

# Alzheimer's disease and type 2 diabetes mellitus: Risk factors and effectiveness of antidiabetic agents in treatment of Alzheimer's disease

Aye Aye Myint<sup>1,\*</sup>, Kyaw Soe Win<sup>2</sup>, Zaw Aung<sup>3</sup>

<sup>1</sup>Jeffrey Cheah School of Medicine and Health Sciences, Monash University Sunway Campus, Clinical School Johor Bahru, Johor Bahru, Malaysia

<sup>2</sup>Lashio General Hospital, Myanmar

<sup>3</sup>Faculty of Medicine and Health Sciences, UCSI University, Terengganu Campus, Terengganu, Malaysia

## Email address:

a2myintster@gmail.com(Myint A. A.), kyawsoewin2006@gmail.com(Win K. S.), za.january@gmail.com(Aung Z.)

## To cite this article:

Aye Aye Myint, Kyaw Soe Win, Zaw Aung. Alzheimer's Disease and Type 2 Diabetes Mellitus: Risk Factors and Effectiveness of Antidiabetic Agents in Treatment of Alzheimer's Disease. *Science Journal of Clinical Medicine*. Vol. 2, No. 3, 2013, pp. 114-121. doi: 10.11648/j.sjcm.20130203.20

---

**Abstract:** The aim of this review is to highlight the association between type 2 diabetes mellitus (DM) and cognitive impairment/Alzheimer's disease (AD) and provide an updated summary of the evidence related to various potentially modifiable risk factors such as hyperinsulinaemia, insulin resistance, hypo- and hyperglycaemia, vascular risk factors like hypertension and obesity, micro and macrovascular complications, depression in AD. Treating modifiable risk factors can reduce the prevalence of AD. In addition we provide the information about potential benefits of antidiabetic agents for slowing of cognitive decline and AD in patients with type 2 DM. There were studies demonstrating the novel effects of antidiabetic agents on neuronal functions by increased insulin signaling in an AD brain with a neuroprotective and neurotrophic effect. In this regard insulin, metformin and thiazolidinediones (in particular, rosiglitazone and pioglitazone) would have potential protective effect for the development of AD.

**Keywords:** Alzheimer's Disease, Anti-Diabetic Medication, Dementia, Type 2 Diabetes

---

## 1. Introduction

Alzheimer's disease is one of the most common types of dementia, comprising about 60-80% of the dementia cases. Dementia is one of the most frequent neurodegenerative disorders in the elderly due to the increasing life expectancy. According to the estimates the number of dementia patients will be raised from 24.3 million in 2001 to 81.1 million in 2040 worldwide [1,2].

Both longitudinal and cross-sectional studies have shown compelling evidence that type 2 diabetes mellitus (type 2DM) has an increased risk of cognitive impairment and dementia [3-9]. In general, the incidence of dementia in diabetes is raised by 50%-100% compared to people without diabetes. Therefore presently 1 in 10-15 cases of dementia are attributable to diabetes [10, 11].

Population based studies identified that type 2 diabetes is one of the modifiable risk factors for Alzheimer's disease (AD) and has a 1.5 to 2 fold increased risk to develop

cognitive impairment [10-17]. Among the various types of predictors the macrovascular disease is a strong predictor of dementia in diabetes. The observational studies have identified an association between type 2 DM and increased risk of cognitive impairment and dementia, Alzheimer's disease. The common pathological finding in both conditions is the deposition of significant quantities of amyloid in the brain and pancreas. They are characterized by fibrillar protein aggregates – amylin in diabetic's pancreatic islets, and  $\beta$ -Amyloid ( $A\beta$ ) and neurofibrillary tangles (NFTs) in AD brain. Amylin accumulation leads to pancreatic  $\beta$ -cell loss in cases of diabetes, and  $A\beta$  and NFT formation cause neuronal cell loss in cases of dementia. Therefore type 2DM and AD is considered as a disease with similar pathological process.

There are two forms of Alzheimer's disease; familial and sporadic forms. The autosomal dominant type, familial forms usually manifest before age 65, and 5% of cases develop AD in the fifth decade or earlier [18].

In sporadic forms, the prevalence has been found to

correlate with various environmental factors related to oxidative stress and aetiology is multifactorial. Age is being a key risk factor in which some genetic polymorphisms are known to be as predisposing factors [19].

## 2. Risk Factors for AD in Type 2 DM

Management of potentially modifiable risk factors may reduce cognitive decline in cases of type 2 diabetes with AD. AD prevention strategies would have the greatest effect on AD prevalence.

