performance [107]. One human prospective study found an association between high tertiles of plasma IL-6 and an increased risk of cognitive decline over a 7-year period in a cohort of high-functioning elderly people without dementia [108]. Similarly, Yaffe et al. [109] found that high levels of both IL-6 and CRP were associated with risk of cognitive decline, using one global measure of cognition, in a community-dwelling cohort of elderly people. These findings are intriguing and suggest a role of plasma IL-6 and CRP on cognitive functioning. The role of inflammation on cognitive functioning and risk of dementia among people with and without type 2 diabetes is an area of research that warrants further study. One study found that those with both metabolic syndrome and high levels of inflammation have the greatest cognitive decline [110], suggesting these factors may act synergistically in impacting cognition. Because inflammation may be a risk factor or indicator of impending diabetes and/or insulin resistance, it may act in concert with glucose metabolism to impact cognitive functioning and risk of neurologic disease.

Future Directions

Current gaps in our knowledge include 1) characterizing associations in more diverse cohorts, particularly in minority populations that have a greater prevalence of diabetes; 2) identifying mitigating risk factors among those who already have diabetes, including the effect of blood sugar control (HbA_{1c}), duration of diabetes, diabetes treatment including medications, and co-morbidities, on risk of dementia and cognitive impairment; 3) demonstrating associations in population studies between precursors to diabetes, such as impaired fasting glucose, and insulin

resistance, on cognitive functioning and risk of cognitive impairment and dementia; 4) understanding whether the effect of glycemia and insulinemia on cognition is domain specific; 5) delineating the possible differential role of microvascular versus macrovascular risk factors on development of subtypes of dementia; and 6) examining the short-term and long-term effects of diabetes on brain morphology and neurodegenerative changes.

Conclusions

There is compelling evidence that cognitive impairment and/or dementia are potential complications of diabetes. This evidence includes the following: 1) prospective population studies showing diabetic patients are at a greater risk for all-cause dementia, AD, vascular dementia, cognitive impairment, and neurodegenerative changes; 2) population studies showing that those with diabetes have poorer cognitive performance, particularly in verbal memory and complex information processing; 3) diabetic patients receiving insulin are at the highest risk for dementia, suggesting a dose-response effect of diabetes on dementia through severity and duration of diabetes; 4) diabetic patients on combination therapy have less cognitive decline than those on monotherapy; 5) studies showing continuous relationships of levels of insulin, glucose, and glycated hemoglobin with cognitive performance, even among those without diabetes; 6) strong evidence of biologic plausibility from animal models that demonstrates induced diabetes is associated with widespread damage in the hippocampus, including decreased synaptic plasticity (which is reversible with improved glycemic control, suggesting that in humans treatment could be a mitigating factor), decreased neuronal density, and pre- and post-synaptic neuronal damage; and 7) human studies involving postmortem neuropathology and in vivo brain imaging also show greater AD-related neurodegeneration in those with diabetes.

Acknowledgment

Funding for this project is from the National Institutes of Health, Grant Number DK066308.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. World Health Organization: *Report of the Expert Committee on Diabetes*. Geneva, Switzerland; 1980. Report No.: 646.
2. Resnick HE, Harris MI, Brock DB, Harris TB: **American Diabetes Association diabetes diagnostic criteria, advancing age, and cardiovascular disease risk profiles: results from the Third National Health and Nutrition Examination Survey**. *Diabetes Care* 2000, **23**:176–180.

