Insulin resistance, diabetes and cognitive function: Consequences for preventative strategies

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Abstract
Cognitive decline and dementia both place a heavy burden on patients and their relatives, and any means of preventing such age-related changes are worthy of consideration. Those who have the metabolic syndrome with or without diabetes suffer more often from dysexecutive problems and slower psychomotor speed than do other patients. In epidemiological studies, diabetes has appeared to be a risk factor for all types of dementia, including vascular dementia, although the role of the metabolic syndrome in the risk of Alzheimer’s disease is still a matter of debate. The possible mechanisms of cognitive alterations are multiple, and may differ according to age group and duration of diabetes or the metabolic syndrome. Drug interventional trials addressing the prevention of cognitive decline through action on the metabolic syndrome are disappointing—albeit scarce at this time. Lifestyle interventions in middle-aged or younger-elderly subjects should also be implemented in the general population.

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1. Introduction
Both dementia and non-dementia cognitive disorders are now the main target of preventative strategies due to their heavy burden on quality of life and their major social impact on patients themselves, as well as on their relatives and familial caregivers. Indeed, once these disorders are established, drug treatments are only able to slow the decline in some cases. In France, dementia prevalence in those aged greater than 75 years was estimated to be 17.8% [1], while diabetes mellitus in people aged greater than 65 years is around 10% [2], with a peak incidence of 14% in those aged 75–79 years. Any effective means of preventing cognitive decline and dementia are currently avidly sought, particularly in the form of primary prevention linked to lifestyle.
Whether or not diabetes is an independent risk factor for Alzheimer’s disease (AD) is still a matter of debate, with both positive [3–7] and negative [8–10] findings in longitudinal epidemiological studies across different populations. Some studies have shown an increased risk of vascular dementia, but not AD, in patients with diabetes [9,11]. In fact, there may be an increased risk of any type of dementia—not only AD and vascular dementia—in patients with diabetes, although the causal mechanisms remain clinically uncertain [12,13]. Modulation of the risk of AD [14] induced by diabetes may be different in carriers of the apolipoprotein E epsilon 4 (APOE ε4) allele, a major vascular risk factor for AD [15]. In the Personnes âgées Quid (PAQUID) study, there was no association between diabetes and AD (unpublished data) and it was, therefore, hypothesized that the PAQUID cohort lacked the power to detect a positive result; it has since been suggested that a cohort of greater than 600 diabetic patients and a greater number of dementia diagnoses are necessary to assess the influence of diabetes [16]. Post-mortem neuropathological studies are, however, not supportive of a causal relationship between diabetes and AD. It has been shown and discussed in an extensive review that cerebrovascular pathology was more frequent—and AD-related pathology less frequent—in those with diabetes than in others [17]. On the other hand, vascular dementia may be more frequent in people with diabetes. The progression to dementia after stroke was increased in subjects with diabetes compared with others [18–20], and the post-stroke improvement of cognitive function was observed less often in patients with diabetes [21]. In the Three Cities study, diabetes or high levels of triglycerides, but not the other features of the metabolic syndrome, were found to be risk factors for all types of dementia and vascular dementia, but not AD [10].

It is now suggested that vascular risk factors may have a strong influence not only on vascular dementia, but on the occurrence of AD as well. Hypertension in mid-life has been shown to be a risk factor for AD although, in the 2 years before a clinical diagnosis of AD, blood pressure tends to decrease and the best cognitive performances have been seen in those with the highest blood pressure [22]. APOE ε4 is a known risk factor for AD, yet the frequency of this phenotype does not appear to be either more or less frequent in those with diabetes [23]. Also, the insulin-resistance syndrome was associated with AD in a cross-sectional study [24], but not in a longitudinal one [25].

The cognitive functions explored in this report are heterogeneous, and the variety of tests used to assess these functions render any analyses complex. Typically, the cognitive domains examined are memory (declarative, semantic, short-term and verbal), executive functions (attention capacity, mental flexibility, inhibition and updating) and processing speed. In addition, cognitive capacities are often evaluated as part of the global or general cognitive functioning (for example, by the Mini-Mental Status Examination [MMSE]) (Table 1). All aspects of such cog-

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DSST: Digital symbol substitution test; TMT-B: Trail Making Test Part B; MMSE: Mini-Mental Status Examination.
nitive dimensions are used to differentiate cognitive changes, starting from mild cognitive impairment (MCI) which refers to a subtle, but measurable, memory disorder greater than normally expected with ageing up to dementia.