## 3. Hyperinsulinaemia and Insulin Resistance

Insulin secretion and action are two important components of glucose metabolism and the development of glucose intolerance in type 2 DM [20]. In general insulin acts as a major role in memory and brain function in patients with AD. On Brain, CNS insulin influences cognitive function by regulating neuronal functions, neurogenesis and neurotransmitter regulation. Insulin also controls levels of the beta amyloid peptide in the brain. In neuropathological studies of patients with AD showed that reduced insulin signaling may alter the normal function of brain insulin. [21-23].

Plasma insulin concentration is elevated in patients with type 2 DM because of peripheral insulin resistance. Hyperinsulinaemia is one of the predictors of memory impairment and AD [24]. Large population's studies on vascular risk factors have demonstrated that an increase in brain insulin is found to be associated with poor performances on the MMSE. Epidemiological studies of non-diabetic adults showed that high concentration of insulin in the brain was associated with poor memory performance and an increased risk of AD [26-30]. AD patients with lower concentrations of insulin in the cerebrospinal fluid may develop neuronal dysfunction [31, 32]. But the mechanism of cognitive impairment of insulin resistance and hyperinsulinaemia remains speculative [25].

## 4. Hyperglycemia

It has been postulated that chronic hyperglycemia is associated with increased speed of cognitive impairment in the elderly. Studies in human and animal models showed that even the moderate increases in glucose levels can affect cognitive function [31].

Studies in patients with type 1 diabetes suggested that chronic hyperglycemia may cause memory impairment. Cross-sectional studies in patients with type 2 diabetes also observed similar finding. The DCCT study demonstrated that cognitive function was deteriorated by cerebral microvascular disease, induced by chronic hyperglycemia [32]. One study highlighted that oxidative stress of

hyperglycemia can have a direct neurotoxic effect on brain cells [33].

Data from the Kungsholmen project showed that very old patients with uncontrolled diabetes (Hb A1C > 11 mmol/L) had the highest risk of AD and stroke independent of vascular co-morbidities [34].

## 5. Hypoglycemia

Hypoglycemia especially is a well-known complication of type 1 diabetes than type 2 DM. In hypoglycemic, if the blood glucose level is low below 3.0 mmol/L, brain cognitive function is rapidly deteriorating and it regains with normal glucose levels [35, 36]. The studies have observed that the frequency of severe hypoglycemia was not associated with poor cognitive function over the 18 year study period [32].

The Fremantle diabetes study has found that there were no significant findings of cognitive impairment by severe hypoglycemia in the older type 2 diabetic patients [37]. So far there are no data to identify the adverse effects of hypoglycemia on cognitive function in type 2 diabetic patients.

## 6. Vascular Risk Factors

One of the contributing factors for AD pathology is poor cerebral perfusion which may be accelerated by pre-existing cerebral microvascular abnormalities [38].

In the general population, the risk of dementia is increased with vascular risk factors such as hypertension, dyslipidaemia and obesity especially present at middle age [39]. In the elderly, the association between cardiovascular risk factors and cognitive impairment is generally less consistent [40, 41].

Diabetes is usually accompanied by common cardiovascular risk factors, such as hypertension, dyslipidaemia and obesity, which might harm the brain function. There is evidence that dyslipidaemia was one of the causes for poor memory function in middle-aged patients with diabetes [42]. One longitudinal study in elderly patients with diabetes observed that cognitive decline has found to be associated with higher baseline total cholesterol [43].

In addition, a cross-sectional study showed better cognitive function with the use of lipid-lowering drugs. [44]. One longitudinal study reported that poor cognitive performance in type 2 diabetic patients was related to long term exposure to hypertension [45].

Obesity is not only an important risk factor for the development of type 2 diabetes mellitus but also modifiable risk factors for AD and dementia [46]. Studies demonstrated that obesity (body-mass index  $\geq 30 \text{ kg/m}^2$ ) was an additional contributor to excess risk of all types dementias including AD [47]. Fitzpatrick et al reported that obesity in midlife was a significant increased risk factor for dementia. On the other side, there was a significant

association between obesity and a reduced dementia risk in older patients [41]. Evidence suggests that low body-mass index in the elderly appears to be associated with an increased risk of cognitive dysfunction and AD [49,50].

## 7. Micro-and Macro Vascular Complications

There is a recognized association between macro- and micro vascular disease and pathogenesis of dementia. Cerebral micro vascular disease like lacunar infarcts are frequently found in people of AD with diabetes. The mechanism of cerebrovascular disease in people with type 2 diabetes is linked with multiple metabolic and haemodynamic defects [51, 52]. Studies in patients with type 1 diabetes, advanced micro vascular disease was known to be associated with poorer cognitive performance [53-55]. However cross-sectional studies in patients with type 2 diabetes did not show a compatible association between mild micro vascular disease and cognition [56,57].

