

# Diabetes mellitus and dementia

F Pasquier<sup>1</sup>, A Boulogne<sup>2</sup>, D Leys<sup>3</sup>, P Fontaine<sup>2</sup>

## SUMMARY

Alzheimer's disease (AD) and diabetes mellitus (DM) are two of the most common and devastating health problems in the elderly. They share a number of common features amongst which high prevalence after 65 years, important impact of patient's quality of life, substantial health care costs. Reviews on the epidemiological studies on cognitive impairment in patients with DM found evidence of cross-sectional and prospective associations between type 2 DM and moderate cognitive impairment, on memory and executive functions. There is also evidence for an elevated risk of both vascular dementia and AD in patients with type 2 DM, albeit with strong interaction of other factors such as hypertension, dyslipidaemia and ApoE genotype. DM is an independent predictor of post-stroke dementia. DM being an atherogenic risk factor, it may increase the risk of dementia through associations with stroke, causing vascular dementia. In addition, vascular reactivity may be adversely affected by advanced glycosylation end products resulting in more subtle perfusion abnormalities. Cerebrovascular disease may exacerbate AD through direct interactions between the two pathological processes or through cognitive impairment secondary to cerebrovascular disease "unmasking" AD at an earlier stage than it would otherwise become apparent. The increased risk of AD may also be mediated by the exacerbation of  $\beta$ -amyloid neurotoxicity by advanced glycosylation end products identified in the matrix of neurofibrillary tangles and amyloid plaques in AD brains, or associations with insulin functions. Decreased cholinergic transport across the blood-brain barrier observed in diabetic animals may exacerbate cognitive impairment in AD. Many interventions could reduce the cognitive decline associated with DM, yet not enough are taken into account so far.

**Key-words:** Dementia · Diabetes · Alzheimer's disease · Vascular dementia · Review.

Pasquier F, Boulogne A, Leys D, Fontaine P. Diabetes mellitus and dementia  
*Diabetes Metab* 2006;32:403-414

## RÉSUMÉ

### Démences et diabète sucré

La maladie d'Alzheimer (MA) et le diabète (DM) sont deux affections chroniques fréquentes chez les sujets âgés. Elles ont toutes deux une prévalence élevée après 65 ans, un fort retentissement sur la qualité de vie des patients et ont un impact médico-économique majeur. La revue des études épidémiologiques sur les altérations cognitives des patients diabétiques suggère l'existence d'une association entre diabète de type 2 et troubles cognitifs modérés. Une telle relation existe aussi entre diabète de type 2, démence vasculaire et MA mais avec une forte influence d'autres facteurs comme l'hypertension artérielle, la dyslipémie ou le polymorphisme de l'ApoE. Le diabète est un facteur de risque indépendant de démence survenant après un accident vasculaire cérébral. Le diabète agit comme agent athérogène et entraîne des anomalies de la réactivité vasculaire par l'action des produits de la glycation avancée sur la paroi des vaisseaux. La maladie cérébro-vasculaire peut favoriser l'expression de la MA soit par interaction directe entre les deux affections, soit en démasquant plus précocement les troubles cognitifs. Le risque de MA peut aussi être médié par l'accentuation par les produits de la glycation avancée de la neurotoxicité des dépôts amyloïdes dans les cerveaux de MA. La baisse du transport cholinergique à travers la barrière hémato-cérébrale, observée chez l'animal diabétique, pourrait influencer les troubles cognitifs de la MA. Certaines interventions, insuffisamment utilisées, pourraient ralentir le déclin cognitif du sujet diabétique.

**Mots-clés:** Démence · Diabète sucré · Maladie d'Alzheimer · Démence vasculaire · Revue générale.

Address correspondence and reprint requests to:  
F Pasquier, CHRU, Clinique Neurologique, 59037 Lille Cedex, France.  
pasquier@chru-lille.fr

Received: June 15th, 2006; accepted: July 5th, 2006.

<sup>1</sup> Department of Neurology, EA 2691, Memory Clinic.

<sup>2</sup> Department of Diabetology,

<sup>3</sup> Stroke Unit, University Hospital, Lille, France.

**A**lzheimer's disease (AD) and type 2 diabetes mellitus are two of the most common and devastating health problems in the elderly. They share a number of common features [1].

The observed prevalence of diabetes mellitus (DM) in people older than 65 years living in the community is 8.5% in the PAQUID study [2]. It is 11.4% in the population aged 55 to 99 years old in the Rotterdam study [3]. The estimated annual incidence of diabetes is 8.6‰ for Canadians aged 65 years or older and decreases with age from 9.5‰ for subjects 65-74 to 3.1‰ for those 85 years of age and older [4]. Diabetes is more frequent in men than in women [2].

Age-standardized prevalence in people aged 65 and over in Europe is 6.4% for dementia (all causes), 4.4% for AD, 1.6% for vascular or so called "mixed" (degenerative + vascular) dementia, and 0.4% for other dementias [5]. The prevalence of dementia increases continuously with age and is 1.2% in the group age 65 to 69 years and 28.5% at age 90 years and older. The prevalence of AD is 0.6% (65-69 years) to 22.2% (90 years and older); the prevalence of vascular or "mixed" (degenerative + vascular) dementia is 0.3% (65-69 years) to 5.2% (90 years and older) [5]. Dementia is more prevalent in women after 80 years (after 70 years for AD, after 85 years for vascular or mixed dementia).

Both AD and DM can have an enormous impact on a patient's quality of life, and both are associated with substantial health care costs. Both have a genetic predisposition [1]. However, there may be considerable heterogeneity in the genetic factors which contribute to both of these conditions. In addition, both are underdiagnosed.

As reviewed by Stachan et al. [6], the impact of diabetes on cognitive function has been of interest for 80 years, since Miles and Root [7] showed that diabetic patients performed less well than controls on measures of memory, mental arithmetic, and psychomotor efficiency. It was suggested that both chronic hyperglycaemia and recurrent episodes of severe hypoglycaemia are associated with cognitive dysfunction in patients with type 1 (insulin-dependent) diabetes. It was also widely reported that type 2 (non-insulin-dependent) diabetes is associated with cognitive impairment, then this link was disputed [7].

The role of DM as a risk factor for cognitive decline in later life has received little epidemiological attention until recently, despite the high prevalence of diabetes (especially type 2) in older populations, the high prevalence of dementia, and several potential mechanisms, vascular or not, by which it may cause cognitive decline [8].

Reviews on the epidemiological studies on cognitive impairment in patients with DM found evidence of cross-sectional and prospective associations between type 2 DM and moderate degree of cognitive impairment, both for memory and executive functions. There is also evidence for an elevated risk of both vascular dementia and AD in

patients with type 2 DM albeit with strong interaction of other factors such as hypertension, dyslipidaemia and apolipoprotein E genotype.