The present review aims to explore the possible influence of the metabolic syndrome in individuals with or without diabetes on the risk of cognitive decline. In particular, the possibility of preventative strategies is also explored.

2. Non-dementia cognitive impairment in elderly people with diabetes

Diabetes has also been studied as a risk factor for non-dementia cognitive impairment (Table 1). Although numerous cross-sectional studies failed to show any effect of diabetes on cognitive function [26,27], we found in the Three Cities study (9000 subjects aged greater than 65 years) a significant decrease in MMSE score—a measure of global cognitive functioning—in subjects with both diagnosed and undiagnosed diabetes compared with the others [2]. Another study of similar size (greater than 7000 subjects) found a baseline association of cognitive impairment in patients with diabetes as well as in those with impaired fasting glycaemia compared with other subjects [28]. A magnetic resonance imaging (MRI) study demonstrated, in middle-aged patients with diabetes, reduced hippocampal and prefrontal volumes associated with impaired declarative memory compared with those without diabetes [29]. Semantic memory was also specifically affected in elderly people with diabetes [30].

Executive functions and processing speed were impaired in those with diabetes compared with other subjects, with increased problems in those with either undiagnosed diabetes or diabetes duration greater than 15 years [31]. Such impairment of executive functioning and psychomotor speed was confirmed in another cross-sectional study, which also showed no influence according to age group in elderly subjects [32]. When global cognitive functioning was tested in 378 high-functioning elderly subjects (aged 70–79 years) treated for diabetes in the Health, Aging and Body Composition (Health ABC) Study, the relationship between cognitive function and fasting glycaemia was U-shaped, with the lowest performances in those with the recommended values of blood glucose and in those with values greater than 2.75 g/L. This relationship was not found with HbA1c [33]. In the younger (mean age 62.5 years) population of the action to control cardiovascular risk in diabetes-memory in Diabetes (ACCORD-MIND) study, a crude negative association was found between general functioning, as measured by MMSE, and higher HbA1c values. However, after multiple adjustments for cardiovascular disease, stroke, diabetes duration and social factors, this relationship was no longer significant.

Indeed, the only function impaired by higher HbA1c values in the fully adjusted model was processing speed, as measured by the digit symbol substitution test (DSST) [34].

Obesity may modulate the relationship between diabetes and cognitive impairment. In a cross-sectional study exploring middle-aged people (mean age 60 years) with and without diabetes, hippocampal volume was inversely related to body mass index (BMI) [29]. One small-scale study also showed that obesity increased the rate of changes in cognitive function in those with diabetes [35].

It has also been hypothesized that physical activity may be able to reduce the deleterious effects of diabetes on cognitive function, based on a cross-sectional study that found a relationship between light-to-moderate exercise and better cognitive functioning [36]. However, as these effects could have been due to other confounding factors, it is necessary to test the effects of diet and exercise in patients with diabetes in an interventional study.

Patients with diabetes may be at higher risk of MCI, as confirmed by several studies [37,38], although the rate of progression from MCI to overt dementia has not been investigated. In patients with diabetes, MCI may be associated with diabetes duration greater than 10 years, age at diabetes onset less than 65 years, use of insulin for treatment [37], high blood pressure and brain atrophy [39,40].

However, the association of diabetes and cognitive changes has been better explored in longitudinal studies (Table 1). In the elderly female cohort of the Study of Osteoporotic Fracture Research Group, diabetes was associated with a 3-year higher risk of cognitive decline, independent of vascular and sociodemographic risk factors [41]. Interestingly, the risk of cognitive decline was greatest for diabetes duration of at least 15 years and was seen in all of the following tests: short-form MMSE (global functioning); DSST (attention, psychomotor performance and perceptual organization); and Trail Making Test Part B (TMT-B; attention, visual scanning, sequential abilities and executive functioning).

