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Is there any relation between insulin resistance and cognitive function in the elderly?

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ABSTRACT

Background: Vascular risk factors are blamed as being involved in the pathogenesis of cognitive dysfunction in the elderly. Alzheimer's disease or vascular-type dementia could be part of a metabolic syndrome. The aim of this study was to evaluate whether there is any relation between insulin resistance and cognitive status of the elderly regarding normal, mild cognitive impairment (MCI), Alzheimer's disease (AD), vascular dementia (VaD) and mixed dementia.

Methods: 267 elderly patients admitted to an outpatient geriatrics clinic were evaluated medically and cognitively in this study. The patients were diagnosed using ARDRA and DSM-IV criteria for AD; NINDS-AIREN and DSM-IV criteria for VaD; and Petersen criteria for MCI. Insulin resistance was calculated using both the homeostasis model assessment (HOMA) and quantitative insulin sensitivity check index (QUICKI) formulas.

Results: The mean values of HOMA and QUICKI scores were 2.79 (SD ± 3.56) and 0.346 (SD ± 0.036) for the normal group, 2.81 (SD ± 3.06) and 0.354 (SD ± 0.047) for AD group, 2.20 (SD ± 1.82) and 0.360 (SD ± 0.048) for VaD group, 2.87 (SD ± 1.81) and 0.339 (SD ± 0.038) for mixed dementia group, 2.79 (SD ± 2.81) and 0,349 (SD ± 0.042) for MCI group, respectively. There were no statistically significant differences between HOMA and QUICKI scores of all the groups.

Conclusion: This is the first study of the possible relation between insulin resistance and cognitive function in people categorized according to five forms of cognitive status. Unfortunately the results do not allow generalizations. Further prospective cohort studies that follow a normal cognitive group and MCI patients with and without insulin resistance are necessary.

Key words: insulin resistance, cognitive status, dementia, elderly

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Introduction

For the maintenance of cognitive functioning in the elderly it has been suggested that normal functioning of the insulin-signaling pathway is important (Abbatecola *et al.*, 2004). Vascular risk factors; especially hypertension and diabetes mellitus, are identified as being involved in the pathogenesis of cognitive dysfunction in the elderly (Kudo *et al.*, 2000). Hyperinsulinemia, hypertension and obesity are potential risk factors for Alzheimer's disease (AD) in different epidemiologic studies (Yaffe *et al.*, 2004). Higher fasting insulin levels and reduced CSF-to-plasma insulin ratios, suggestive of insulin resistance, have been observed in patients with AD without apolipoprotein $\varepsilon 4$ alleles (Watson and Craft, 2003). Alzheimer's disease or vascular dementia (VaD) could be a part of a metabolic syndrome or even type-III diabetes (Hoyer, 1998; Pilcher, 2006).

How insulin resistance effects the cognitive profile is still not completely understood. The age-associated decline in the metabolic rate and utilization of glucose by the frontal cortex suggests that insulin resistance can produce executive dysfunctions in older people, not just global cognitive impairment (Razay and Wilcock, 1994; Taubes, 2003; Yaffe *et al.*, 2004). In transgenic mouse models of AD, studies show that diet-induced insulin resistance promotes amyloidosis suggesting that insulin resistance can influence amyloid β production in the brain (Gasparini *et al.*, 2002; Ho *et al.*, 2004). Insulin and insulin receptors are densely but selectively expressed in the brain; including the medial temporal regions which support formation of the memory (Watson and Craft, 2003). Insulin sensitive glucose transporters are localized to the same regions supporting the memory. The increased occurrence of insulin resistance in dementia suggests that if insulin effectiveness can be improved (Stolk *et al.*, 1997; Taubes, 2003; Ho *et al.*, 2004) this may have therapeutic benefits for patients with AD and also for the prevention of dementia using thiazolidinediones and other drugs that decrease insulin resistance (Watson and Craft, 2003). Affective disorders and AD have been associated for almost a century and various neurophysiologic factors have been implicated as common biological markers. Persistent regional hypometabolism and vascular changes resulting from long-lasting insulin resistance may lead to irreversible structural changes and cause cognitive decline and affective disorders (Rasgon and Jarvik, 2004).

The aim of this study was to establish whether there is a possible relation between insulin resistance and cognitive status of the elderly regarding normal, mild cognitive impairment (MCI), AD, VaD and mixed dementia.