Diabetes is one of the established risk factors for atherosclerotic disease [58]. In patients with type 2 diabetes with an atherosclerotic disease was found to be associated with cognitive impairment [44,59,60]. Moreover, cognitive impairment was found in patients with stroke in diabetes or peripheral arterial disease. [43, 61].

Studies on cognitive function of patients with type 2 diabetes, a history of macro vascular disease and elevated HbA1c levels were the most consistent risk factors for cognitive dysfunction. Even without macro vascular disease; type 2 DM was still associated with cognitive decrements, showing that the vascular risk factors were merely affecting cognitive impairment [59, 62, 63].

## 8. Genetic Factors

### ApoE

ApoE-ε4 is associated with an increased risk for cognitive impairment and AD. The Cardiovascular Health Study showed that subjects with any ApoE-ε4 allele with DM have an increased risk of cognitive decline than those without the ApoE-ε4 allele [64].

The studies provided evidence that type 2 diabetes with ApoE-ε4 allele had a higher risk of cognitive decline or dementia [65,66]. Another factor, insulin-degrading enzyme is indicated to intervene the connection between type 2 diabetes and Alzheimer's disease [67]. Insulin-degrading enzyme breakdowns insulin and amyloid-β, the main component of amyloid plaques deposited in the brain of patients with AD. The risk of type 2 diabetes and AD was higher in the conditions with changes the insulin-degrading enzyme [68, 69].

## 9. Depression

Depression is a recognized risk factor for cognitive

impairment in patients with diabetes. Patients with type 2 diabetes have a higher rate of depression, compared to non-diabetic persons [70]. The proportion of depressive cases was 31% in the patients with type 2 diabetes and a major depressive disorder was comprised of a 11%. [61]. The relationship of type 2 diabetes and depression is merely understood. It is postulated that depression is due to dysfunction of neurotransmitters resulting from metabolic changes of type 2 DM [71]. Besides that, depression might result from cerebro vascular disease in the brain [72,73]. Moreover, the relation between diabetes and depression may be bidirectional as type 2 diabetes may develop from depression [74].

## 10. Others

### Inflammation

The inflammatory process is involved in the development of macro vascular disease, one of the risk factors for AD in patients with type 2 diabetes. Studies showed that there was an association between systemic inflammatory marker-reactive protein and increased risk of AD [75, 76]. As an evidence; inflammatory cytokine IL-6 is present in senile plaques in AD patients [77].

Insulin resistance, a main feature of type 2 diabetes is associated with elevated levels of the inflammatory markers like interleukin-6, C-reactive protein and Alpha-1 antichymotrypsin [77, 78]. Raised inflammatory markers in type 2 DM correlates with an increased risk of cognitive decline and or dementia [26].

## 11. Treatment of Cognitive Impairment & AD in Type 2 DM

To date there is no effective and curative therapy for poor cognitive function in type 2 DM. However, there are studies revealed that modest cognitive decline in patients with type 2 DM were partially reversible with improvement of glycemic control, but that concept is still uncertain [79].

## 12. Glycemic Control on Cognitive Function

Intensive diabetic therapy vs conventional diabetes therapy

The DCCT trial indicated that there was no evidence of differences in cognitive improvement between patients with type 1 diabetes on conventional treatment and those with intensive treatment [32].

The studies, (UKPDS 1999 and ADVANCE) were designed to compare the effect of intensive inpatient glycemic treatment with standard treatment on cognitive function in patients with type 2 diabetes. Both studies showed that the difference between these two groups was statistically insignificant [80,81]. This finding was supported by ACCORD MIND (Memory in Diabetes)

study; a sub study of ACCORD, a randomized study to evaluate the effect of intensive glucose lowering on cognitive function in elderly type 2 diabetes. The results of this study suggested that there was no significant effect on cognitive function by intensive glycemic control [80-82].

## 13. Role of Antidiabetic Agents in Alzheimer's Disease

### 13.1. Clinical Trials of Antidiabetic Agents in Alzheimer's Patients

There is some evidence that antidiabetic agents have potential benefits in treating Alzheimer's disease (AD). Studies on the effect of antidiabetic agents such as intranasal insulin, rosiglitazone (RSG), pioglitazone (PGZ), and metformin in non-diabetic AD patients have shown a possible pathophysiological association between diabetes and AD.

Following trials have been done to evaluate the potential benefits of antidiabetic drugs in Alzheimer's patients.