The Vascular Aging Study examined the cognitive evolution of cognitively “healthy” subjects (aged 59–71 years), according to glucose categories (normal, impaired fasting glucose and diabetes) and extensive psychometric testing [42]. Those with diabetes worsened in tasks involving attention, psychomotor speed and short-term memory (immediate recall) compared with other categories. Adjustment for vascular risk factors did not modify the relationship, although adjustment for BMI clearly weakened it. Only a slower psychomotor speed remained significantly predicted by diabetes. Similarly, in the Rancho Bernardo Study of aging, a 4-year cognitive decline was found more frequently in the presence of diabetes, but only in women and in the verbal-fluency test, a task that requires psychomotor speed, according to the authors [43]. Baseline HbA1c values correlated with the follow-up test, but not the baseline test. After logistic-regression analysis, the relationship between diabetes and impairment in the verbal-fluency test was not weakened by either BMI or blood pressure, but by baseline HbA1c and lipids. However, this study may not have had sufficient power due to the small number of subjects with diabetes (118 out of 1000). In a 4-year follow-up of 1983, post-menopausal women (mean age 67.2 years, 53 with diagnosed diabetes), a one-point increase in baseline HbA1c value was associated with MCI or dementia incidence [44] while, in another longitudinal study of a population of 1789 elderly subjects with a high rate of diabetes (32.7%), baseline diabetes was not predictive of 2-year cognitive decline [45].
Although severe hypoglycaemia can induce encephalopathy with typical white-matter injury [46], the role of hypoglycaemia in the incidence of cognitive impairment is still unclear. Among older people with diabetes, the occurrence of severe hypoglycaemia was not related to the incidence of cognitive impairment. However, dementia was a strong predictor of severe hypoglycaemia [47], and a much larger study has suggested a role for severe hypoglycaemia in the 4-year incidence of any type of dementia [48].

In summary, elderly people with diabetes appear to have a higher rate of dysexecutive syndrome and a slower psychomotor speed. However, the respective roles of glucose variations and components of the metabolic syndrome are not fully understood. On the other hand, both of these cognitive alterations may play an important role in the management of the disease—whether by the patients themselves or with the help of their caregivers [49]—and in the overall quality of life.

2.1. Insulin and cognition

With normal physiology, insulin facilitates memory, as demonstrated when administered in optimal doses and with sufficient glucose availability. However, insulin resistance, a condition that impairs insulin function, may reverse this effect.

A positive relationship has been shown on MRI between whole-brain and hippocampal volumes and the area under the curve (AUC) in post-glucose tolerance tests for insulin and glucose in early-stage AD patients, but not in non-dementia subjects [50]. In this study, the insulin AUC was also associated with better cognitive performance. Thus, this study confirmed previous similar findings [51].

AD has been called “type 3 diabetes” because a defect in insulin signalling is associated with the accumulation of pathological β-amyloid peptide (Aβ) and hyperphosphorylated tau protein. IDE (insulin-degrading enzyme) is a protease involved in the degradation of Aβ, and insulin and Aβ may compete for degradation. IDE expression found in the post-mortem hippocampus of AD patients who expressed the APOE ε4 allele was reduced by 50% compared with ε4 in AD patients and controls [52]. A genetic association between IDE polymorphism and AD is still being debated in light of the conflicting results [53,54], and it has been suggested that IDE may be related to dementia risk through an increase in insulin rather than the IDE polymorphism itself [55]. However, a recent report on the post-mortem brains of 700 diabetic patients could find no differences in the load of Aβ, neuritic plaques or neurofibrillary tangles, which were, in contrast, higher in the brains of APOE ε4 carriers [56], confirming previous findings [57] in a small population.

Oxidative stress and microinflammation mediate insulin resistance in the brain through the pathway of docosahexaenoic acid (DHA) and, thus, omega-3 fatty acids may also be protective [58].