3. Narayan KM, Gregg EW, Fagot-Campagna A, et al.: **Diabetes: a common, growing, serious, costly, and potentially preventable public health problem**. *Diabetes Res Clin Pract* 2000, **50**(Suppl 2):77–84.
4. Zimmet P: **The burden of type 2 diabetes: Are we doing enough?** *Diabetes Metab* 2003, **29**:6S9–18.
5. Harris MI, Flegal KM, Cowie CC, et al.: **Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994**. *Diabetes Care* 1998, **21**:518–524.
6. Hebert LE, Beckett LA, Scherr PA, Evans DA: **Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050**. *Alzheimer Dis Assoc Disord* 2001, **15**:169–173.
7. Schulingkamp RJ, Pagano TC, Hung D, Raffa RB: **Insulin receptors and insulin action in the brain: review and clinical implications**. *Neurosci Biobehav Rev* 2000, **24**:855–872.
8. Zhao W, Chen H, Xu H, et al.: **Brain insulin receptors and spatial memory. Correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats**. *J Biol Chem* 1999, **274**:34893–34902.
9. Gispen WH, Biessels GJ: **Cognition and synaptic plasticity in diabetes mellitus**. *Trends Neurosci* 2000, **23**:542–549.
10. Zhao WQ, Alkon DL: **Role of insulin and insulin receptor in learning and memory**. *Mol Cell Endocrinol* 2001, **177**:125–134.
11. Zhao WQ, Chen H, Quon MJ, Alkon DL: **Insulin and the insulin receptor in experimental models of learning and memory**. *Eur J Pharmacol* 2004, **490**:71–81.
12. Frolich L, Blum-Degen D, Bernstein HG, et al.: **Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease**. *J Neural Transm* 1998, **105**:423–438.
13. Hoyer S: **Is sporadic Alzheimer disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis**. *J Neural Transm* 1998, **105**:415–422.
14. Edland SD: **Insulin-degrading enzyme, apolipoprotein E, and Alzheimer's disease**. *J Mol Neurosci* 2004, **23**:213–217.
15. Farris W, Mansourian S, Chang Y, et al.: **Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo**. *Proc Natl Acad Sci U S A* 2003, **100**:4162–4167.
16. Farris W, Leissring MA, Hemming ML, et al.: **Alternative splicing of human insulin-degrading enzyme yields a novel isoform with a decreased ability to degrade insulin and amyloid beta-protein**. *Biochemistry* 2005, **44**:6513–6525.
17. Blomqvist ME, Chalmers K, Andreassen N, et al.: **Sequence variants of IDE are associated with the extent of beta-amyloid deposition in the Alzheimer's disease brain**. *Neurobiol Aging* 2005, **26**:795–802.
18. Vanhanen M, Soininen H: **Glucose intolerance, cognitive impairment and Alzheimer's disease**. *Curr Opin Neurol* 1998, **11**:673–677.
19. Watson GS, Peskind ER, Asthana S, et al.: **Insulin increases CSF Abeta42 levels in normal older adults**. *Neurology* 2003, **60**:1899–1903.
20. Watson GS, Craft S: **The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment**. *CNS Drugs* 2003, **17**:27–45.
21. Craft S, Peskind E, Schwartz MW, et al.: **Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease: relationship to severity of dementia and apolipoprotein E genotype**. *Neurology* 1998, **50**:164–168.
22. Craft S, Watson GS: **Insulin and neurodegenerative disease: shared and specific mechanisms**. *Lancet Neurol* 2004, **3**:169–178.
23. Ott A, Stolk RP, Hofman A, et al.: **Association of diabetes mellitus and dementia: the Rotterdam Study**. *Diabetologia* 1996, **39**:1392–1397.