## Type 2 diabetes mellitus and cognitive impairment

Most studies investigating cognitive impairment associated with type 2 DM are case-control studies and show methodological problems [6,8], including the use of different test batteries [6]. Although comorbid neurological illness is generally considered as an exclusion factor for these studies, other potential mediating factors such as physical morbidity, alcohol intake, or use of centrally acting medication are rarely addressed [6,9]. Stewart and Liolitsa [8] examined the role of hypertension and depression that are commonly associated with diabetes [2], but rarely taken into account in these studies, although hypertension is associated with cognitive impairment by itself [10] as well as depressive symptoms [11,12]. The published case-control studies showed that patients with DM tend to have a less effective attention-concentration-working memory (assessed by backward digit span or serial 7 subtraction task), slightly worse constructional abilities (assessed by block design and object assembly), decreased verbal fluency, psychomotor speed, mental flexibility and abstract reasoning than controls, but no significantly different global cognitive scores. Usually, verbal memory was impaired (immediate and delayed recall of word lists), and recognition was normal, suggesting retrieval difficulties and preserved storage. The same observation is made for visuospatial memory. Some early case-control studies which controlled the factor "hypertension" did not show any significant difference between patients with and without DM. However, one study, controlled for demographic factors within the logistic models, found that DM was a significant independent correlate of abstract reasoning deficits (OR 10.9; 95% confidence interval 2.2-54.9) and visuospatial dysfunction (OR, 3.5, confidence interval 1.2-10.7) in 249 stroke-free community volunteers (age 70.8±7 years) [13]. Very old diabetic persons performed significantly worse on tests of verbal fluency and episodic memory but this effect was less pronounced in tasks involving higher degrees of semantic structure and follow-up analyses revealed that preclinical dementia accounted for much of the observed associations [14].

Population studies show inconsistent results [8]. Prospective studies are still scarce. In a cohort of more than 1500 community-dwelling older adults tested with a comprehensive battery of memory and executive function tests, no significant differences were found between subjects with type 2 DM or impaired glucose tolerance and controls after adjustment for age, education, obesity, depression, blood pressure, and current oxygen use [15]. In the Kupio study, DM did not affect memory significantly and, in con-

trast, hyperinsulinaemia was associated with impaired verbal memory independently of the presence of dementia or diabetes [16]. DM was not associated with “cognitive impairment, or dementia” according to the definition of the Canadian Study of Health and Aging [17], or “age-related cognitive decline” according to the definition of the DSM-IV [18] in the Italian Longitudinal Study on Aging [19].

On the other hand, the Zutphen Study of community-dwelling elderly in the Netherlands found that diabetes and impaired glucose tolerance in nondiabetic subjects were associated significantly with poorer cognitive functions [20]. In a 4-year prospective study Yaffe et al. also showed that older women with impaired fasting glucose levels performed more poorly on cognitive tests than those with normal glycaemia [21]. In that mildly hyperglycaemic population the risk of developing overt cognitive impairment appeared to be intermediate between the risk of diabetic and normoglycaemic women, suggesting a continuous risk potentially linked to glycaemic level. The Melton surveys further showed that subjects with known diabetes are more likely to have a low Mini Mental Status Examination (MMSE) score than subjects with normal glucose tolerance [22]. Carmelli et al. [23] investigated prospectively the combined effect of midlife vascular risk factors (including hyperglycaemia) and ApoE4 on decline in cognitive function in a sample from a population-based registry of pairs of male veteran twins (43–53 years old). Midlife hyperglycaemia was defined as 1-hour postload glucose level >200 mg/dL or the use of a hypoglycaemic agent or insulin preparation at any one of the first three examinations. Hyperglycaemics experienced a significantly greater decline over 10 years on the Digit Symbol Substitution Test (DSS) from the Wechsler Adult Intelligence Scale-Revised [24], the Benton Visual Retention Test (BVRT) [25], and the MMSE [26] than normal subjects. Hypertensives also experience a significantly greater decline than normotensives on the DSS test, but not on the MMSE and BVRT. The effect on the DSS test was not significantly greater in subjects with both risks than expected from the separate effects combined. Decline on the BVRT was associated significantly with midlife hyperglycaemia, regardless of the subjects' hypertensive status. ApoE4 carriers with midlife hyperglycaemia experienced the greatest decline in performance on all the cognitive tests, a decline significantly greater than that expected from the separate effects of these risk factors combined. The Framingham study also showed that poor performance on delayed verbal memory was associated with a previous diagnosis of type 2 DM and diabetes duration was associated with poor performance on immediate verbal recall, delayed verbal recall and abstract reasoning [27]. These findings were independent of age, gender, education and other vascular risk factors including hypertension. However, important interactions were seen

between diabetes and blood pressure levels in examining impairment on a test of visual memory in the composite scores derived from the whole battery. Diabetes diagnosis and duration were only associated with impairment in these measures in hypertensive subjects with no association seen in the normotensive group and although blood pressure levels were still associated with a significant risk of impaired composite scores in non diabetic subjects, effects were noticeably greater in those with diabetes. Another prospective cohort of community-dwelling white women 65 years and older study showed that diabetes was associated with lower levels of cognitive function and greater cognitive decline [28]. And the presence of diabetes at baseline was associated with greater decline in scores on digit symbol subtest and first-letter word fluency test in a cohort of 10,963 subjects assessed on two occasions separated by 6 years [29]. The association of diabetes and cognitive decline was shown with multivariate analyses controlling for demographic and other vascular risk factors, and persisted when analysis was restricted to the 47–57 year old subgroup.

Frisoni et al. [30] hypothesized that different insults, either degenerative or vascular, may result in greater damage when a particular ApoE allelic variant is present. Vascular risk factors such as hyperglycaemia interact with ApoE4 to increase the risk of cognitive decline above and beyond the effect of ApoE4 alone. Recent data from the Canadian Study of Health and Aging [31] are also in favour of an association between possessing an apoE epsilon 4 allele and increased risk of developing AD from cognitive impairment. The polymorphism is also associated in the same study with a decrease in the age at onset of AD. The implication of these results is that genetic factors are important to consider when studying the effect of midlife cardiovascular risk factors on cognitive decline in the elderly. With the rapid advances being made in molecular genetics, these types of studies of the pattern of gene-environment interaction effects have the potential to contribute to new treatment modalities as well as further our understanding of cognitive decline and dementia in the elderly [23]. In addition, higher midlife glucose level was an independent predictor of greater changes in white matter hyperintensities (besides midlife lower HDL cholesterol, and midlife higher systolic blood pressure) [32]. Glucose intolerance was not related to decreased brain volume in this study. After adjustment for education and clinical stroke, twins with more white matter hyperintensities had lower scores on “memory” and “speed” summary cognitive scales, more impairment of walking and standing balance and more depression symptoms than co-twins with fewer white matter changes [33]. It has been hypothesised that white matter abnormalities due to disruption in frontal subcortical neuronal circuits may lead to impairment of frontally mediated executive tasks, including mood disorders and depression [33–35].

## Type 2 diabetes mellitus and dementia

Some case-control studies have reported a negative association between type 2 DM and AD [36-38] that suggested a possible protective effect of high glucose on the brain, but these studies have been of small size or have used referred patients with AD open to selection bias [39].

The Hisayama study, a 7 year follow up of 828 residents aged 65 and over and without dementia, found an increased risk of vascular dementia associated with a diagnosis of diabetes close to significance [40]. The Rotterdam study, the first cross-sectional population study to have used "dementia" as a variable, reported small but significant association between DM and dementia (odds ratio: 1.3, 95% confidence interval: 1.0-1.9) [3]. Diabetes was diagnosed as use of anti-diabetes medication or random or post-load serum glucose level over 11 mmol/l. In particular, strong associations were found between dementia and diabetes treated with insulin. The relation was strongest with vascular dementia, but was also observed with AD. These associations were independent of educational level, smoking, body mass index, atherosclerosis, blood pressure and antihypertensive drug treatment, and could not be explained by clinical cerebral infarctions [3]. A higher risk for AD was seen in the presence of what was felt to be unrelated cerebrovascular disease but significant risk was found in the absence of cerebrovascular disease and the adjustment for other vascular risk factors and indices of cardiovascular disease made little difference to the association. The fraction of incident dementia in this population attributable to diabetes was 8.8% [41]. The Canadian Study of Health and Aging (more than 5,500 subjects without cognitive impairment at baseline followed for 5 years) found an association between DM at baseline and incident vascular cognitive impairment (RR 1.62 [CI 1.12-2.33]) including vascular dementia (RR 2.03 [CI 1.15-3.57]) [42]. The association was not significant between DM and incident AD (RR:1.30, [CI 0.83-2.03]). However, in this epidemiological study, the etiological diagnosis of dementia is not as good as in memory clinics.