### 13.2. Peroxisome Proliferator-Activated Receptor- $\gamma$ (Pparg) Agonists

The studies concluded that glitazone activates PPAR that decreases plasma glucose by (1) directly intensify insulin-mediated glucose up-take in skeletal muscle, (2) directly suppressing hepatic glucose production and (3) indirectly by transcriptional up regulation of adiponectin expression in adipose tissue. In addition, it acts on PPAR-gamma receptors in the brain, anti inflammatory, neuroprotective and neurotropic effect of rosiglitazone could be a potential mechanism of action in treating AD. Peroxisome proliferator-activated receptor- $\gamma$  is a key neuromodulator found in increased amounts in the brain of AD patients. Peroxisome proliferator-activated receptor- $\gamma$  plays various processes supposed to be considered the pathogenesis of both diabetes and AD. Thiazolidinediones (in particular, rosiglitazone and pioglitazone) diminish cerebral inflammation through inhibition of IL-6 and tumor necrosis factor. Such actions create a theory to regulate the rapid growth of  $\beta$ -amyloid peptide and enhance cognitive function in AD patients [83, 84].

There were studies which demonstrated the potential benefits of PPAR  $\gamma$  agonists in patients with type 2 DM and mild cognitive impairment and/or mild to moderate AD. [85]

The results of Watson et al. [86] showed a direct relationship between insulin levels and cognitive improvement in the rosiglitazone group compared with a placebo group. Another, two recent pilot studies [87, 88] are consistent with the findings of Watson et al.

In summary, based on the studies reviewed, thiazolidinediones might aid an adjuvant therapeutic benefit in patients of AD with type 2 DM.

### 13.3. Insulin Therapy

Massimiliano et al 2009 studied effects of insulin therapy on cognitive impairment in patients with Alzheimer disease and type 2 diabetes. A total of 104 patients with type 2 DM and AD were divided into 2 groups; group A, patients assigned oral antidiabetic drugs and group B, assigned insulin combined with other oral antidiabetic agents. Cognitive function was assessed by the Mini Mental State Examination (MMSE) and the Clinician's Global Impression (CGI). The study indicated that MMSE scores showed a significant low in 56.5% patients of group A and in 23.2% patients of group B, compared to baseline MMSE scores. [89, 90]

This study suggested that insulin therapy could have benefited in decrease cognitive decline in patients with AD.

### 13.4. Intranasal Insulin

Intranasal insulin enhances brain insulin signaling in patients with AD with no effect on peripheral insulin levels. Intranasal insulin has been shown to increase CSF insulin which causes e memory improvement within a very short period of time in older adults with MCI and AD. Animal models confirm intranasal insulin makes a rapid appearance in areas important to memory, including the hippocampus. Insulin follows extracellular pathways and directly to the brain within 15 minutes. There was no risk of hypoglycemia as large amount of insulin bypassed peripherally. Two randomized placebo-controlled trials supported the beneficial effects of intranasal insulin on memory in subjects with dementia. [90, 91].

### 13.5. Metformin

Metformin is a biguanide that enhance insulin-sensitivity, increase glucose uptake, decrease hepatic glucose synthesis, activate AMP activated protein kinase (AMPK, an enzyme involved in glucose and fatty acid metabolism), and cause mitochondria inhibition.

It probably acts independently of the PPAR pathways, has a similar effect on APP/A $\beta$  metabolism. The cohort study of Chih et al showed that sulfonylureas and metformin decreases the risk of dementia in patients with diabetes by 35% over 8 years [92]. Further studies of mechanisms of metformin action could contribute to its wider use for the prevention of type 2 DM, cancer, and Alzheimer's disease. This finding has been supported by some studies to explore the potential benefits of metformin therapy on cognitive function in patients with type 2 DM [93].

### 13.6. Glucagon-Like Peptide-1 Analogue

Glucagon-like peptide-1 (GLP-1), secreted from the gastrointestinal tract lower blood glucose level by increasing insulin secretion by the pancreatic islet  $\beta$  cell proliferation. It also has neurotrophic properties through GLP-1 receptors and can reduce the amyloid- $\beta$  peptide (A $\beta$ )

in the hippocampus which is a pathological marker of AD. GLP-1 may also be important for the production of new nerve cells in the mouse brain [94].

This potential therapeutic effect of GLP-1 analogue in AD was supported by one animal (Alzheimer's mouse) study which demonstrated the neurotrophic effect of GLP-1 analogue by reducing A $\beta$  levels in the mice brain [95]

## 14. Conclusion

This review article provides the association of diabetes in the pathogenesis of AD. It highlights that management of vascular risk factors may be beneficial for preventing cognitive decline and dementia including Alzheimer's disease in persons with type 2 DM. There is no definite consensus about the value of any type of diabetic treatment to prevent cognitive impairment in people with Type 2 DM. However recent data suggest that antidiabetic agents such as intranasal insulin, rosiglitazone (RSG), pioglitazone (PGZ), and metformin could have potential benefit to promote cognitive impairment in patients with AD. This knowledge may assist to motivate researchers to make greater efforts on potential new pharmacotherapy for AD patients.