24. Ott A, Stolk RP, van Harskamp F, et al.: Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999, 53:1937-1942.
25. Munch G, Schinzel R, Loske C, et al.: Alzheimer's disease: synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. *J Neural Transm* 1998, 105:439-461.
26. Brownlee M: Advanced protein glycosylation in diabetes and aging. *Annu Rev Med* 1995, 46:223-234.
27. Brownlee M: Negative consequences of glycation. *Metabolism* 2000, 49(2 Suppl 1):9-13.
28. Singh R, Barden A, Mori T, Beilin L: Advanced glycation end-products: a review. *Diabetologia* 2001, 44:129-146.
29. Heitner J, Dickson D: Diabetics do not have increased Alzheimer-type pathology compared with age-matched control subjects. A retrospective postmortem immunocytochemical and histofluorescent study. *Neurology* 1997, 49:1306-1311.
30. Peila R, Rodriguez BL, Launer LJ: Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes* 2002, 51:1256-1562.
31. Schmidt R, Launer LJ, Nilsson LG, et al.: Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) Study. *Diabetes* 2004, 53:687-692.
32. Biessels GJ, Kappelle AC, Bravenboer B, et al.: Cerebral function in diabetes mellitus. *Diabetologia* 1994, 37:643-650.
33. Kamal A, Biessels GJ, Urban IJ, Gispen WH: Hippocampal synaptic plasticity in streptozotocin-diabetic rats: impairment of long-term potentiation and facilitation of long-term depression. *Neuroscience* 1999, 90:737-745.
34. Magarinos AM, McEwen BS: Experimental diabetes in rats causes hippocampal dendritic and synaptic reorganization and increased glucocorticoid reactivity to stress. *Proc Natl Acad Sci U S A* 2000, 97:11056-11061.
35. Li ZG, Zhang W, Grunberger G, Sima AA: Hippocampal neuronal apoptosis in type 1 diabetes. *Brain Res* 2002, 946:221-231.
36. Whitmer RA, Sidney S, Selby J, et al.: Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005, 64:277-281.
37. Bruce DG, Harrington N, Davis WA, Davis TM: Dementia and its associations in type 2 diabetes mellitus: the Fremantle Diabetes Study. *Diabetes Res Clin Pract* 2001, 53:165-172.
38. Curb JD, Rodriguez BL, Abbott RD, et al.: Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. *Neurology* 1999, 52:971-975.
39. Leibson CL, Rocca WA, Hanson VA, et al.: The risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Ann N Y Acad Sci* 1997, 826:422-427.
40. Luchsinger JA, Tang MX, Stern Y, et al.: Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 2001, 154:635-641.
41. Macknight C, Rockwood K, Awalt E, McDowell I: Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dement Geriatr Cogn Disord* 2002, 14:77-83.
42. Curb JD, Rodriguez BL, Abbott RD, et al.: Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. *Neurology* 1999, 52:971-975.
43. Hassing LB, Johansson B, Nilsson SE, et al.: Diabetes mellitus is a risk factor for vascular dementia, but not for Alzheimer's disease: a population-based study of the oldest old. *Int Psychogeriatr* 2002, 14:239-248.
44. Ott A, Stolk RP, Hofman A, et al.: Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia* 1996, 39:1392-1397.
45. Brayne C, Gill C, Huppert FA, et al.: Vascular risks and incident dementia: results from a cohort study of the very old. *Dement Geriatr Cogn Disord* 1998, 9:175-180.