2.2. Nutriment administration and cognitive function

An acute glucose load was shown to improve memory performance in both healthy and AD elderly subjects without diabetes across numerous previously published reports [59–65]. In contrast, in patients with diabetes, acute ingestion of carbohydrates has been shown to impair declarative memory (paragraph or word-list delayed recall), but had no effect on executive functions [66]. However, this was not confirmed by either 90-min high-glycaemic (10 mmol/L) or euglycaemic clamp testing [67]. Thus, the influence of glucose metabolism status on the acute effects of an oral glucose load has been assessed. Kaplan et al. [68] found, in 20 healthy elderly subjects, that poor β-cell function, low BMI, good insulin sensitivity and larger post-meal glucose AUC were associated with baseline decreased cognitive performance. On the other hand, in the same group of subjects, poor β-cell function and poor baseline memory performance were both associated with improvements in memory performance after ingesting 50 g of carbohydrates (glucose, potatoes or barley) compared with placebo. The memory-enhancing effects of these carbohydrates were independent of their effect on plasma glucose [68]. Similar conclusions were drawn from a larger study involving subjects with a wider age range (55–84 years) [69]. Also, Kaplan et al. [70] performed further studies with fat, protein and glucose intakes, and observed improvements in cognitive performance in 22 healthy elderly subjects for all nutriments, independent of their effects on blood glucose concentrations. Another recent study found that subjects with better glucose tolerance performed better in working memory and attention testing than did others, and that post-prandial cognitive improvement was better with low glycaemic index (GI) foods than with high GI ones [71]. However, in 21 patients with diabetes, low GI foods were also associated with poorer post-prandial verbal memory performance, but not with changes in the other cognitive tasks that were tested (TMT-B, forward digit span, attention) [72].

Among the diabetic women in the US Nurses’ Health Studies, higher dietary intake of trans fatty acids after the diagnosis of diabetes was associated with an accelerated decline in global cognitive function—in particular, verbal memory-independent of age, other items of dietary intake, education, diabetes treatment, BMI, diabetes duration and physical activity [73].

2.3. Brain and hippocampus changes in diabetes and the metabolic syndrome

Several diseases—namely, AD, diabetes and infarcts—could affect the hippocampal region through different pathogenic mechanisms. In its preclinical stage, AD involved atrophy of the anterior part of the hippocampus, and progression of the disease was associated with progressive atrophy towards the posterior region [74]. Insulin resistance was shown to be negatively associated with right hippocampal volume and overall cognitive function in a group of middle-aged women without diabetes [75]. However, in apparently healthy elderly people, silent brain infarcts were more prevalent in those with the metabolic syndrome, and the main component linked to these abnormalities was—as expected—elevated blood pressure [76]. Diabetes has been associated with hippocampal atrophy [51]. In a non-dementia population, diabetes and infarcts induced global hippocampal dysfunction: with diabetes, changes mainly
involved the dentate gyrus (head of the hippocampus) and entorhinal cortex; with infarcts, the cornu ammonis 1 (CA1) and subiculum regions were more affected. In the whole study population, blood glucose levels were inversely correlated with dentate gyrus cerebral blood volume (CBV), assessed by functional MRI (fMRI) in the brain, whereas a trend towards an inverse relationship between insulin level and entorhinal CBV was observed. This was especially seen in those with infarcts in the hippocampal vascular territory, and was not observed in those with no infarcts. On the other hand, CA1 dysfunction resulted to large-vessel occlusions and subsequent hippocampal hypoperfusion, as shown by CBV mapping in vivo [77].

Thus, the main anatomical alterations related to diabetes appear to be the consequence of elevated blood glucose, and changes due to cerebral infarcts are linked to hyperinsulinaemia as a vascular risk factor. However, in contradiction to these statements, hippocampal volume was positively associated with the metabolic syndrome, and with visceral fat volume in particular, in a group of 48 middle-aged to elderly non-dementia patients with diabetes [78]. Among these subjects, the metabolic syndrome was not associated with any cognitive alterations.