Methods

Two hundred and sixty-seven patients admitted to an outpatient geriatrics clinic, one of the reference hospitals for dementia cases in Ankara, were evaluated in

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this study. Their demographic and clinical characteristics and their diagnosis of cognitive status were further evaluated. Diabetic patients were not included in the study to exclude the possible effects of exogenous insulin and insulin resistance on treatment.

Blood samples were collected in the morning after at least eight hours of fasting for glucose, insulin, high density lipoprotein (HDL), triglycerides, and cholesterol. Serum glucose levels were determined by using an enzymatic calorimetric assay and a modified glucose oxidase-peroxidase method (Roche Diagnostics, Germany). Plasma insulin was determined using a commercial double antibody solid phase assay (Sorinbiomedika, Italy). Plasma C-peptide levels were also measured in order to ensure that the insulin measurements were valid and did not interfere with pancreas pathology.

Insulin resistance was calculated both with HOMA and QUICKI formulas (Gokcel *et al.*, 2003; Kanauchi *et al.*, 2003). For the metabolic syndrome diagnosis, the National Cholesterol Education Program (NCEP) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) was used (Alexander *et al.*, 2003). Hypertension was defined as systolic (>140 mmHg) or diastolic (>90 mmHg) after measurement by standard sphygmomanometers, and history of hypertension if present was recorded.

All patients were evaluated according to comprehensive geriatric assessment methods used by Munshi *et al.* (2006) and Hachinski Ischemic Scoring (Hachinski *et al.*, 1975). The patients were diagnosed using ARDRA (McKhann *et al.*, 1984) and DSM-IV criteria for Alzheimer's disease, NINDS-AIREN (Gold *et al.*, 1997) and DSM-IV criteria for vascular dementia, and Petersen criteria for MCI (Petersen *et al.*, 1999). In addition, every patient with dementia was evaluated by Magnetic Resonance Imaging.

Statistical analyses were performed using SPSS software version 11.0 (Chicago IL, SPSS Inc). Descriptive results of the continuous variables are presented by means ± SD. The Kruskal-Wallis test was used to analyze the scores of the two formulas and the four cognitive groups both separately and together (a p value < 0.05 was accepted as statistically significant). The Kruskal-Wallis test was used for the HOMA score and the one-way ANOVA Tukey used for QUICKI scores of the women patients with four different cognitive scores. Comparison of metabolic syndrome presence was analyzed by collapsing categories for the χ^2 test.

Results

Diagnoses of the cognitive status of 267 patients are shown in Figure 1. Demographic properties of the patients including hypertension, total and HDL

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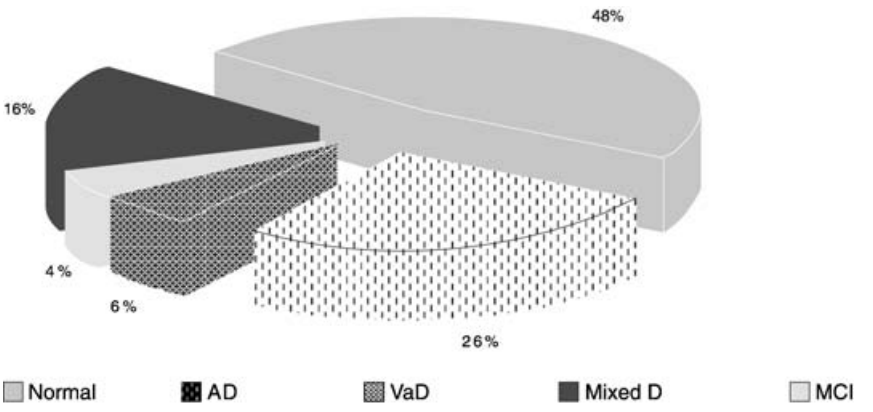


Figure 1. The cognitive status of the study sample (N = 267).

cholesterol, triglyceride levels, level of education and smoking history are shown in Tables 1 and 2. Hypertension and a history of smoking were higher in the VaD group, and the percentage of illiterate people was higher in the AD group, in agreement with the literature.