46. Haan MN, Shemanski L, Jagust WJ, et al.: The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA* 1999, 282:40-46.
47. Xu WL, Qiu CX, Wahlin A, et al.: Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology* 2004, 63:1181-1186.
48. Nielson KA, Nolan JH, Berchtold NC, et al.: Apolipoprotein-E genotyping of diabetic dementia patients: Is diabetes rare in Alzheimer's disease? *J Am Geriatr Soc* 1996, 44:897-904.
49. Moroney JT, Tang MX, Berglund L, et al.: Low-density lipoprotein cholesterol and the risk of dementia with stroke. *JAMA* 1999, 282:254-260.
50. Yanagisawa K: Cholesterol and pathological processes in Alzheimer's disease. *J Neurosci Res* 2002, 70:361-366.
51. Hofman A, Ott A, Breteler MM, et al.: Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* 1997, 349:151-154.
52. Frishman WH: Are antihypertensive agents protective against dementia? A review of clinical and preclinical data. *Heart Dis* 2002, 4:380-386.
53. in't Veld BA, Ruitenberg A, Hofman A, et al.: Antihypertensive drugs and incidence of dementia: the Rotterdam Study. *Neurobiol Aging* 2001, 22:407-412.
54. Skoog I, Lernfelt B, Landahl S, et al.: 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996, 347:1141-1145.
55. Tzourio C, Anderson C, Chapman N, et al.: Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003, 163:1069-1075.
56. Elias PK, Elias MF, D'Agostino RB, et al.: NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. *Diabetes Care* 1997, 20:1388-1395.
57. Hachinski V, Munoz DG: Cerebrovascular pathology in Alzheimer's disease: cause, effect or epiphenomenon? *Ann N Y Acad Sci* 1997, 826:1-6.
58. Breteler MM, Claus JJ, van Duijn CM, et al.: Epidemiology of Alzheimer's disease. *Epidemiol Rev* 1992, 14:59-82.
59. de la Torre JC, Mussivand T: Can disturbed brain microcirculation cause Alzheimer's disease? *Neurol Res* 1993, 15:146-153.
60. Wong TY, Klein R, Sharrett AR, et al.: Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study. *Stroke* 2002, 33:1487-1492.
61. Merchant C, Tang MX, Albert S, et al.: The influence of smoking on the risk of Alzheimer's disease. *Neurology* 1999, 52:1408-1412.
62. Tyas SL, White LR, Petrovitch H, et al.: Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging* 2003, 24:589-596.
63. Mooradian AD: Central nervous system complications of diabetes mellitus: a perspective from the blood-brain barrier. *Brain Res Brain Res Rev* 1997, 23:210-218.
64. Hachinski V, Munoz D: Vascular factors in cognitive impairment: Where are we now? *Ann N Y Acad Sci* 2000, 903:1-5.
65. Miyakawa T, Uehara Y, Desaki J, et al.: Morphological changes of microvessels in the brain with Alzheimer's disease. *Jpn J Psychiatry Neurol* 1988, 42:819-824.
66. Kalaria RN: The blood-brain barrier and cerebral microcirculation in Alzheimer disease. *Cerebrovasc Brain Metab Rev* 1992, 4:226-260.
67. Farkas E, Luiten PG: Cerebral microvascular pathology in aging and Alzheimer's disease. *Prog Neurobiol* 2001, 64:575-611.
68. Moody DM, Brown WR, Challa VR, et al.: Cerebral microvascular alterations in aging, leukoaraiosis, and Alzheimer's disease. *Ann N Y Acad Sci* 1997, 826:103-116.