## 15. Data Sources

All the relevant articles from Medline, PubMed and Medscape were searched using the key terms Alzheimer's disease, dementia, antidiabetic agents and type 2 DM.

## Acknowledgments

The special thanks go to my helpful supervisor, Prof. Dato Dr. Khalid Bin Abdul Kadir for proof reading this report. The authors of this report would like to extend our sincere acknowledgement to all the Library staffs from Clinical School Johor Bahru especially to Zubaidah Binti Abd Rahman, Farah Raihana Binti Mohd Yasin, Mohd Azrul Azwan Ngahat, Norhidayah Binti Jamiaan for assistance with literature resources.

## References

- [1] Ferri CP, Prince M, Brayne C, et al. Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. *Lancet*. 2005;366:2112–7.
- [2] Alzheimer's Association. 2010 Alzheimer's disease facts and figures. *Alzheimers Dement* 2010; 6: 158–94.
- [3] E Duron and Olivier Hanon. Vascular risk factors, cognitive decline, and dementia. *Vasc Health Risk Manag*. 2008 April; 4 (2): 363–381.
- [4] Allen KV, Frier BM, Strachan MW. The relationship between type 2 diabetes and cognitive dysfunction: longitudinal studies and their methodological limitations. *Eur J Pharmacol*. 2004;490:169–75.
- [5] Curb JD, Rodriguez BL, Abbott RD, et al. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. *Neurology*. 1999;52:971–5.
- [6] Peila R, Rodriguez BL, Launer LJ, Honolulu-Asia Aging Study Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes*. 2002;51:1256–62.
- [7] Yamada M, Kasagi F, Sasaki H, et al. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. *J Am Geriatr Soc*. 2003;51:410–4.
- [8] Schnaider Beerli M, Goldbourt U, Silverman JM, et al. Diabetes mellitus in midlife and the risk of dementia three decades later. *Neurology*. 2004;63:1902–7.
- [9] Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol*. 2006;5:64–74.
- [10] Yael D. Reijmer, Esther van den Berg, Carla Ruis. Cognitive dysfunction in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2010; 26: 507–519.
- [11] Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 2001; 154:635–641.
- [12] Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology* 2004; 63: 1882–1891.
- [13] T. Cukierman, H. C. Gerstein and J. D. Williamson. Cognitive decline and dementia in diabetes—systematic overview of prospective observational studies. 2005, Volume 48, Number 12, Pages 2460-2469.
- [14] Yos. itake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's. Disease in a defined elderly Japanese population: the Hisayama Study. *Neurology* 1995; 45: 1161–1168
- [15] Ott A, Stolk RP, van Harskamp F, Pols HA, et al. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999; 53: 1937–1942.
- [16] 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: 1256–1262.
- [17] XuWL, Qiu CX, 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. XuWL,
- [18] Thomas J, Steven T, et al. Clinical manifestations and diagnosis of Alzheimer disease: *J Neurology and psychiatry*; September 2010.
- [19] Kua EH. The prevalence of dementia in elderly Chinese. *Acta Psychiatr Scand* 1991; 83: 350-352.
- [20] E. Rönnekaa, B. Zethelius, J. Sundelöf, et al. Glucose metabolism and risk of Alzheimer's disease and dementia: a population-based 12 year follow-up study in 71-year-old men: 2009, Volume 52. Number 8, Pages 15
- [21] Neumann KF, Rojo L, Navarrete LP, et al. Insulin resistance and Alzheimer's disease: molecular links and clinical