The mean values of HOMA scores were 2.79 ± 3.56 for 126 normal cognitive functions, 2.81 (± 3.06) for 70 AD patients, 2.20 ± 1.82 for 16 VaD, 2.87 ± 1.81 for 11 mixed dementia patients, and 2.79 ± 2.81 for 44 MCI patients. The mean values of QUICKI scores were 0.346 ± 0.036 for 126 normal cognitive functions, 0.354 ± 0.047 for 70 AD patients, 0.360 ± 0.048 for 16 VaD, 0.339 ± 0.038 for 11 mixed dementia patients, and 0.349 ± 0.042 for 44 MCI patients. The HOMA and QUICKI scores for all the groups are shown in Figure 2. There was no statistically significant difference between HOMA and QUICKI scores for these groups ($p = 0.74$ and 0.706, respectively).

When we carried out all these analyses for women patients only, the mean values of HOMA scores in women were 2.83 ± 3.73 for 75 with normal cognitive functions, 2.89 ± 3.1 for 51 AD patients, 2.67 ± 2.45 for 10 VaD, 3.28 ± 1.68 for 7 mixed dementia patients, and 2.11 ± 1.78 for 27 MCI patients. The mean values of QUICKI scores in women were 0.344 (SD $\pm$ 0.033) for 75 with normal cognitive functions, 0.351 ± 0.045 for 51 AD patients, 0.359 ± 0.045 for 10 VaD, 0.327 ± 0.029 for 7 mixed dementia patients, and 0.357 ± 0.037 for 27 MCI patients. Neither HOMA nor QUICKI scores were related to gender ($p = 0.35$ and 0.332, respectively).

The diagnoses of metabolic syndrome rather than HOMA and QUICKI formulas were also determined infor each group. The percentage of metabolic syndrome according to NCEP criteria was 40.5% in the 126 people with normal cognitive function, 41.4% for 70 AD patients, 43.8% for 16 VaD patients, 45.4%

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Table 1. Demographic characteristics of the study population according to cognitive status

	SEX M/F	WEIGHT (KG)	HEIGHT (CM)	AGE MEAN (YEARS)	EDUCATION % ILLITERATE	HT %	SMOKING %
Normal	75/51	75.2 ± 14.3	158.8 ± 12.8	72.96	10.3	67.5	10.3
AD	51/19	68.5 ± 16.0	151.8 ± 19.1	76.32	24.3	71.4	15.7
VaD	10/6	72.8 ± 13.6	154.3 ± 12.6	78.00	18.8	81.3	37.5
Mixed D	7/4	72.9 ± 10.2	152.8 ± 8.1	76.50	18.2	72.7	27.3
MCI	27/17	73.2 ± 10.8	156.1 ± 9.1	73.97	11.4	68.2	13.6

HT = hypertension; AD = Alzheimer's disease; VaD = vascular dementia; Mixed D = mixed dementia; MCI = mild cognitive impairment

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Table 2. Clinical and metabolic characteristics of the study population according to cognitive status

	GLUCOSE (MMOL/L)	CHOL. (MMOL/L)	TG (MMOL/L)	HDL-CHOL (MMOL/L)	HOMA	QUCKI	C-PEPTIDE (NMOL/L)	IADL (17/17)	MMSE (30/30)	CDT 10/10)	GDS (15/15)
Normal n = 126	5.82 ± 1.76	5.41 ± 1.67	1.76 ± 0.53	1.35 ± 0.45	2.79 ± 3.56	0.346 ± 0.036	1.50 ± 0.41	14.5 ± 3.7	26.5 ± 2.4	8.53 ± 1.61	3.65 ± 3.55
AD n = 70	5.82 ± 1.73	5,27 ± 1.62	1.49 ± 0.55	1.40 ± 0.44	2.81 ± 3.06	0.354 ± 0.047	1.47 ± 0.37	14.7 ± 4.1	16.4 ± 4.5	5.59 ± 2.75	5.16 ± 3.67
VaD n = 16	6.23 ± .82	5.22 ± 1.61	1.47 ± 0.56	1.23 ± 0.39	2.20 ± 1.82	0.360 ± 0.048	1.28 ± 0.31	12.5 ± 3.7	15.7 ± 4.0	6.14 ± 2.04	5.14 ± 3.02
Mixed D n = 11	5.80 ± 1.73	5.53 ± 1.72	1.24 ± 0.41	1.24 ± 0.42	2.87 ± 1.81	0.339 ± 0.038	1.71 ± 0.43	13.1 ± 3.6	14.6 ± 3.7	3.00 ± 2.12	6.00 ± 2.92
MCI n = 44	5.69 ± 1.68	5.20 ± 1.57	1.61 ± 0.49	1.30 ± 0.43	2.79 ± 2.81	0.349 ± 0.042	1.42 ± 0.35	14.3 ± 3.2	24.8 ± 1.9	8.07 ± 2.70	3.14 ± 3.08