69. Kalmijn S, Feskens EJ, Launer LJ, et al.: Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995, 38:1096–1102.
70. Kalmijn S, Feskens EJ, Launer LJ, Kromhout D: Cerebrovascular disease, the apolipoprotein e4 allele, and cognitive decline in a community-based study of elderly men. *Stroke* 1996, 27:2230–2235.
71. Strachan MW, Deary IJ, Ewing FM, Frier BM: Is type II diabetes associated with an increased risk of cognitive dysfunction? A critical review of published studies. *Diabetes Care* 1997, 20:438–445.
72. Stewart R, Liolitsa D: Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabet Med* 1999, 16:93–112.
73. Yaffe K GE: Diabetes Mellitus and Cognition. In *Harrison's Principles of Internal Medicine*. Edited by Braunwald E, Fauci AS, Isselbacher KJ, et al.: New York: McGraw-Hill; 2001.
74. Gregg EW, Yaffe K, Cauley JA, et al.: Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000, 160:174–180.
75. Kanaya AM, Barrett-Connor E, Gildengorin G, Yaffe K: Change in cognitive function by glucose tolerance status in older adults: a 4-year prospective study of the Rancho Bernardo study cohort. *Arch Intern Med* 2004, 164:1327–1333.
76. Elias PK, Elias MF, D'Agostino RB, et al.: NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. *Diabetes Care* 1997, 20:1388–1395.
77. Wu JH, Haan MN, Liang J, et al.: Impact of diabetes on cognitive function among older Latinos: a population-based cohort study. *J Clin Epidemiol* 2003, 56:686–693.
78. Hassing LB, Grant MD, Hofer SM, et al.: Type 2 diabetes mellitus contributes to cognitive decline in old age: a longitudinal population-based study. *J Int Neuropsychol Soc* 2004, 10:599–607.
79. Arvanitakis Z, Wilson RS, Bienias JL, et al.: Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol* 2004, 61:661–666.
80. Yaffe K, Blackwell T, Kanaya AM, et al.: Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* 2004, 63:658–663.
81. Wu JH, Haan MN, Liang J, et al.: Impact of antidiabetic medications on physical and cognitive functioning of older Mexican Americans with diabetes mellitus: a population-based cohort study. *Ann Epidemiol* 2003, 13:369–376.
82. Logroscino G, Kang JH, Grodstein F: Prospective study of type 2 diabetes and cognitive decline in women aged 70–81 years. *BMJ* 2004, 328:5480.
83. Gavin JR: New classification and diagnostic criteria for diabetes mellitus. *Clin Cornerstone* 1998, 1:1–12.
84. Newcomer JW, Craft S, Hershey T, et al.: Glucocorticoid-induced impairment in declarative memory performance in adult humans. *J Neurosci* 1994, 14:2047–2053.
85. Messier C, Gagnon M, Knott V: Effect of glucose and peripheral glucose regulation on memory in the elderly. *Neurobiol Aging* 1997, 18:297–304.
86. Messier C, Desrochers A, Gagnon M: Effect of glucose, glucose regulation, and word imagery value on human memory. *Behav Neurosci* 1999, 113:431–438.
87. Messier C, Gagnon M: Glucose regulation and brain aging. *J Nutr Health Aging* 2000, 4:208–213.
88. Worrall GJ, Chaulk PC, Moulton N: Cognitive function and glycosylated hemoglobin in older patients with type II diabetes. *J Diabetes Complications* 1996, 10:320–324.
89. Naor M, Steingruber HJ, Westhoff K, et al.: Cognitive function in elderly non-insulin-dependent diabetic patients before and after inpatient treatment for metabolic control. *J Diabetes Complications* 1997, 11:40–46.
90. Testa MA, Simonson DC: Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* 1998, 280:1490–1496.
91. Gradman TJ, Laws A, Thompson LW, Reaven GM: Verbal learning and/or memory improves with glycemic control in older subjects with non-insulin-dependent diabetes mellitus. *J Am Geriatr Soc* 1993, 41:1305–1312.
92. Meneilly GS, Cheung E, Tessier D, et al.: The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. *J Gerontol* 1993, 48:117–121.
- 93.●● Yaffe K, Whitmer RA, Krueger K, et al.: Glycosylated hemoglobin level and development of cognitive impairment or dementia in older women. *J Nutr Health Aging* 2006, 4:293–295.
- Important study.
94. Enzinger C, Fazekas F, Matthews PM, et al.: Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology* 2005, 64:1704–1711.
95. Kalmijn S, Feskens EJ, Launer LJ, et al.: Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995, 38:1096–1102.
96. Kuusisto J, Koivisto K, Mykkanen L, et al.: Essential hypertension and cognitive function. The role of hyperinsulinemia. *Hypertension* 1993, 22:771–779.
97. Kern W, Peters A, Fruehwald-Schultes B, et al.: Improving influence of insulin on cognitive functions in humans. *Neuroendocrinology* 2001, 74:270–280.
98. Craft S, Asthana S, Newcomer JW, et al.: Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* 1999, 56:1135–1140.
99. Biessels GJ, Kamal A, Ramakers GM, et al.: Place learning and hippocampal synaptic plasticity in streptozotocin-induced diabetic rats. *Diabetes* 1996, 45:1259–1266.
100. Lannert H, Hoyer S: Intracerebroventricular administration of streptozotocin causes long-term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. *Behav Neurosci* 1998, 112:1199–1208.
101. Biessels GJ, Kamal A, Urban IJ, et al.: Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: effects of insulin treatment. *Brain Res* 1998, 800:125–135.
102. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM: Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 2002, 51:1131–1137.
103. Barzilay JI, Abraham L, Heckbert SR, et al.: The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes* 2001, 50:2384–2389.
104. Pradhan AD, Manson JE, Rifai N, et al.: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001, 286:327–334.
105. Festa A, D'Agostino R Jr, Howard G, et al.: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* 2000, 102:42–47.
106. Schmidt R, Schmidt H, Curb JD, et al.: Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol* 2002, 52:168–174.
107. Campbell IL, Abraham CR, Masliah E, et al.: Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6. *Proc Natl Acad Sci U S A* 1993, 90:10061–10065.
108. Weaver JD, Huang MH, Albert M, et al.: Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. *Neurology* 2002, 59:371–378.
109. Yaffe K, Lindquist K, Penninx BW, et al.: Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 2003, 61:76–80.
110. Yaffe K, Kanaya A, Lindquist K, et al.: The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA* 2004, 292:2237–2242.