3. Cognitive alterations in the metabolic syndrome

The Rotterdam Study showed a positive relationship between the current post-load insulin concentration and cognitive performance independent of other cardiovascular risk factors, but only in women aged greater than 55 years. This relationship persisted even after exclusion of women with diabetes or cardiovascular disease [79]. The profile of cognitive changes observed in those with the metabolic syndrome was similar to that observed in diabetes, and was characterized by decreased psychomotor speed and alterations in executive function [80] (Table 1), thereby suggesting that the cognitive decline in people with diabetes can develop during the first phase of the disease and mainly in relation to cardiovascular risk factors [81].

Obesity and markers of visceral fat were associated with a decrease in cognitive functions, although physical activity reduced the strength of the relationship [82]. In subjects with impaired glucose tolerance, lower MMSE scores have also been found. In particular, higher insulin levels—both fasting and 2-h values—and age were both risk factors for lower MMSE scores [83,84]. The Invecchiare in Chianti (InCHIANTI) [ageing in the Chianti Region] study (523 subjects, aged 70–90 years) showed that, in people with insulin-resistance syndrome, cognitive changes were found only in those with clinical signs of subcortical alteration [85]. In a stroke-free Brazilian population in which 40% of subjects had the metabolic syndrome, the latter was associated with cognitive decline as well as other clinical conditions related to unsuccessful ageing, such as depression, falls, impaired balance and slow gait speed [86]. Association of the metabolic syndrome with cognitive impairment, however, was not found in elderly Koreans, irrespective from their APOE4 genotype. Nevertheless, the authors did find a significant interactive effect between decreased high-density lipoprotein cholesterol (HDL-C) or triglycerides and the APOE ε4 allele on cognitive impairment [87].

Longitudinal studies have addressed the effects of increased fasting and post-load insulin, and decreased insulin secretion (Table 1). In one cohort, hyperinsulinaemia was associated with impaired baseline cognitive function and subsequent cognitive decline after 4 years [88]. In women aged 65–79 years included in an anti-osteoporosis trial, the rate of cognitive decline was accelerated depending on the presence of components-alone and in combination—of the metabolic syndrome [89]. In a community-based cohort of 683 elderly subjects, the 5-year incidence of dementia was associated with baseline hyperinsulinaemia, diabetes, obesity and hypertension, with an increased risk in the upper third and fourth quartiles of fasting insulin. After adjusting the multivariate model for APOE ε4 or for diabetes, it was found that BMI, low-density lipoprotein (LDL) levels, hypertension, heart disease and stroke had no affect on the risk of hyperinsulinaemia [90]. However, the association was more pronounced in carriers of the APOE ε4 allele. In the Honolulu-Asia Aging Study (HAAS), which included only men, an increased risk of dementia was found in the lowest 15th and upper 15th percentiles of fasting insulin [91]. In the younger-old women without diabetes in the Nurses’ Health Study, the 4-year cognitive decline was faster in those with increased insulin secretion (fasting C-peptide concentration), independent of other vascular risk factors, hypertension, dyslipidaemia and cardiovascular disease [92]. The authors further analyzed the relationship between fasting insulin and C-peptide and cognitive decline in these women, and found that the group with low C-peptide and high insulin had a greater risk than those with low C-peptide and low insulin [93]. The authors suggest that this might have been a reflection of impaired insulin degradation and, thus, an impairment of IDE function. They also estimated that being in the upper quartile for fasting C-peptide was equivalent to being 3 years older [92], and that being in the group with low C-peptide combined with high insulin was equivalent to being 5 years older, for cognitive status [93]. In a study of Swedish men followed from age 50 years, low baseline insulin secretion was associated with a 30-year increased risk of AD, particularly in those carrying the APOE ε4 allele. Also, in the latter subjects, higher fasting insulin or insulin resistance, according to the homoeostatic model assessment (HOMA) index, was predictive of incident AD [94]. In non-diabetic subjects, vascular dementia was predicted by insulin resistance at 50 years of age.