- implications. *Curr Alzheimer Res* 2008 (5): 438–447.
- [22] De Felice FG, Vieira MN, Bomfim TR et al .Protection of synapses against Alzheimer's-linked toxins: Insulin signalling prevents the pathogenic binding of A (beta) oligomers. *Proc Natl Acad Sci U S A* 10:1971–1976.
- [23] Araki A. Dementia and insulin resistance in patients with diabetes mellitus. *Nihon Rinsho*.2010 Mar; 68 (3): 569-74.
- [24] Hsueh, W. Genetic discoveries as the basis of personalized therapy: rosiglitazone treatment of Alzheimer's disease : *The Pharmacogenomics Journal*6. 4 (Jul 2006): 222-4.
- [25] Pasquier F , Boulogne A , Leys D , Fontaine P. Diabetes mellitus and dementia.*Diabetes Metab* 2006;32:403.
- [26] Mark W. J. Strachan, Rebecca M. Reynolds, Brian M. Frier, The relationship between type 2 diabetes and dementia.*Br Med Bull* (2008) 88 (1): 131-146.
- [27] Strachan MWJ.. Insulin and cognitive function. *Lancet* 2003;362. 1253 (letter).
- [28] Kuusisto J, Koivisto K, Mykkanen L, et al. Essential hypertension and cognitive function. The role of hyperinsulinemia. *Hypertension*. 1993;22:771-779.
- [29] Almjijn S,Feskens EJM, Launer LJ, et al.Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995;38:1096-1102.
- [30] Stolk RP, Breteler MMB, Ott A, et al. Insulin and cognitive function in an elderly population. *The Rotterdam study. Diabetes Care* 1997;20:792-795.
- [31] Gold PE. Role of glucose in regulating the brain and cognition. *Am J Clin Nutr* 1995;61:987S-95S.
- [32] The Diabetes Control and Complications Trial/Epidemiology of Diabetes interventions and Complications (DCCT/EDIC) Study Research Group. Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes. *New England Journal of Medicine*; 2005 vol. 353 no. 25
- [33] Kumari M, Brunner E, Fuhrer R. Minireview: mechanisms by which the metabolic syndrome and diabetes impair memory. *J Gerontol A Biol Sci Med Sci*. 2000;5: B228–32.
- [34] Xu WL, Qiu CX, Wahlin A, Winblad B, Fratiglioni L.Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Neurology*. 2004 Oct 12;63 (7): 1181-6.
- [35] Deary IJ. Symptoms of hyperglycemia and effects on mental performance and emotions. In *Hypoglycaemia in Clinical Diabetes*, (2nd edn), Frier BM, Fisher M (Eds). John Wiley & Sons: Chichester, 2007; 25.
- [36] Warren RE, Frier BM. Hypoglycemia and cognitive function. *Diabetes Obes Metab* 2005; 7: 493–503.
- [37] Bruce DG, Davis WA, Casey GP, et al. Severe hypoglycemia and cognitive impairment in older patients with diabetes: The Fremantle Diabetes Study. *Diabetologia* 2009; 52: 1808–1815.
- [38] Snowdon DA, Greiner LH,et al. Brain infarction and the clinical expression of Alzheimer's disease. The Nun Study. *J Am Med Assoc* 1997;277:813-7.
- [39] Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *Eur J Pharmacol* 2008; 585: 97–108.
- [40] Gustafson D. A life course of adiposity and dementia. *Eur J Pharmacol* 2008; 585: 163–175.
- [41] Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; 347: 1141–1145.
- [42] Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle aged and elderly individuals with type 2 diabetes mellitus. *Brain Res* 2009; 1280: 186–194.
- [43] Bruce DG, Davis WA, Casey GP, et al. Predictors of cognitive impairment and dementia in older people with diabetes. *Diabetologia* 2008; 51: 241–248.
- [44] Manschot SM, Biessels GJ, de Valk HW, et al. Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia* 2007; 50: 2388–2397.
- [45] van den Berg E, Dekker JM, Nijpels G, et al. Blood pressure levels in pre-diabetic stages are associated with worse cognitive functioning in patients with type 2 diabetes. *Diabetes MetabRes Rev* 2009; 25: 657–664.
- [46] Goodpaster BH, Krishnaswami S, Harris TB, Katsiaras A,Kritchevsky SB, Simonsick EM,et al.Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. *Arch Intern Med* 2005; 165: 777–83.
- [47] Beydoun MA, Lhotsky A,Wang Y, Dal Forno G, An Y,Metter EJ, Ferrucci L, et al. AB. An association of adiposity status and changes in early mid-adulthood with incidence of Alzheimer's disease. *Am J Epidemiol* 2008; 168: 1179–89.
- [48] Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 2009; 66: 336–42.
- [49] Dahl AK, Lopponen M, Isoaho R, Berg S, Kivela SL. Overweight and obesity in old age are not associated with greater dementia risk. *J Am Geriatr Soc* 2008; 56: 2261–66
- [50] Knopman DS, Edland SD, Cha RH, Petersen RC, Rocca WA. Incident dementia in women is preceded by weight loss by at least a decade. *Neurology* 2007; 69: 739–46.
- [51] Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol* 2006; 5: 64–74.
- [52] Iehuis AM, van der Graaf Y, Visseren FL, et al. . Diabetes increases atrophy and vascular lesions on brain MRI in patients with symptomatic arterial disease. *Stroke* 2008;39:1600-1603.
- [53] Ferguson SC, Blane A, Perros P, et al. Cognitive ability and brain structure in type 1 diabetes: relation to microangiopathy and preceding severe hypoglycemia. *Diabetes* 2003; 52:149–156.
- [54] Ryan CM, Geckle MO, Orchard TJ. Cognitive efficiency declines over time in adults with Type 1 diabetes: effects of

