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노인에서 인지기능에 영향을 미치는 대사적 특성에 관한 안성 코호트 기반 연구

Effects of Metabolic Factors on Cognitive Function in Elderly Korean: A Prospective Community-Based Cohort Study

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공 성 혜

Abstract

Effects of Metabolic Factors on Cognitive Function in Elderly Korean: A Prospective Community-Based Cohort Study

Sung Hye Kong

College of Medicine, Department of Translational Medicine

The Graduate School

Seoul National University

Objective

As geriatric population grows continuously, cognitive dysfunction becomes a major problem in quality of life of both patients and their families. It is important to understand whether metabolic factors such as hyperglycemia, insulin resistance, and obesity could be risk factors of cognitive dysfunction.

Method

The study was conducted in the Ansung Cohort Study, the ongoing prospective community-based cohort study in Korea. A total of 1,387 participants aged over 65

years at baseline were followed up for a mean of 6 years. Of them, the final analysis was performed in 422 participants who were evaluated with Korean mini-mental status examination score (K-MMSE) at both baseline and follow-up. Pearson's correlation analyses and multivariate linear regression analyses for change of K-MMSE score were carried out.

Results

Mean age at baseline was 69.3 ± 2.9 years, and 222 participants (52.6%) were men. Mean duration of education was 7.1 ± 3.6 years. During a mean follow-up of 6 years, K-MMSE score was significantly decreased with 1.0 (interquartile range [IQR] of 4.0), homeostasis model assessment of insulin resistance (HOMA-IR) was not significantly changed during follow-up.

Participants with more decreased K-MMSE score (Δ K-MMSE) had shorter duration of education ($p = 0.001$), older age ($p = 0.022$), higher baseline K-MMSE score ($p < 0.001$), and increased insulin resistance (Δ HOMA-IR, $p = 0.002$).

Participants with lower K-MMSE at their baseline had shorter education duration ($r = 0.393$, $p < 0.001$), higher KDSQ score ($r = -0.129$, $p = 0.008$), and higher GDS-K score ($r = -0.128$, p 0.008). Also, participants with lower K-MMSE at follow-up had older age ($r = -0.119$, $p = 0.014$) and shorter duration of education ($r = 0.400$, $p < 0.001$).

The correlation between Δ K-MMSE and Δ HOMA-IR remained significant after adjustments for age, gender, baseline K-MMSE score, duration of education,

baseline Korean geriatric depression scale, smoking status, history of diabetes and hypertension, body mass index, and apolipoprotein E4 genotype status (B = -0.201, p = 0.002). Correlations between Δ K-MMSE and baseline HbA1c, Δ K-MMSE and BMI were not significantly associated after the adjustments (B = -0.055, p = 0.257 for HbA1c, B = -0.008, p = 0.873 for BMI).

Conclusions

During 6 years of follow-up in Korean elderly population, increased insulin resistance was significantly associated with decreased cognitive function.

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Keywords: Cognitive dysfunction; insulin resistance; obesity; HbA1c; K-MMSE; HOMA-IR.

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Introduction

The world is growing old, and Korea is not an exception. According to Population and Housing Census from Statistics Korea, proportion of geriatric population was 6.28% in 1995, 11.3% in 2010, and increasing continuously (1). If geriatric population continues to grow, it could be 14.3% in 2018, even up to 20.8% in 2026 (1). At the same time, the prevalence of dementia and cognitive dysfunction has also been increased together in many countries including Korea (2-4). Dementia in geriatric population is not only related to quality of life of each individuals, also closely related to the quality of lives of family members, and eventually causes cost to the society. According to the report of dementia population by Korean Ministry of Health and Welfare, social cost of dementia was 11,700,000,000,000 won, almost 1.0% of total gross domestic product (GDP) in 2013 (5).

On the other hand, the prevalence of type 2 diabetes mellitus (T2DM) and obesity have also increased over time (4, 6, 7). The prevalence of diabetes was 5.6% in 2006, has increased to 8.0% in 2013, and increment in geriatric population was prominent according to Korean Diabetes Fact Sheet (4). Also, prevalence of obesity in geriatric population was 22.0% in 1998, 33.8% in 2013 according to Korea National Health and Nutrition Examination Survey (26.0% in 1998 and 32.5% in 2013 in total population) (7).

Although it has been questioned whether metabolic factors such as hyperglycemia, insulin resistance, and obesity have influence on development of cognitive dysfunction, there are still remained questions.