HT: hypertension, **Chol**: cholesterol; **TG**: triglyceride, **HDL**: high density lipoprotein; **IADL:** Instrumental Activities of Daily Living; **MMSE:** Mini-mental State Examination; **CDT:** Clock Drawing Test; **GDS:** Geriatric Depression Scale

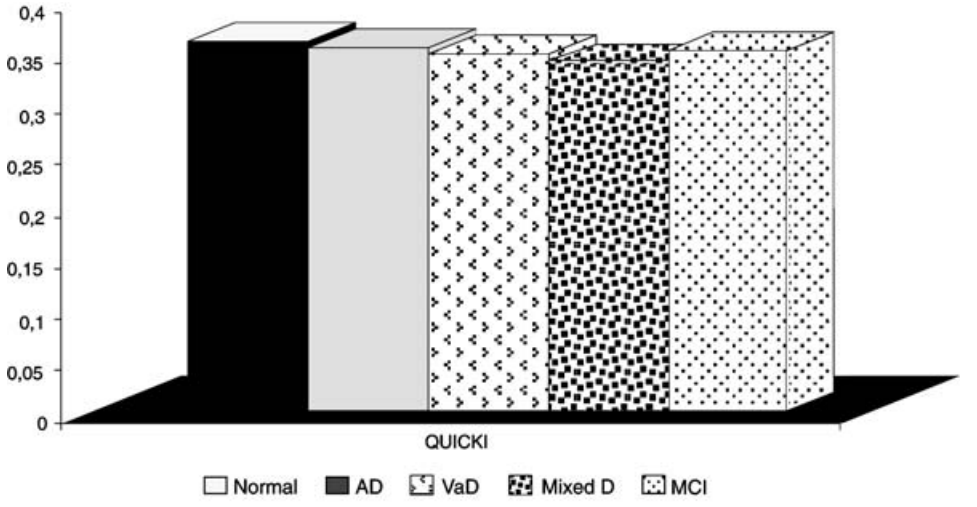


Figure 2. QUICKI scores of the sample population.

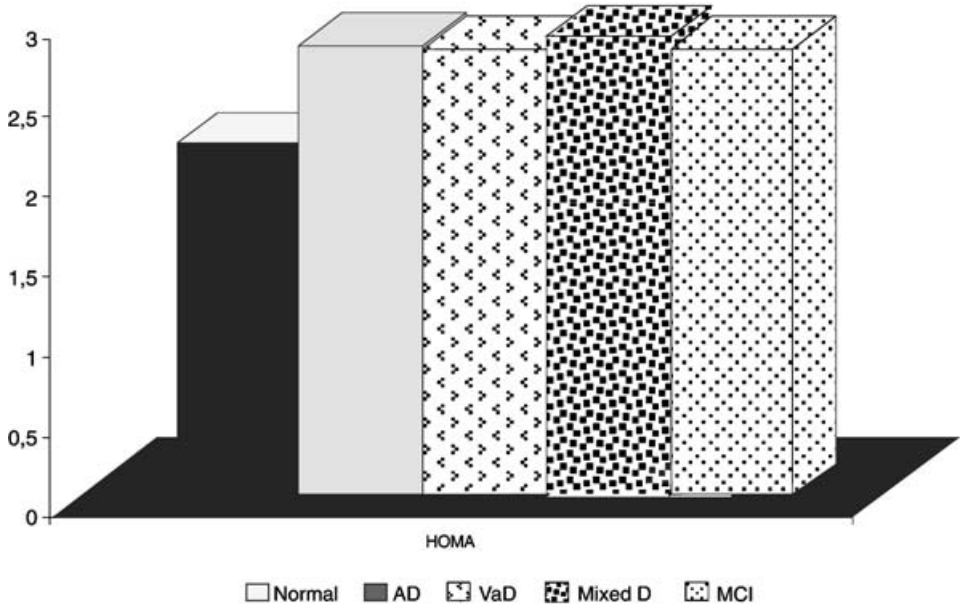


Figure 3. HOMA scores of the sample population.

for 11 mixed dementia patients, and 38.6% for 44 MCI patients. When we compared all of the groups for metabolic syndrome, there was no statistical significance ($p = 0.68$).