The Rochester study retrospectively examined case notes of 1455 subjects with adult onset DM followed up over a period of 9981 person-years and found an increased incidence of AD, particularly in men, compared with general population estimates [43]. Incident cases of dementia in a population aged 75 and over were associated with diabetes (OR 1.4) only if, clinically diagnosed AD was included [44]. At first, the Honolulu-Asia Aging Study, a prospective epidemiological study of 8,000 men of Japanese ancestry, did not find any association between AD and diabetes, present either 25 or 15 years previously (determined by interview), but a significant association was found between impaired glucose tolerance at baseline and vascular dementia [45]. On a population-based cohort of 2,574

Japanese-American men including 216 subjects who underwent autopsy, this Honolulu Asia Aging Study found that type 2 DM was associated with total dementia (RR 1.5 [CI 1.01-2.2]), AD (1.8 [1.1-2.9]), and vascular dementia (2.3 [1.1-5.0]) [46]. Individuals with both type 2 DM and the APOE epsilon4 allele (a risk factor for AD as well as for cardiovascular diseases) had a RR of 5.5 (CI 2.2-13.7) for AD compared with those with neither risk factor. The neuropathological data were consistent with the clinical results [46]. It is possible that severely decreased probability of survival associated with a combination of diabetes and Alzheimer's dementia relative to either of the conditions alone could have reduced the apparent association between the two factors initially. In New York, Cox proportional hazards models were used to analyse longitudinal data from 1,262 elderly subjects without dementia at baseline who were followed for an average of 4.3 years [47]. Outcomes were incident AD and dementia associated with stroke (that could have been called vascular dementia before the publication of research criteria for vascular dementia [48]). The prevalence of diabetes was 20% at baseline. The adjusted relative risk of AD amongst persons with diabetes as compared with those without diabetes was 1.3 (CI: 0.8-1.9). More significant is the conclusion of a recent prospective study including 824 participants and finding a 65% increase in the risk of developing AD (hazard ratio 1.65; CI: 1.10-2.47) in diabetic people compared to those without DM, during a mean of 5.5 years of observation in a model adjusted for age, gender and educational level [49]. In subjects with diabetes, the adjusted relative risk for the composite outcome of AD and cognitive impairment without dementia, without stroke, (close to what is called "Mild Cognitive Impairment" [50]) was 1.6 (CI: 1.2-2.1). The adjusted risk of stroke-associated dementia in persons with diabetes was 3.4 (CI: 1.7-6.9). The risk of stroke-associated dementia attributable to diabetes was 36% in Hispanics, 33% in African Americans and 17% in Caucasians [47].

Cross-sectional studies report more vascular risk factors (including DM) in vascular dementia than in AD which may be biased by the use of criteria for probable AD [51] that emphasises the exclusion of underlying disorders, particularly cerebrovascular disease. Few epidemiological studies have been conducted to identify the potential risk factors for vascular dementia, although it is generally assumed that these factors are the same as for stroke, and include hypertension, DM, advanced age, male sex, smoking and cardiac diseases [52,53].

DM is an atherogenic risk factor, with hypertension, cigarette smoking, and hypercholesterolemia. It is associated with thrombosis, myocardial infarction, and cerebrovascular disease, which can lead secondarily to infarctions and white matter ischemia. All indicators of atherosclerosis were associated with dementia (OR 1.3-1.9), AD (OR 1.3-1.8) and vascular dementia (OR 1.9-3.2) in the Rotterdam study [54]. The risk of vascular diseases in patients with type 2

DM is reduced by lowering the blood pressure of patients with hypertension [55-57], which reduces costs and improves health outcomes [58]. Antihypertensive drugs reduce the incidence of dementia by 50%, and treatments are more beneficial in patients with diabetes as compared with those without diabetes at entry [59,60]. However, treatment and control of cardiovascular risk factors are suboptimal in older population, especially amongst those with DM [61].

On the other hand, case-control studies showed that normoglycaemic patients with AD or vascular dementia had higher fasting glucose levels [62-64], and insulin levels (although not consistently in all studies) than age-matched controls. Hyperinsulinaemia in AD might be a transient phenomenon and discrepant glucose and insulin levels in responses to oral glucose tolerance test may simply reflect different stages of the disease [65]. In Carantoni et al. study [64], these parameters were adjusted for gender, body mass index, albumin level and presence of arterial hypertension. Since glucose and insulin levels are inversely related to insulin sensitivity [66], it could be added that patients with dementia are more insulin resistant than subjects without dementia. Though the pathogenetic mechanism(s) of this association are not entirely understood, some epidemiological surveys have shown that elderly patients with high insulin levels have lower cholesterol levels [67,68], which is another matter of debate in dementia.

Modest increases in glucose levels can enhance learning and memory both in rodents and in humans [69]. In a longitudinal study, Craft et al. found that patients with very mild AD showed memory facilitation and elevations in plasma insulin in the 225-mg/dl glucose condition relative to baseline; 18 months later, the patients whose dementia had progressed showed significant decreases in insulin and hyperglycaemic memory facilitation [70]. The Canadian Study of Health and Aging did not find significant differences in mean random blood glucose levels between probable AD and vascular dementia, between subjects with no cognitive loss and either severe probable AD or severe vascular dementia, or across the stages of either probable AD or vascular dementia [71].

## Post-stroke dementia

Little progress has been made in understanding when dementia will develop in persons who have had strokes [72]. Stewart and Liolitsa [8], reviewed the studies which have examined the role of diabetes in the development of dementia after stroke and found conflicting findings: some found that demented patients had significantly more diabetes [73,74], others did not [75-78], or did not look for it [79]. More recently, Desmond et al. [80] found that 26.3% of patients were demented 3 months after ischemic stroke (57% vascular dementia, 39% AD with concomitant stroke,

4% other reasons). Logistic regression suggested that dementia was associated with DM (RR 1.8). Likewise, Hénon et al. [81] found that 28.5% of patients were demented after 3 years of follow-up with most of post-stroke dementia (prestroke dementia having been excluded) occurring during the first 6 months (68% vascular dementia; 33% AD with concomitant stroke). Using multivariate analysis, independent predictors of post-stroke dementia were DM, besides ageing, preexisting cognitive decline, severity of deficit at admission, and silent infarct.

It may be that if diabetes has an effect on dementia after stroke, it is to accelerate the onset rather than increase the longer term risk. Another consideration is that raised mortality associated with stroke in the presence of diabetes may mask an association with dementia. Diabetes was associated with death (RR 1.87; 95% confidence interval 1.59-2.19) and institution entry (RR 1.58; 95% confidence interval 1.28-1.94) in the Canadian Study of Health and Aging [4]. However, in a Chinese study on 304 consecutive stroke patients, in spite of having similar glucose concentrations to those patients with stress hyperglycaemia, diabetics did not have a worse immediate and 3-month outcome compared with non diabetics [82].