Peripheral insulin resistance as a risk factor for cognitive dysfunction

It is proposed that peripheral insulin resistance acts as a risk factor in declining cognitive function. A cross-sectional relationship between brain volume and peripheral insulin resistance has been reported that whole brain and hippocampal volume was smaller in those who had higher insulin resistance, measured by brain magnetic resonance imaging and oral glucose tolerance test (8). Also, participants with peripheral insulin resistance showed poorer cognitive function than those without insulin resistance in other cross-sectional studies (9-11). In a longitudinal study with 7,148 middle-aged adults, higher fasting insulin level and homeostasis model assessment of insulin resistance (HOMA-IR) were associated with greater decline of cognitive function test during 6 years (12). Another community-based cohort study of 683 elderly participants reported that incidence of dementia and decline of memory-related cognitive function was associated with increased fasting insulin level. The risk of Alzheimer's disease (AD) doubled in the participants with hyperinsulinemia (hazard ratio [HR] 2.1, 95% confidence interval [CI] 1.5 – 2.9), and memory-related cognitive function was negatively correlated with hyperinsulinemia (r = -0.08, p = 0.01) (13). In Hisayama Study, 135 autopsies results showed that postprandial glucose, fasting insulin, and HOMA-IR were associated with increased risk of neuritic plaques (14).

However, against previous expectations that insulin sensitizer could improve cognitive function, trials with peroxisome proliferator activated receptors (PPAR) γ agonist to cognitive impaired participants showed inconsistent results (15, 16). In one study with rosiglitazone, cognitive function was improved only in non-carriers of apolipoprotein ε4 (APOE ε4) genotype (15), while the other study failed to show the same result (16).

Possible mechanisms of insulin resistance related cognitive dysfunction

Insulin receptor is widely distributed in the brain, suggesting that the brain is one of major target organs of insulin (17). Insulin receptors are highly expressed in the hippocampus, the region mainly involved in memory function (18). It has been known that insulin has a protective effect on neurons and modulates synapse plasticity mechanisms (19, 20). In the brains of AD, insulin resistance of the neuronal cells were observed, suggesting that insulin resistance might cause neuronal cell dysfunction, leads to cognitive dysfunction and dementia (21, 22).

Peripheral insulin resistance and chronic peripheral hyperinsulinemia could down-regulate insulin transport into the brain, leading to insulin-deficient state of the brain (23). Peripheral hyperinsulinemia could increase amyloid beta levels (24) and cytokines such as interleukin 6, tumor necrosis factor alpha in plasma and cerebrospinal fluid (25). Increased levels of amyloid beta and inflammatory

cytokines could induce neuronal loss, amyloid beta plaques and neurofibrillary tangles (26). There was a report that high fat diet (HFD) fed mice with peripheral insulin resistance became to have insulin resistance in the brain (27). In aforementioned study, competitive saturation binding assays of insulin demonstrated impairment of insulin receptor binding in the brain of HFD fed mice, and this phenomenon correlates with the findings of the brain in early stages of Alzheimer disease. Reduced β-actin and increased ubiquitin expression was also observed, consistent with the findings in AD (27). Reduced β-actin and increased ubiquitin could lead to cytoskeletal collapse and increased oxidative stress of neuronal cells, related to progressive loss of synaptic plasticity (28, 29), supporting the potential role of insulin resistance in AD.

There was a remained question about peripheral insulin resistance as a consistent risk factor for cognitive dysfunction. Most studies about peripheral insulin resistance and cognitive dysfunction were cross-sectional studies (8, 9, 11, 30). Although there are some longitudinal studies (12-14), effect of change of insulin resistance over time on cognitive dysfunction has not been studied yet. It is important to know whether improvement of insulin resistance over time could slower, or even improve cognitive dysfunction in elderly.

Baseline HbA1c level as a risk factor of cognitive dysfunction

Evidences have been accumulated since Rotterdam study that T2DM is a strong risk factor for dementia and cognitive dysfunction (31). Rotterdam study with 6,330 participants aged 55 to 99 years old reported that participants with T2DM had increased risk of dementia (odds ratio [OR] 1.9, 95% CI 1.3 – 2.8). In particular, strong association between dementia and diabetes treated with insulin (OR 3.2, 95% CI 1.4 – 7.5) were found (31). In Honolulu-Asia Aging Study, a population-based longitudinal cohort study with 2,574 Japanese-American men, T2DM was associated with increased risk of all forms of dementia (risk ratio (RR) 1.5, 95% CI 1.0 – 2.2), AD (RR 1.8, 95% CI 1.1 – 2.9), and vascular dementia (RR 2.3, 95% CI 1.1 – 5.0) (32).