- micro- and macrovascular complications. *Diabetologia* 2003;46: 940–948.
- [55] Wessels AM, Rombouts SA, Remijnse PL, *et al.* Cognitive performance in type 1 diabetes patients is associated with the cerebral white matter volume. *Diabetologia* 2007; 50: 1763–1769.
- [56] De Luis DA, Fernandez N, Arranz M, Aller R, Izaola O. Total homocysteine and cognitive deterioration in people with type 2 diabetes. *Diabetes Res Clin Pract* 2002; 55: 185–190.
- [57] Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002; 287: 2570–2581.
- [58] van den Berg E, de Craen AJ, Biessels GJ, Gussekloo J, Westendorp RG. The impact of diabetes mellitus on cognitive decline in the oldest of the old: a prospective population-based study. *Diabetologia* 2006; 49: 2015–2023.
- [59] Umegaki H, Iimuro S, Kaneko T, *et al.* Factors associated with lower Mini Mental State Examination scores in elderly Japanese diabetes mellitus patients. *Neurobiol Aging* 2008; 29:1022–1026.
- [60] Brands AMA, van den Berg E, Manschot SM, *et al.* A detailed profile of cognitive dysfunction and its relation to psychological distress in patients with type 2 diabetes mellitus. *J Int Neuropsychol Soc* 2007; 13: 288–297.
- [61] van den Berg E, Dekker JM, Nijpels G, *et al.* Cognitive functioning in elderly persons with type 2 diabetes and metabolic syndrome: the Hoorn study. *Dement Geriatr Cogn Disord* 2008; 26: 261–269.
- [62] Kalmijn S, Feskens EJM, Launer LJ, Kromhout D. Cerebrovascular disease, the apolipoprotein ε4 allele, and cognitive decline in a community-based study of elderly men. *Stroke* 1996;27:2230-5.
- [63] HaanMN, Shemanski L, JagustWJ, *et al.* The role of APOE epsilon4 in modulating the effects of other risk factors for cognitive decline in elderly persons. *JAMA* 1999;282: 40–46.
- [64] Blair CK, Folsom AR, Knopman DS, *et al.* APOE genotype and cognitive decline in a middle-aged cohort. *Neurology* 2005; 64: 268–276.
- [65] Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiol Aging* 2006; 27: 190–198.
- [66] Edland SD, Wavrant-De-Vriese F, Compton D, *et al.* Insulin degrading enzyme (IDE) genetic variants and risk of Alzheimer's disease: evidence of effect modification by apolipoprotein E (APOE). *Neurosci Lett* 2003; 345: 21–24.
- [67] Edland SD. Insulin-degrading enzyme, apolipoprotein E, and Alzheimer's disease. *J Mol Neurosci* 2004; 23: 213–217.
- [68] Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 2001; 24: 1069–1078.
- [69] Krabbe KS, Nielsen AR, Krogh-Madsen R, *et al.* Brain-derived neurotrophic factor (BDNF) and type 2 diabetes. *Diabetologia* 2007; 50: 431–438.
- [70] Baldwin RC, O'Brien J. Vascular basis of late-onset depressive disorder. *Br J Psychiatry* 2002; 180: 157–160.
- [71] Bruce DG, Casey G, Davis WA, *et al.* Vascular depression in older people with diabetes. *Diabetologia* 2006; 49: 2828–2836
- [72] Knol MJ, Twisk JWR, Beekman ATF, *et al.* Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia* 2006; 49:837–845
- [73] Schmidt R, Schmidt H, Curb JD, Masaki K, *et al.* Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. *Ann Neurol* 2002; 52: 168–74.
- [74] Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, *et al.* Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch Neurol* 2004; 61: 668–72.
- [75] Hak AE, Pols HA, Stehouwer CD, Meijer J, *et al.* Markers of inflammation and cellular adhesion molecules in relation to insulin resistance in nondiabetic elderly: the Rotterdam study. *J Clin Endocrinol Metab* 2001; 86: 4398–405.
- [76] Hotamisligil GS. Inflammatory pathways and insulin action. *Int J Obes Relat Metab Disord* 2003; 27 (Suppl. 3): S53–5.
- [77] Columbia University, Institute for the Study of Aging, National Institute on Aging. Metformin in amnesic mild cognitive impairment (MCI). Available at top: //clinical trials. Gov/ct2/show/NCT00620191 (last accessed 19 August 2010).
- [78] Killick R, Scales G, Leroy K, Causevic M, *et al.* Deletion of *Irs2* reduces amyloid deposition and rescues behavioral deficits in APP transgenic mice. *Biochem Biophys Res Comm* 2009; 386: 257–62.
- [79] Paromita King, Ian Peacock, Richard Donnelly. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol.* 1999 November; 48 (5): 643–648.
- [80] UK Prospective Diabetes Study Group. Quality of life in type 2 diabetic patient patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control. *Diabetes care* 1999;22(7):1125-36.
- [81] A. P. Kengne, A. Patel, S. Colagiuri, S. Heller and P. Hamet, *et al.* The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular event. in a large ethnically diverse sample of patients with diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation (ADVANCE) Study. 2010, Volume 53, Number 5, Pages 821-831.
- [82] Williamson JD, Miller ME, Bryan RN, Lazar RM, Coker LH, Johnson J, Cukierman T. *et al.* The Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes Study (ACCORD-MIND): rationale, design, and methods. ACCORD Study Group. *Am J Cardiol.* 2007 Jun 18;99 (12A): 112i-122i.
- [83] Takashi Sakurai, MD, PhD. Targets of the Peroxisome Proliferator-Activated Receptor  $\alpha$  Agonist Trials for the Prevention of Alzheimer Disease. *Arch Neurol/VOL 68 (NO. 4), APR 2011; Pg 542*
- [84] Luis Escribano, Ana-María Simón, Alberto Pérez-Mediavilla, Pablo Salazar-Colocho, Joaquín Del Río, Diana Frechilla. Rosiglitazone reverses memory decline and hippocampal glucocorticoid receptor down-regulation in an Alzheimer's disease mouse model: Biochemical and