## Possible mechanisms of association

In its critical review of published studies on cognitive function in diabetic patients, Strachan et al. concluded that the etiology of any cognitive decrease in type 2 DM is likely to result from an interaction between metabolic abnormalities intrinsic to diabetes, diabetes-specific complications, and other diabetes-related disorders [6]. DM being an atherogenic risk factor, it may increase the risk of dementia through well recognised associations with stroke, causing a classical vascular dementia. In addition to cerebral infarction, vascular reactivity may be adversely affected by advanced glycosylation end products resulting in more subtle perfusion abnormalities [83,84]. If cerebrovascular disease exacerbates AD, this may be through direct interactions between the two pathological processes or through cognitive impairment secondary to cerebrovascular disease "unmasking" AD at an earlier stage than it would otherwise become apparent [39,85].

## Direct effects of vascular disease on the pathology of AD

Severe coronary artery disease has been associated with increased senile plaques counts in a necropsy series of subjects without dementia [86], suggesting that the burden of Alzheimer's pathology may be increased by systemic vascular disease, possibly to a threshold beyond which it becomes progressive and self generating [39]. Subcortical infarctions, or disturbances in cerebral perfusion may be exacerbated by

pre-existing microvascular abnormalities associated with AD [87]. The distribution of amyloid in white matter is related to blood vessels, suggesting a vascular rather than a neuronal source [88]. Increased permeability of the blood-brain barrier has been found to occur secondary to transient ischaemia [89], and this process may underlie both perivascular amyloid deposition and white matter lesions [90]. Increased  $\beta$ -amyloid production has been shown in response to ischemia in the selectively vulnerable hippocampal region [91].

However, the increased risk of AD associated with type 2 DM may be mediated to a large extent by non-vascular mechanisms [39]. These may include hyperglycaemia compounding the ischemic burden of pre-existing vascular disease by increasing anaerobic metabolism and lactic acidosis [92], the exacerbation of beta-amyloid neurotoxicity by advanced glycation end products [93] identified in the matrix of neurofibrillary tangles and amyloid plaques in AD brains [94,95], or associations with insulin functions (see below). In addition, decreased cholinergic transport across the blood-brain barrier has been reported in diabetic rats, which may be potentially important in exacerbating cognitive impairment in the presence of subclinical AD [96]. Several studies performed in animal models suggest an early role of diabetes in dysfunctional glutamate receptors leading to an impaired hippocampal synaptic plasticity [97]. This mechanism may also contribute to the development of cognitive defects in diabetic patients.

### Insulin resistance

Peripheral insulin resistance has been hypothesised as mediating the noted clustering of vascular risk factors such as type 2 DM, hypertension, dyslipidaemia, and obesity [66]. Findings from the Kuopio population study reporting hyperinsulinaemia to be associated with recent onset AD in non-diabetic subjects [98] support this hypothesis. However, it was a cross section study that does not permit to conclude if hyperinsulinaemia would be a cause or effect of AD. Insulin has been shown to inhibit synaptic activity at excessively high or low levels [99], and down regulate choline acetyltransferase [100], *in vitro*. Moreover, a role for insulin and insulin growth factor-1 (IGF-1) in the regulation of tau protein phosphorylation has been suggested [101], the process underlying the formation of neurofibrillary tangles. IGF-1 prevents amyloid-related neurotoxicity in rats [102]. Deposition of amyloid deposit in pancreatic islet beta cells appears to be a consistent pathologic marker in type 2 DM. An islet peptide known as amylin has been identified as the key component of such amyloid deposit [103]. Although amylin and beta-amyloid protein are both cell secretory products, and both have the propensity under some circumstances to form insoluble amyloid fibrils that are toxic to host cells, these polypeptides are completely different. While the role of each of these molecules in the pri-

mary pathogenesis of AD or DM is still unclear, it is tempting to speculate that an alteration in the protein folding leading to aggregation and amyloid deposits may be a key mechanism in both disease [1]. Janson et al. have recently reported an increased frequency of islet amyloid deposition in the pancreas of patients with AD compared with control subjects without AD [104]. Amylin is colocalized and cosecreted with insulin, but its physiologic role is unknown. Amylin antagonized insulin-induced glycogen synthesis in diabetes [105]. Processes which regulate tau phosphorylation may be affected by a state of decreased insulin sensitivity resulting in a predisposition to AD as well as to vascular disease, or a common genetic abnormality affecting insulin dependent pathways may result in AD [39].

Hyperinsulinaemia has been found to be associated with MMSE impairment in large populations studies remaining significant even after adjusting for cardiovascular disease, diabetes, and other vascular risk factors [106,107]. By contrast, with an experimental design allowed to compare cognitive parameters under two conditions presenting markedly different insulin levels, but with minimal incidence on blood glucose concentrations since these were kept constant by glucose infusion, the "high insulin" condition was associated with enhanced performance on memory tests, on the Stroop test and subjects expressed less difficulty in thinking than during the "low insulin" condition [108]. However, this experiment was performed on healthy subjects, without control group to avoid leaving patients infused with glucose without insulin treatment. Furthermore polymorphic variations in genes involved in mediation of insulin metabolic effects and correlated with increased insulin resistance appear to contribute to the risk of AD, supporting the hypothesis that both diseases may share a common genetic background [109].

Though the mechanism by which insulin resistance and hyperinsulinemia could be associated with cognitive impairment remains speculative, a reduction of brain glucose metabolism has been found in patients with dementia and it has been hypothesised that a neuronal resistance to the action of insulin exists [62]. An insulin action upon brain glucose metabolism is exerted by a receptor binding to specific areas like neocortex, hippocampus, amygdala and hypothalamus which are often affected in dementia, especially AD [110].

### The role of glycaemic control

The respective roles of hypo- and hyperglycaemia in mediating cognitive impairment remain controversial [8]. Chronic hyperglycaemia and advanced age may be associated with increased cerebral sensitivity to hypoglycaemic episodes [111]. The association between cognitive decline and severity of diabetes may indeed be mediated by a combination of chronic hyperglycaemia and episodic hypogly-

caemia [8]. Although acute hypoglycaemia impairs complex, attention-demanding and speed dependent responses, (with accuracy often preserved at the expense of speed) [112], intensive therapy and the attendant risk for hypoglycaemia were not associated with neuropsychological impairment in the Stockholm Diabetes Intervention Study [113], as well as in the Diabetes Control and Complications Trial [114,115], in type 1 DM. Previous episodes of hypoglycaemic coma are not associated with permanent impairment of cognitive function in these patients, compared with patients without such episodes [116]. The hypothetical long-term cognitive risk of hypoglycaemia should not prevent an intensive control of hyperglycaemia, whose risk is well established [117]. However, behavioural changes and mood disorders (depression, and anxiety) observed after severe hypoglycaemia in insulin-treated diabetes adults may be persistent [118].

So far, no significant associations were found between glycosolated haemoglobin concentrations and cognitive test scores in participants with diabetes of a community survey of cognition [9].