On the other hand, it is relatively controversial whether baseline HbA1c level is associated with cognitive dysfunction. In one dementia-free cohort, 1,248 population over 75 years old were followed up for 9 years. They showed that people with fasting glucose levels over 11.0 mmol/L had increased risk of AD (HR 3.3, 95% CI 1.2 – 9.0) (33). In another study with adults with their mean age of 74 years followed up for 9 years, higher HbA1c level was associated with lower average mean cognitive scores (34). However, there are studies that did not show any association between HbA1c level and cognitive dysfunction (35, 36). The Leiden 85-plus Study – a prospective population study of 599 persons from age 85 – showed that HbA1c level was not associated with cognitive impairment (35). Also in a study with 205 participants with diabetes, HbA1c level and fasting glucose levels was not associated with cognitive dysfunction (36). The different

results of aforementioned studies might be explained by different baseline age of the studies. Because population over 80 years old have high rates of cognitive decline in both diabetic and non-diabetic participants, it may have masked additional effects of hyperglycemia, leading to ceiling effect (35). It is still controversial that HbA1c level of elderly population is related to cognitive dysfunction. Also, it has not been studied whether HbA1c is associated with change of cognitive dysfunction in Korean elderly population.

Possible mechanisms of hyperglycemia related cognitive dysfunction

There are several explanations for influence of hyperglycemia on cognitive dysfunction. First, there is hypothesis that increased polyol pathway in hyperglycemia could reduce neuronal growth (37). The polyol pathway is a minor pathway of glucose metabolism that increases the intracellular sorbitol and inositol. The increment of intracellular sorbitol was associated with cellular tissue damage (38), and it is assumed that it is because of increased intracellular osmolality or the reduced cellular redox state (39). In a study, hyperglycemia induced rats were associated with significant increment in brain sorbitol and inositol, and reduction of dendritic branching (37). Second, increased advanced glycation end products in hyperglycemia state could induce neuronal damage (40, 41). There was a study with long-term (9 months) experimental diabetes model of mice. It showed that increased receptor for advanced glycation end products (RAGE) expression was found at sites of white matter damaged regions. RAGE null diabetic mice had less

neurodegenerative changes than wild type diabetic mice (41). These results implies that peripheral hyperglycemia may have effect on central neuronal damage.

Obesity as a risk factor of cognitive dysfunction

In recent years, there has been an increasing interest that obesity could be a risk factor for dementia and cognitive dysfunction (42-44), but it is still unclear. In a longitudinal study with a 21-year follow-up, obesity at midlife (body mass index [BMI] > 30 kg/m^2) was associated with the risk of dementia and AD (OR 2.4, 95% CI 1.2 – 5.1) (43). Also, cognitive impairments have been reported in obese participants in almost all domains including executive function, memory, and learning (45, 46). However, there are other studies that does not support previous results (47, 48). In a longitudinal study with an 8-year follow-up, obesity in elderly was not associated with major and minor cognitive decline (OR 1.0, 95% CI 0.9 – 1.0) (47). In another longitudinal study with a 6-year follow-up, obesity was not associated with change of cognitive function in elderly population with normal cognitive function (coefficient 0.0008, p = 0.086 in non-black participants, coefficient 0.0003, p = 0.415 in black participants) (48). Even in one study, participants with declining BMI was associated with increased risk of incident AD (49). As described above, the association between body composition and cognitive function in elderly is more complex and has been inconsistent.

Possible mechanisms of body composition and cognitive dysfunction

There is a hypothesis that obesity may have direct influence on brain pathology and can increase the risk of AD (50). One suggested mechanism is insulin resistance and impaired glucose metabolism induced by obesity (51). Peripheral hyperinsulinemia could increase amyloid beta levels and inflammatory cytokines, and this could result in neuronal loss, amyloid beta plaques and neurofibrillary tangle accumulation (24-26). Also, polyol pathway and increased advanced glycation products in hyperglycemia could damage neurons and dendritic branching (37, 40, 41). Another suggested mechanism is impaired leptin signaling pathway. A recent study showed that leptin plays a significant role in the regulation of brain functions, which implicates that impaired leptin pathway could lead to cognitive dysfunction (52). On the other hand, mechanisms underlying relation between low relative BMI may be the deposition of AD pathology in areas of the brain that regulate body composition. A recent study reported that participants with the lowest levels of BMI showed higher AD pathology (49).

Aim of the study

As population with cognitive dysfunction is increasing consistently, it is very important to find out whether metabolic factors are related to cognitive dysfunction. The aim of the present study is to investigate whether metabolic factors such as insulin resistance, hyperglycemia, and obesity are associated with change of cognitive function in Korean prospective community-based cohort study.