Obesity was predictive of a 2-year decline in the composite cognitive scores of subjects in the US Framingham Heart Study in a multivariate model, adjusted for cardiovascular risk factors, and social and educational factors—but only in men [95]. The authors also found an interaction between obesity and gender, and the different patterns of obesity observed in men and women were proposed as a possible explanation of this gender difference, although a lack of power in this study is also possible. A healthcare cohort of around 1000 subjects who surfaced after an active search for dementia and other chronic diseases, and who were anthropometrically characterized at ages 40–45 years, showed that obesity was an independent risk factor for dementia 30 years later, but only in women [96]. However, in this report,
the respective mortality rates and causes of attrition in women and men according to their build were not shown. Hypertension has also been found to increase the risk of cognitive disorders 20 years later, particularly in men [97].

The effect of the insulin-resistance syndrome on cognitive function may also be modulated by low-grade inflammation, which further increases the risk of cognitive decline [98].

All of these studies involved middle-aged or younger-old subjects, whereas the Leiden 85-Plus Study involved a cohort that specifically included only the oldest-old. Within such a population, the risk of cognitive decline was not increased in those who had features of the metabolic syndrome [99]. Furthermore, the decline was slower in those aged 85–90 years with the metabolic syndrome compared with the others. Other evidence suggests that the metabolic syndrome in this age group does not have the same significance it has in younger people [100]. Another intriguing finding in the Health ABC Study was the lesser cognitive decline found in those in the highest tertile of leptin concentrations compared with those in the lowest tertile. The association was strongest after adjusting for fat mass [101]. The authors suggest that leptin may act as a neurotrophic factor and could therefore be a protective factor.

In summary, multiple arguments favour the metabolic syndrome and diabetes as risk factors for cognitive decline in middle-aged and younger-old subjects. Thus, it follows that the metabolic syndrome in this age group does not have the same significance it has in younger people [100]. Another intriguing finding in the Health ABC Study was the lesser cognitive decline found in those in the highest tertile of leptin concentrations compared with those in the lowest tertile. The association was strongest after adjusting for fat mass [101]. The authors suggest that leptin may act as a neurotrophic factor and could therefore be a protective factor.

4. Interventions

Improving blood glucose control could reverse the cognitive problems associated with diabetes. In one small-scale study, a global intervention to improve glucose control in patients with diabetes resulted in an improvement in psychomotor speed and global intervention to improve glucose control in patients with problems associated with diabetes. In one small-scale study, a control in this age group are of major interest.

In summary, interventions targeting one or two components of the metabolic syndrome or blood glucose control in this age group are of major interest.

5. Conclusion

Patients with the metabolic syndrome, with or without diabetes, invariably suffer from cognitive decline. However, the mechanisms of these changes are manifold, differ according to age group and disease duration, and are modulated by the APOE4 phenotype. It is possible that the cognitive alterations observed in diabetes were present before the onset of diabetes as a result of the metabolic syndrome. Regardless, such cognitive alterations can interfere with disease management. Once diabetes is diagnosed, the effects of blood variations on cognitive decline may involve different pathways from those caused by the metabolic syndrome. Consequentially, at this time, it is not

the use of a calcium antagonist [110]. However, this effect has not been confirmed in other trials, as described in the extensive Cochrane review by McGuinness et al. [111].

However, a pilot 2-year, uncontrolled, lifestyle intervention has shown promising effects. The intervention consisted of exercise two to four times a week and healthy-diet training every 6 months, and was applied only to older patients with diabetes, but without drug treatment, and to those with impaired glucose tolerance (mean age 80 years). At baseline, these subjects had poorer cognition than those with normal glucose tolerance, according to MMSE scores and delayed-recall testing. Yet, after 2 years, cognitive function was similar across all three-study groups [112].

In summary, interventions targeting one or two components of the metabolic syndrome, or hyperglycaemia when diabetes is present, in middle-aged or young elderly subjects can modulate the decline in cognitive function associated with those factors. However, in general, the reports of interventional trials are not encouraging, and better definition of the studied populations (age group, other risk factors) and/or interventional strategies are needed.
possible to define a unique preventative strategy for all patients with the metabolic syndrome or diabetes. The results, thus far, of the preventative strategies targeting the metabolic syndrome or blood glucose control are somewhat disappointing. However, a clearer definition of the population who might benefit from such interventions is needed, and it is likely that early interventions will have the best effects.

Conflict of interest statement

None of the authors have any conflict of interest related to this paper.

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