### Vascular disease unmasking subclinical AD

Cerebrovascular and Alzheimer's pathologies may interact their clinical effect. The Nun study found that fewer neuropathological lesions of AD appeared to result in dementia in those with lacunar infarcts in the basal ganglia, thalamus or deep white matter than in those without infarcts [119]. Lacunar infarcts had a strong association with atherosclerosis in the arteries of the circle of Willis. DM, as well as hypertension, ischemic cardiac disease and lacunas are significantly more common in demented patients with white-matter changes, whereas the frequency of transient ischemic stroke episodes did not differ between groups of patients with and without white-matter changes [120]. The Oxford Project to Investigate Memory and Ageing (OPTIMA) also found that for any given level of cognitive deficit, the densities of either all plaques or neuritic plaques alone in the neocortex were significantly lower in cases of AD mixed with other pathology than in cases of AD with no other pathology [121]. In AD combined with cerebrovascular disease, the total plaque density made a significant contribution to cognitive deficit, while neurofibrillary tangle densities did not [121]. A large community-based neuropathology study in an elderly [70-103] UK population in relation to prospectively evaluated dementia status showed that Alzheimer-type and vascular pathology were the major pathological correlates of cognitive decline, but most patients had mixed disease [122]. Cerebrovascular disease was very common and significantly more common in demented than in non-demented individuals. Small-vessel disease was the commonest cerebrovascular pathological feature, generally a component of mixed vascular disease. Severe subcortical vessel disease was the vascular feature

that was most clearly related to dementia in demented patients with cerebrovascular disease and no Alzheimer-type pathology [123]. This UK study has drawn attention to the importance of congophilic angiopathy which increased evidence on the interaction of vascular and Alzheimer-type changes in the pathogenesis of dementia. However, the study showed an extensive overlap of intermediate Alzheimer-type pathology among demented and non-demented older patients despite equivalent degrees of vascular pathology, in agreement with another population-based clinicopathological study in the UK [124]. Educational attainment appears to delay, protect from the presence of, and possibly development of dementia [125] with several possible underlying biological mechanisms, and may also relate to less vascular pathology [126].

It is possible that AD and vascular dementia affect parallel cognitive functions which, when impaired, interact to manifest dementia. Memory impairment secondary to hippocampal damage in AD may in itself not be sufficient to present as dementia until a relatively advanced stage is reached, but dementia may be precipitated at an earlier stage in the presence of impaired executive function secondary to vascular disease and related to frontosubcortical disruption [39].

Many factors may mediate an association between diabetes and AD. It raises the question as to whether these act to induce or exacerbate AD pathology [8]. A post-mortem study of brains of diabetic patients found no evidence of increased Alzheimer's pathology compared to age-matched controls [127] suggesting more a role of exacerbating pre-existing disease [8].

### Role of ApoE and gene-environment interaction

ApoE4 is recognised to be an independent genetic risk factor for cognitive decline, AD and possibly vascular dementia [106]. The  $\epsilon 4$  allele has been reported to be associated with increased insulin resistance in non diabetic subjects [128] and with increased rate of macrovascular complications in subjects with type 2 DM [129], possibly mediated by effects on lipid levels. ApoE4 may therefore be a shared risk factor underlying both dementia and diabetes. Close control of diabetes may be particularly important for those patients with  $\epsilon 4$  since they may be more likely than others to develop both diseases [130]. The Cardiovascular Health Study showed that subjects with any APOE  $\epsilon 4$  allele in combination with DM were at substantially higher risk of cognitive decline than those without the APOE  $\epsilon 4$  allele [131].

### Comorbid medical conditions

Besides centrally acting medications, conditions are known to be associated with DM and cognitive impairment, such as depression. Depression may cause a worsening of diabetic control, and cognitive complaints. Depression may

also bring to medical attention a patient with undiagnosed DM and thus be a confounding or a mediating factor [8].

## Consequences of associated dementia and DM in care practice

Perlemuter et al., who consistently found decreased cognitive function in ageing type 2 diabetic patients, suggested that the apparent cognitive impairment in ageing patients with type 2 DM may complicate adherence to medical regimens [132,133]. The Canadian Study of Health and Aging showed that undertreatment of vascular risk factors occurred more often in patients with cognitive impairment than in subjects with no cognitive loss [134]. It was particularly observed in patients with a history of stroke that were not taking aspirin, but it was not statistically significant in patients with DM. There is an important need for reappraisal of diabetes care in long-term institutional settings [135]. In addition, elderly subjects with type 2 DM and MMS score <23, are significantly less likely to be involved in diabetes self-care and diabetes monitoring. A low MMSE score was also significantly associated with reduced activities of daily living, increased need for assistance in personal care, and higher hospitalisation rates [136]. Thus routine screening of cognition in older subjects with DM is recommended.

## Conclusions and perspectives

Both prospective and cross-sectional studies suggest that type 2 DM is associated with an increased risk of both AD and vascular dementia. Various pathological changes contribute to the dementia process. These findings raise concerns about limitations of the effectiveness of therapeutic interventions aimed at only one type of lesion in the aged population [122]. Diabetes is associated with an increased risk of cardiovascular disease, which is amplified in the presence of hypertension, and a reduction in blood pressure confers measurable benefits [137].

Medications that decrease the risk of cerebrovascular disease might be expected to be associated with better cognitive function in older people. It has been shown for anti-hypertensives [59,138,139], hypolipemic agents [140,141], but not yet demonstrated for antidiabetics [139]. Better glycaemic control may result in better cognitive function [142,143]. The UKPDS 38 study showed that tight blood pressure control in patients with hypertension and type 2 DM reduces the risk of deaths and complications related to diabetes, progression of diabetic retinopathy, and deterioration in visual acuity [144]. Unfortunately the cognitive aspects were not taken into account. Statins (pravastatine) may reduce the risk of DM [145], of stroke [146] and of AD [140,141]. In the same vein, postmenopausal hormone

replacement improves proteinuria and impaired creatinine clearance related to the renal microvascular damage in type 2 DM and hypertension [147]. Hormone replacement was shown to improve cognitive functions [148-150]. The multifactorial pathogenesis of diabetic cognitive impairment involves both metabolic and vascular changes, related to chronic hyperglycaemia, but probably also defects in insulin action in the brain. Treatment with insulin might therefore not only correct hyperglycaemia, but could also directly affect the brain [151]. More prospective studies are needed that should consider cognitive functions in observational and in interventional studies in patients with DM.

## References

- Halter JB. Alzheimer's disease and non-insulin-dependent diabetes mellitus: common features do not make common bedfellows. *J Am Geriatr Soc* 1996;44:992-3.
- Bourdel-Marchasson I, Dubroca B, Manciet G, Decamps A, Emeriau JP, Dartigues JF. Prevalence of diabetes and effect on quality of life in older French living in the community: the PAQUID Epidemiological Survey. *J Am Geriatr Soc* 1997;45:295-301.
- Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia* 1996;39:1392-7.
- Rockwood K, Awalt E, MacKnight C, McDowell I. Incidence and outcomes of diabetes mellitus in elderly people: report from the Canadian Study of Health and Aging. *Can Med Assoc J* 2000;162:769-72.
- Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;54:S4-S9.
- 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;20:438-45.
- Miles WR, Root HF. Psychologic tests applied to diabetic patients. *Arch Intern Med* 1922; 30:767-77.
- Stewart R, Liolitsa D. Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabet Med* 1999;16:93-112.
- Lindeman RD, Romero LJ, LaRue A, et al. A biethnic community survey of cognition in participants with type 2 diabetes, impaired glucose tolerance, and normal glucose tolerance: the New Mexico Elder Health Survey. *Diabetes Care* 2001;24:1567-72.
- Leys D, Pasquier F. Hypertension artérielle et déclin cognitif. *Rev Neurol (Paris)* 1999;155:743-8.
- Bäckman L, Hill RD, Forseel Y. The influence of depressive symptomatology on episodic memory functioning among clinically nondepressed older adults. *J Abnorm Psychol* 1996;105:97-105.
- Dufouil C, Fuhrer R, Dartigues JF, Alépovitch A. Longitudinal analysis of the association between depressive symptomatology and cognitive deterioration. *Am J Epidemiol* 1996;144:634-41.
- Desmond DW, Tatemichi TK, Paik M, Stern Y. Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort. *Arch Neurol* 1993;50:162-6.
- Wahlin A, Nilsson E, Fastbom J. Cognitive performance in very old diabetic persons: the impact of semantic structure, preclinical dementia, and impending death. *Neuropsychology* 2002;16:208-16.