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Discussion

There is growing evidences about the effect of diabetes on cognition (Razay and Wilcock, 1994; Rasgon and Jarvik, 2004). Epidemiological evidence has suggested that diabetes mellitus significantly increases the risk for AD independent of vascular risk factors (Yaffe *et al.*, 2004). However, the role of insulin and insulin resistance on cognition in nondiabetic patients is obscure, especially in the elderly.

Insulin resistance may cause decreased cortical glucose utilization particularly in the hippocampus and entorhinal cortex and also increased oxidative stress with advanced glycation end products (Abbatecola *et al.*, 2004; Rasgon and Kenna, 2005). Insulin resistance may also cause Tau phosphorylation and neurofibrillary tangle formation, and increased beta amyloid aggregation (Xie *et al.*, 2002). Although the current literature suggests that insulin resistance and hyperinsulinemia are important for cognitive decline, especially in elderly women (Razay and Wilcock, 1994) without apolipoprotein $\varepsilon 4$ (Stolk *et al.*, 1997), in this study we did not find any statistical significant difference among the five different cognitive status groups – AD, VaD, mixed dementia, MCI and normal cognition group. In fact the results are somewhat different from the current literature supporting the evidence for insulin resistance and cognitive function (Razay and Wilcock, 1994; Abbatecola *et al.*, 2004). In addition, Gokcel *et al.* (2003) established the mean values to assess insulin resistance in Turkish adults as 2.24 for the HOMA index and 0.347 for the QUCKI index. When compared with our data, these insulin resistance indices were obviously lower than in our population. In the Kanauchi *et al.* (2003) study, the HOMA score was 1.51 for the subjects without hypertension in the normal group. However, in our study, the HOMA score and hypertension ratio are 2.79 and 67.5% respectively in the patients with normal cognition. When the QUICKI scores were compared, calculated logarithmically, the QUICKI scores of subjects in both normal groups appear to be similar. Both the higher hypertension ratio and the older age may explain the high insulin resistance indices in our study compared with the Kanauchi and Gokcel studies. Moreover, the subjects in the normal group were non-obese in Kanauchi's study. If the aging process is seen to associate with relative insulinopenia and insulin resistance itself, it seems likely that aging may be responsible for insulin resistance independent of cognitive status.

In our study, the ratio of patients with AD is higher than the general prevalence (10–15%) because our hospital is a reference center for dementia patients in the Turkish capital.

In a prospective study carried out in Rotterdam, Stolk *et al.* (1997) point out that increased insulin levels may be associated with a cognitive decline but only in women patients. The results showed no significance when the analysis

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was applied to the whole group. Our study supports the total results of the Rotterdam study. Razay and Wilcock (1994) have also found that women with AD have higher plasma insulin levels, higher plasma glucose and a higher body mass index whereas men do not. Unfortunately, these results were similar among women in the five cognitive groups but the literature supports the idea that insulin resistance mostly affects women. These results may be affected by the low number of patients in the VaD and mixed dementia groups, but also by the genetic differences in the patients. This is the first study among a Turkish population; and this may affect the results. Genetic variability in the signaling pathway may contribute to the risk of onset of AD (Liolitsa *et al.*, 2002). However, some of our data are contrary to those in the current literature, and must be confirmed with further large studies.

Yaffe *et al.* (2004) describe the role of metabolic syndrome and cognition in their study of 2632 elderly patients. Their conclusion is that in a prospective manner metabolic syndrome contributes to cognitive impairment in the elderly but significant results are primarily to be found in those with high levels of inflammation. However, our study does not indicate the interleukin-6 or C-reactive protein levels showing inflammation, suggesting that there may be a statistically significant difference between the degree of inflammation and cognitive status of the patients with metabolic syndrome. Metabolic syndrome is according to NCEP results, did not differ among groups in the present study. The prevalence of the metabolic syndrome, as well as the characteristics of subjects fulfilling the diagnostic criteria varied depending on the definitions used. The International Diabetes Federation (IDF) definition requires central obesity as a mandatory component for diagnosis of the metabolic syndrome, using ethnicity-specific values. For Turkish people, the IDF definition of central obesity is a waist circumference ≥ 94 cm for men and ≥ 80 cm for women. The National Cholesterol Education Program Adult Treatment Panel III (NCEP) definition is a waist circumference >102 cm in men and >88 cm in women. In the NCEP definition, the fact that both of the definitions include the same five components but with different emphasis on central obesity may be responsible for the lower prevalence of the metabolic syndrome. Application of the IDF criteria resulted in a higher prevalence of central obesity as well as metabolic syndrome; but the NCEP criteria were used in this study because of its suitability for people aged ≥ 50 years.