Biophysical Research Communications 379 (2009) 406–410

- [85] C. Harrington, S. Sawchak, C. Chiang, J. Davies, C. Donovan, A.M. Saunders, *et al.* Rosiglitazone Does Not Improve Cognition or Global Function when Used as Adjunctive Therapy to AChE Inhibitors in Mild-to-Moderate Alzheimer's Disease: Two Phase 3 Studies: *Current Alzheimer Research*, 2011, 8, 592-606
- [86] Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, *et al.* Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry* 2005; 13:950–8
- [87] Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. *Neurobiol Aging* in press
- [88] Hanyu H, Sato T, Kiuchi A, Sakurai H, Iwamoto T. Pioglitazone improved cognition in a pilot study in patients with Alzheimer's disease and mild cognitive impairment with diabetes mellitus. *J Am Geriatr Soc* 2009;57: 177–9
- [89] Massimiliano Plastino , Antonietta Fava , Domenico Pirritano , Piero Cotronei , Natalina Sacco , Teresa Sperli , *et al.* Effects of insulinic therapy on cognitive impairment in patients with Alzheimer disease and Diabetes Mellitus type-2; *Journal of the Neurological Sciences* 288 (2010) 112–116
- [90] Suzanne Craft, PhD; Laura D. Baker, PhD; Thomas J. Montine, MD, PhD; Satoshi Minoshima, MD, *et al.* Intranasal Insulin Therapy for Alzheimer Disease and Amnesic Mild Cognitive Impairment.: A Pilot Clinical Trial ; Author Affiliations: Geriatric Research, Education, and Clinical Center (Drs Craft, Baker, Watson, Claxton, Callaghan, and Plymate and Mr Arbuckle) and Mental Illness Research, Education, and Clinical Center (Drs Leverenz and Gerton), Veterans Affairs Puget Sound Health Care System, and Departments of Psychiatry and Behavioral Sciences (Drs Craft, Baker, Watson, Claxton, and Leverenz), Pathology (Dr Montine), Radiology (Drs Minoshima and Cross), Medicine (Drs Tsai, Plymate, and Green), and Neurology (Drs Leverenz and Gerton), University of Washington School of Medicine, Seattle, *Arch Neurol.* 2012;69(1):29-38.
- [91] Helgi B Schiöth, William H Frey .Insulin to Treat Alzheimer's Disease: *Expert Rev Clin Pharmacol.* 2012;5(1):17-20. © 2012 Expert Reviews Ltd.
- [92] Chih-Cheng Hsua, Mark L. Wahlqvist, Meei-Shyuan Leec and Hsin-Ni Tsaia. Incidence of Dementia is Increased in Type 2 Diabetes and Reduced by the Use of Sulfonylureas and Metformin. *Journal of Alzheimer's Disease* 24 (2011) 485–493.
- [93] Grzybowska M, Bober J, Olszewska M. Metformin - mechanisms of action and use for the treatment of type 2 diabetes mellitus]. *Postepy Hig Med Dosw (Online)*. 2011 May 6;65:277-85.
- [94] Luchsinger JA. Type 2 diabetes, related conditions, in relation and dementia: an opportunity for prevention? *J Alzheimers Dis.* 2010;20(3):723-36. Review.
- [95] Stephen F.J, McGovern, Kerry Hunter, Christian Hölscher. Effects of the glucagon-like polypeptide-1 analogue (Val8)GLP-1 on learning, progenitor cell proliferation and neurogenesis in the C57B/16 mouse brain. *Brain Research*, 2012;1473:204