15. Scott RD, Kritz-Silverstein D, Barrett-Connor E, Wiederholt WC. The association of non-insulin-dependent diabetes mellitus and cognitive function in an older cohort. *J Am Geriatr Soc* 1998;46:1217-22.
16. Vanhanen M, Kuusisto J, Koivisto K, et al. Type-2 diabetes and cognitive function in a non-demented population. *Acta Neurol Scand* 1999;100:97-101.
17. Ebly EM, Hogan DB, Parhad IM. Cognitive impairment in the non-demented elderly. Results from the Canadian Study of Health and Aging. *Arch Neurol* 1995;52:612-9.
18. American Psychiatric Association A. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association 1994.
19. Di Carlo A, Baldereschi M, Amaducci L, et al. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *J Am Geriatr Soc* 2000;48:775-82.
20. Kalmijn S, Feskens EJM, Launer LJ, Stijnen T, Kromhout D. Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. *Diabetologia* 1995;38:1096-102.
21. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* 2004;63:658-63.
22. Croxson SCM, Jagger C. Diabetes and cognitive impairment: a community-based study of elderly subjects. *Age Ageing* 1995;24:421-4.
23. Carmelli D, Swan GE, Reed T, et al. Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins. *Neurology* 1998;50:1580-5.
24. Wechsler D. Manual: Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corp. 1974.
25. Eslinger PJ, Damasio AR, Benton AL. The Iowa battery for mental decline. Iowa City, IA: University of Iowa 1984.
26. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-98.
27. Elias PK, Elias MF, D'Agostino RB, et al. NIDDM and blood pressure as risk factors for poor cognitive performance. *Diabetes Care* 1997;20:1388-95.
28. Gregg EW, Yaffe K, Cauley JA, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? *Arch Intern Med* 2000;160:174-80.
29. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 2001;56:42-8.
30. Frisoni GB, Calabresi L, Geroldi C, et al. Apolipoprotein E  $\epsilon$ 4 allele in Alzheimer's disease and vascular dementia. *Dementia* 1994;5:240-2.
31. Hsiung GY, Sadovnik AD, Feldman H. Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. *Can Med Assoc J* 2004;171:863-7.
32. Carmelli D, Swan GE, Reed T, Wolf PA, Miller BL, DeCarli C. Midlife cardiovascular risk factors and brain morphology in identical older male twins. *Neurology* 1999;52:1119-24.
33. Mega MS, Cummings JL. Frontal-subcortical circuits and neuropsychiatric disorders. *J Psychiatr Clin Neurosci* 1994;6:358-70.
34. DeCarli C, Murphy DM, Tranh M, et al. The effect of white matter hyperintensity volume on brain structure, cognitive performance, and cerebral metabolism in 51 healthy adults. *Neurology* 1995;45:2077-84.
35. Longstreth WTJ, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke* 1996;27:1274-82.
36. Wolf-Klein GP, Silverstone FA, Brod MS, et al. Are Alzheimer patients healthier? *J Am Geriatr Soc* 1988;36:219-24.
37. Landin K, Blennow K, Wallin A, Gottfries C-G. Low blood pressure and blood glucose levels in Alzheimer's disease. Evidence for a hypometabolic disorder? *J Intern Med* 1993;233:357-63.
38. Tariot PN, Ogden AM, Cox C, Williams F, T. Diabetes and dementia in long-term care. *J Am Geriatr Soc* 1999;47:423-9.
39. Stewart R. Cardiovascular factors in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1998;65:143-7.
40. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementias and Alzheimer's disease in a defined elderly Japanese population: the Hisayama study. *Neurology* 1995;45:1161-8.
41. Ott A, Stolk RP, van Harskamp F, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia in an elderly population. In: Ott A, eds. "Risk of Dementia". Delft: Judels En Brinkman BV 1997,49-62.
42. 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.
43. Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. *Am J Epidemiol* 1997;145:301-8.
44. 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;9:175-80.
45. Curb JD, Rodriguez BL, Abbott RD, et al. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose intolerance. *Neurology* 1999;52:971-5.
46. Peila R, Rodriguez BL, Launer LJ, Study. H-AA. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. *Diabetes* 2002;51:1256-62.
47. 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;154:635-41.
48. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993;43:250-60.
49. Arvanitakis Z, Wilson RS, Bienas JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol* 2004;61:661-6.
50. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985-92.
51. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Forces on Alzheimer's disease. *Neurology* 1984;34:939-44.
52. Skoog I. Risk factors for vascular dementia: a review. *Dementia* 1994;5:137-44.
53. Moncayo J, Bogousslavsky J. Vascular dementia: persisting controversies and questions. *Eur J Neurol* 1996;3:299-308.
54. Hofman A, Ott A, Breteler MMB, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet* 1997;349:151-4.
55. McAlister FA, Zarnke KB, Campbell NR, et al. The 2001 Canadian recommendations for the management of hypertension: Part two – Therapy. *Can J Cardiol* 2002;18:625-41.
56. Jandeleit-Dahm K, Cooper ME. Hypertension and diabetes. *Curr Opin Nephrol Hypertens* 2002;11:221-8.

57. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002;61:1086-97.
58. The CDS Diabetes Cost-effectiveness Group. Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. *J Am Med Assoc* 2002;287:2542-51.
59. Forette F, Seux M-L, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998;352:1347-51.
60. Celis H, Fagard RH, Staessen JA, Thijs L, Investigators. SHiET. Risk and benefit of treatment of isolated systolic hypertension in the elderly: evidence from the Systolic Hypertension in Europe Trial. *Curr Opin Cardiol* 2001;16:342-8.
61. Smith NL, Savage PJ, Heckbert SR, et al. Glucose, blood pressure, and lipid control in older people with and without diabetes mellitus: the Cardiovascular Health Study. *J Am Geriatr Soc* 2002;50:416-23.
62. Fisman M, Gordon B, Feleki V, Helmes E, McDonald T, Dupre J. Metabolic changes in Alzheimer's disease. *J Am Geriatr Soc* 1988;36:298-300.
63. Meneilly GS, Hill A. Alterations in glucose metabolism in patients with Alzheimer's disease. *J Am Geriatr Soc* 1993;41:710-4.
64. Carantoni M, Zuliani G, Munari MR, D'Elia K, Palmieri E, Fellin R. Alzheimer disease and vascular dementia: relationships with fasting glucose and insulin levels. *Dement Geriatr Cogn Disord* 2000;11:176-80.
65. Vanhanen M, Soininen H. Glucose intolerance, cognitive impairment and Alzheimer's disease. *Curr Opin Neurol* 1998;11:673-7.
66. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-607.
67. Calori G, Garancini P, Ruotolo G, Ragona F, Ruggeria P, Gallus G. Relationship between insulinemia and LDL-cholesterol in non-diabetic subjects: The Cremona population study. *Diabetologia* 1995;38:A248.
68. Strandberg TE, Tilvis RS, Lindberg O, et al. High plasma insulin associates with lower LDL-cholesterol in elderly individuals. *Atherosclerosis* 1996;121:267-73.
69. Gold PE. Role of glucose in regulating the brain and cognition. *Am J Clin Nutr* 1995;61:987S-95S.
70. Craft S, Dagogo-Jack SE, Wiethop BV, et al. Effects of hyperglycemia on memory and hormone levels in dementia of the Alzheimer type: a longitudinal study. *Behav Neurosci* 1993;107:926-40.
71. Hogan DB, Eby EM, Rockwood K. Weight, blood pressure, osmolarity, and glucose levels across various stages of Alzheimer's disease and vascular dementia. *Dement Geriatr Cogn Disord* 1997;8:147-51.
72. Foster NL, Hickenbottom SL. When do strokes cause dementia? Effects of subcortical cerebral infarction on cortical glucose metabolism and cognitive function. *Arch Neurol* 1999;56:778-9.
73. Tatemichi TK, Desmond DW, Paik M, et al. Clinical determinants of dementia related to stroke. *Ann Neurol* 1993;33:568-75.
74. Corsi B, Manara O, Agostinis C, et al. Dementia after first stroke. *Stroke* 1996;27:1205-10.
75. Loeb C, Gandolfo C, Croce R, Conti M. Dementia associated with lacunar infarction. *Stroke* 1992;23:1225-9.
76. Kokmen E, Whisnant JP, O'Fallon WM, Chu CP, Beard CM. Dementia after ischemic stroke: a population-based study in Rochester, Minnesota (1960-1984). *Neurology* 1996;46:154-9.
77. Inzitari D, Di Carlo A, Pracucci G, et al. Incidence and determinants of poststroke dementia as defined by an informant interview method in a hospital-based stroke registry. *Stroke* 1998;29:2087-93.
78. Pohjasvaara T, Erkinjuntti T, Ylikoski R, Hietanen M, Vataja R, Kaste M. Clinical determinants of post-stroke dementia. *Stroke* 1998;29:75-81.
79. Kase CS, Wolf PA, Kelly-Hayes M, Kannel WB, Beiser A, D'Agostino RB. Intellectual decline after stroke. The Framingham Study. *Stroke* 1998;29:805-12.
80. Desmond DW, Moroney JT, Paik MC, et al. Frequency and clinical determinants of dementia after ischemic stroke. *Neurology* 2000;54:1124-31.
81. Hénon H, Durieu I, Guerouaou D, Lebert F, Pasquier F, Leys D. Poststroke dementia: incidence and relationship to prestroke cognitive decline. *Neurology* 2001;57:1216-22.
82. Woo J, Lam CW, Kay R, Wong AH, Teoh R, Nicholls MG. The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. *Arch Neurol* 1990;47:1174-7.
83. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *J Clin Invest* 1991;87:432-738.
84. Vlassara H, Fuh H, Makita Z, Krungkrai S, Cerami A, Bucala R. Exogenous advanced glycosylation end products induce complex vascular dysfunction in normal animals: a model for diabetic and aging complications. *PNAS* 1992;89:12043-7.
85. Pasquier F, Leys D. Why are stroke patients prone to develop dementia? *J Neurol* 1997;244:135-42.
86. Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker JCr. Increased incidence of neurofibrillary tangles in non-demented individuals with hypertension. *J Neurol Sci* 1995;131:162-9.
87. De la Torre JC, Mussivand T. Can disturbed brain microcirculation cause Alzheimer's disease? *Neurol Res* 1993;15:146-53.
88. Iwamoto N, Nishiyama E, Ohwada J, Arai H. Distribution of amyloid deposits in the cerebral white matter of the Alzheimer's disease brain: relationship to blood vessels. *Acta Neuropathol (Berl)* 1997;93:334-40.
89. Pluta R, Barcikowska M, Januszewska S, Misicka A, Lipkowski AW. Evidence of blood-brain barrier permeability/leakage for circulating human Alzheimer's  $\beta$ -amyloid-(1-42)-peptide. *Neuroreport* 1996;7:1261-5.
90. Tomimoto H, Akiguchi I, Suenaga T, et al. Alterations of the blood-brain barrier and glial cells in white-matter lesions in cerebrovascular and Alzheimer's disease patients. *Stroke* 1996;27:2069-74.
91. Hall ED, Oostveen JA, Dunn E, Carter DB. Increased amyloid protein precursor and apolipoprotein E immunoreactivity in the selectively vulnerable hippocampus following transient forebrain ischemia in gerbils. *Exp Neurol* 1995;135:17-27.
92. Chew W, Kucharczyk J, Moseley M, Derugin N, Norman D. Hyperglycemia augments ischemic brain injury: in vivo MR imaging/spectroscopic study with nicardipine in cats with occluded middle cerebral arteries. *Amer J Neuroradiol* 1991;12:603-9.
93. Yan SD, Chen X, Fu J, et al. RAGE and amyloid- $\beta$  peptide neurotoxicity in Alzheimer's disease. *Nature* 1996;382:685-91.
94. Dickson DW, Sinicropi S, Yen SH, et al. Glycation and microglial reaction in lesions of Alzheimer's disease. *Neurobiol Aging* 1996;17:733-43.
95. Takeda A, Yasuda T, Miyata T, et al. Advanced glycation end products co-localized with astrocytes and microglial cells in Alzheimer's disease brain. *Acta Neuropathol (Berl)* 1998;95:555-8.
96. Mooradian AD. Blood-brain barrier choline transport is reduced in diabetic rats. *Diabetes* 1987;36:1094-7.
97. Trudeau F, Gagnon S, Massicotte G. Hippocampal synaptic plasticity and glutamate receptor regulation: influences of diabetes mellitus. *Eur J Pharmacol*, 2004;490:177-86.