Although hyperinsulinemia is a critical component of the causal pathway to global cognitive impairment, the studies of these associations are not consistent. Insulin resistance was not previously found to be a significant determinant of global cognitive functioning when measured using MMSE as in our study (Abbatecola *et al.*, 2004), so the results for all five groups in this study do not produce any surprises. The present study is valuable for its conclusion that

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insulin resistance is not very important after diagnosis of dementia and does not differ among groups. But it can still be a valuable area for research in earlier stages before dementia is identified. This is also the first study to compare the HOMA and QUICKI formulas with metabolic syndrome criteria among five different cognition groups. Studies concerning the potential therapeutics such as PPAR (peroxisome proliferated activated receptor) agonists, are now emerging (Samuels and Grossman, 2003; Rasgon and Jarvik, 2004; Alarcon de la Lastra *et al.*, 2004; Smith *et al.*, 2006). One study showed that infusion of insulin enhances the performance of cognitive functions in non-diabetic people (Rasgon and Kenna, 2005). Glycogen syntase-3 is also a potential target for central nervous system (CNS) therapies (Bhat *et al.*, 2004). The problem is identifying which patients will benefit from the drugs and who will be the non-responders. There are also studies looking at agents that target the cardiovascular and cerebrovascular risk factors such as hypertension, hyperlipidemia and also insulin resistance, which have produced epidemiological and preclinical evidence to warrant further investigation (Samuels and Grossman, 2003). The present study may shed light on which factors affect the potential role of insulin resistance in cognition so that we can prevent dementia in such cases; in other words, the negative findings of this study are critical to the current literature in establishing the negligible role of insulin resistance following diagnosis, especially in moderate or severe dementia cases. In its advanced form, AD is experienced as a catabolic state and this may also affect the role of insulin resistance in severe cases (Abbatecola *et al.*, 2004). Gauthier (2005) clearly emphasizes that initiating treatment early in AD is important and reinforces the necessity to assess behavior and the activities of daily living. Improving insulin resistance may prevent dementia and our data suggests that insulin resistance must therefore be studied in predementia stages, not after diagnosis.

There are some limitations to the study. The number of patients in the VaD and mixed dementia groups was low and this may have affected the results. Also, we do not have the apolipoprotein E status of the patients, which is again one of the important factors affecting the cognitive status especially in $\varepsilon 4$ positive patients. There are studies about the possible mechanisms of insulin resistance and cognition involving measurements of amyloid precursor protein, amyloid β 40 and 42 levels, in lumbar puncture samples of the patients (Strachan, 2003; Abbatecola *et al.*, 2004). Insulin may stimulate the secretion of β amyloid from neurons or compete for binding sites on insulin degrading enzymes that play a role in the breakdown of β amyloid protein (Strachan, 2003; Craft *et al.*, 2003). In this study there were no lumbar puncture results to compare with these values. Another limitation of our study is that it is prospective but cross sectional, so we could not see direct further effects of insulin resistance on cognitive function but we could compare different groups of cognitive function according to the presence of current insulin resistance or metabolic syndrome diagnosis.

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According to the present literature this is the first human study of the possible relation of insulin resistance and cognitive function in five different groups of cognitive status, but unfortunately the results are too limited to allow generalizations to be made (Razay and Wilcock, 1994; Stolk *et al.*, 1997; Abbatecola *et al.*, 2004). However, aging seems more important than insulin resistance; thus further prospective cohort studies which follow a normal cognitive group and MCI patients with and without insulin resistance are necessary to demonstrate any relationship.

Conflict of interest

None.

Description of authors' roles

Ahmet Turan Isik designed the study and, with Mustafa Cankurtaran and Ergun Bozoglu, supervised the data collection and wrote the paper, assisted by Bilgin Comert, Huseyin Doruk and M. Refik Mas. Ahmet Turan Isik, Mustafa Cankurtaran and Bilgin Comert were responsible for the statistical design of the study and for carrying out the statistical analyses.

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