98. Kuusisto J, Koivisto K, Mykkanen L, et al. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of the apolipoprotein E4 phenotype: cross sectional population based study. *BMJ* 1997;315:1045-9.
99. Palovcik RA, Phillips MI, Kappy MS, Raizada MK. Insulin inhibits pyramidal neurons in hippocampal slices. *Brain Res* 1984;309:187-91.
100. Brass BJ, Nonner D, Barrett JN. Differential effects of insulin on choline acetyltransferase and glutamic acid decarboxylase activities in neuron-rich striatal cultures. *J Neurochem* 1992;59:415-24.
101. Hong M, Lee VM-Y. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. *J Biol Chem* 1997;272:19547-53.
102. Dore S, Kar S, Quirion R. Insulin-like-growth factor I protects and rescues hippocampal neurons against  $\beta$ -amyloid- and human amylin-induced toxicity. *PNAS* 1997;94:4772-7.
103. Johnson KH, O'Brien TD, Betsholtz C, Westermark P. Islet amyloid, islet-amyloid polypeptide, and diabetes mellitus. *N Engl J Med* 1989;321:513-8.
104. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes* 2004;53:474-81.
105. Edgington SM. Amyloid plaque and diabetes. New research suggests Alzheimer's disease and type II diabetes share a similar pathology. *Biotechnol* 1994;12:593-4.
106. Kalmijn S, Feskens EJM, Launer LJ, Kromhout D. Cerebrovascular disease, the apolipoprotein E4 allele, and cognitive decline in a community-based study of elderly men. *Stroke* 1996;27:2230-5.
107. Stolk RP, Breteler MM, Ott A, et al. Insulin and cognitive function in an elderly population. *Diabetes Care* 1997;20:792-5.
108. Kern W, Peters A, Fruehwald-Schultes B, Deininger E, Born J, Fehm HL. Improving influence of insulin on cognitive functions in humans. *Neuroendocrinology* 2001;74:270-80.
109. Liolitsa D, Powell J, Lovestone S. Genetic variability in the insulin signalling pathway may contribute to the risk of late onset Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2002;73:261-6.
110. Unger JW, Livingston JN, Moss AM. Insulin receptors in the central nervous system: localization, signalling mechanisms and functional aspects. *Prog Neurobiol* 1991;36:343-62.
111. Matyka K, Evans M, Lomas J, Cranston I, MacDonald I, Amiel SA. Altered hierarchy of protective responses against severe hypoglycemia in normal aging and in healthy men. *Diabetes Care* 1997;20:135-41.
112. Frier BM. Hypoglycaemia and cognitive function in diabetes. *Int J Clin Pract* 2001;(Suppl. 123):30-37.
113. Reichard P, M. P, Rosenqvist U, Sule J. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. *Diabetologia* 1996;39:1483-8.
114. The Diabetes Control and Complications Trial Research Group. Effects of intensive diabetes therapy on neuropsychological functions in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 1996;124:379-88.
115. Austin EJ, Deary IJ. A psychometrically validated reanalysis of the Diabetes Control and Complications Trial data. *Diabetes Care* 1999;22:1273-7.
116. Kramer L, Fasching P, Madl C, et al. Previous episodes of hypoglycemic coma are not associated with permanent cognitive brain dysfunction in IDDM patients on intensive insulin treatment. *Diabetes* 1998;47:1909-14.
117. Selam JL. Risque cognitif des hypoglycémies répétées chez le diabétique. *Diabetes Metab* 1998;24:167-72.
118. Strachan MW, Deary IJ, Ewing FM, Frier BM. Recovery of cognitive function and mood after severe hypoglycemia in adults with insulin-treated diabetes. *Diabetes Care* 2001;23:305-12.
119. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer's disease. The Nun Study. *J Am Med Assoc* 1997;277:813-7.
120. Wallin A, Sjogren M, A. E, Blennow K, Regland B. Symptoms, vascular risk factors and blood-brain barrier function in relation to CT white-matter changes in dementia. *Eur Neurol* 2000;44:229-35.
121. Nagy Z, Esiri MM, Jobst KA, et al. The effects of additional pathology on the cognitive deficit in Alzheimer's disease. *J Neuropathol Exp Neurol* 1997;56:165-70.
122. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study MC. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet* 2001;357:169-75.
123. Esiri MM, Wilcock GK, Morris JH. Neuropathological assessment of the lesions of significance in vascular dementia. *J Neurol Neurosurg Psychiatry* 1997;63:749-53.
124. Xuereb JH, Brayne C, Dufouil C, et al. Neuropathological findings in the very old. Results from the first 101 brains of a population-based longitudinal study of dementing disorders. *Ann NY Acad Sci* 2000;903:490-6.
125. Letenneur L, Launer LJ, Andersen K, et al. Education and the risk for Alzheimer's disease: sex makes difference. EURODEM Incidence Research Group. *Am J Epidemiol* 2000;151:1064-71.
126. Del Ser T, Hachinski V, Merskey H, Munoz DG. An autopsy-verified study of the effect of education on degenerative dementia. *Brain* 1999;122:2309-19.
127. Heitner J, Dickson D. Diabetics do not have increased Alzheimer type pathology compared with age-matched control subjects. *Neurology* 1997;49:1306-11.
128. Uusitupa MIJ, Karhunen L, Rissanen A, et al. Apolipoprotein E phenotype modifies metabolic and hemodynamic abnormalities related to central obesity in women. *Am J Clin Nutr* 1996;64:131-6.
129. Ukkola O, Kervinen K, Salmela PI, von Dickhoff K, Laasko M, Kesäniemi YA. Apolipoprotein E phenotype is related to macro- and microangiopathy in patients with non-insulin-dependent diabetes mellitus. *Atherosclerosis* 1993;101:9-15.
130. Nielson KA, Nolan JH, Berchtold NC, Sandman CA, Mulnard RA, Cotman CW. Apolipoprotein-E genotyping of diabetic dementia patients: Is diabetes rare in Alzheimer's disease? *J Am Geriatr Soc* 1996;44:897-904.
131. Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *J Am Med Assoc* 1999;282:40-6.
132. Perlmutter LC, Hakami MK, Hodgson-Harrington C, et al. Decreased cognitive function in aging non-insulin-dependent diabetic patients. *Am J Med* 1984;77:1043-8.
133. Rost K, Roter D, Quill T, Bertakis K. Capacity to remember prescription drug changes: deficits associated with diabetes. *Diabetes Res Clin Pract* 1990;10:183-7.
134. Rockwood K, Ebly EM, Hachinski V, Hogan D. Presence and treatment of vascular risk factors in patients with vascular cognitive impairment. *Arch Neurol* 1997;54:33-9.
135. Sinclair AJ, Allard I, Bayer A. Observations of diabetes care in long-term institutional settings with measures of cognitive function and dependency. *Diabetes Care* 1997;20:778-84.
136. Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and

- use of care services. All Wales Research into Elderly (AWARE) Study. *Diabetes Res Clin Pract* 2000;50:203-12.
137. Cooper ME, Johnston CI. Optimizing treatment of hypertension in patients with diabetes. *J Am Med Assoc* 2000;283:3177-9.
  138. Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad B, Viitanen M. Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use. *Arch Neurol* 1999;56:991-6.
  139. Richards SS, Emsley CL, Roberts J, et al. The association between vascular risk-factor-mediating medications and cognition and dementia diagnosis in a community-based sample of African-Americans. *J Am Geriatr Soc* 2000;48:1035-41.
  140. Wolozin B, Kellman W, Ruisseau P, Celesia GG, Siegel G. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 2000;57:1439-43.
  141. Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000;356:1627-31.
  142. Meneilly GS, Cheung E, Tessier D, Yakura C, Tuokko H. The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. *J Gerontol* 1993;48:M117-M21.
  143. Naor M, Steingrüber HJ, Westhoff K, Schottenfeld-Naor Y, Gries AF. Cognitive function in elderly non-insulin-dependent diabetic patients before and after inpatient treatment for metabolic control. *J Diabet Complications* 1997;11:40-6.
  144. UK Prospective Diabetes Study Group Ug. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317.
  145. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 2001;103:357-62.
  146. Sirol M, Bouzamondo A, Sanchez P, Lechat P. Does statin therapy reduce the risk of stroke? A meta-analysis. *Ann Med Interne (Paris)* 2001;152:188-93.
  147. Szekacs B, Vajo Z, Varbiro S, et al. Postmenopausal hormone replacement improves proteinuria and impaired creatinine clearance in type 2 diabetes mellitus and hypertension. *Br J Obstet Gynaecol* 2000;107:1017-21.
  148. Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline. Evidence of gene-environment interaction. *Neurology* 2000;54:1949-53.
  149. Maki PM, Zonderman AB, Resnick SM. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. *Am J Psychiatry* 2001;158:227-33.
  150. Carlson MC, Zandi PP, Plassman BL, et al. Hormone replacement therapy and reduced cognitive decline in older women. The Cache County Study. *Neurology* 2001;57:2210-6.
  151. Gispen WH, Biessels GJ. Cognition and synaptic plasticity in diabetes mellitus. *Trends Neurosci* 2000;23:542-9.