Methods

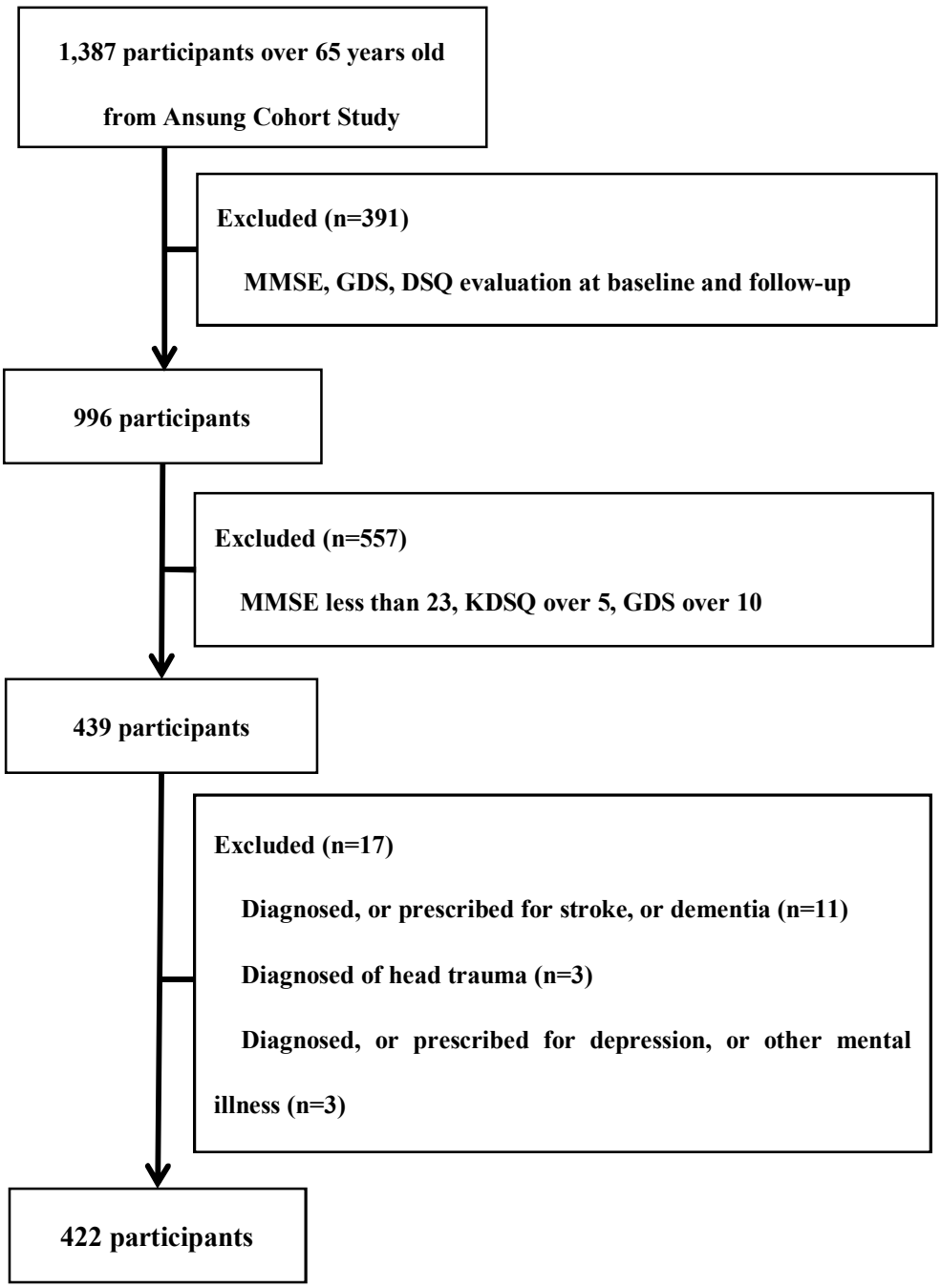
Study population

The study was based on data from the Ansung cohort study. Ansung cohort study is a prospective study which began in 2001 supported by National Genome Research Institute (Korea Centers for Disease Control and Prevention, Cheongju, Korea). The study is a part of the Korean Genome Epidemiology Study (KoGES), a community-based epidemiological survey with a population-sample of Korean participants from 40 to 69 years of age. Participants were recruited from dwellers of Ansung who have lived in the survey area for at least 6 months before enrollment. According to the 2000 census, Ansung is a rural community with 132,906 residents. Detailed information on the selection criteria and sampling plan for the cohort study has been published previously (53, 54). This study protocol was approved by the Korea Centers for Disease Control and Prevention Institutional Review Board.

A total of 1,387 participants over 65 years old completed a baseline examination in 2001 and surveyed biennially until 2014. For the analysis, 391 participants were excluded if they do not have Korean mini-mental status examination (K-MMSE), 15-item Korean geriatric depression score (GDS-K), or Korean dementia screening questionnaire (KDSQ) evaluation at baseline or follow-up. Also, 557 participants whose K-MMSE score were less than 23, KDSQ score over 5, or GDS-K score

over 10 were excluded. Additionally, 17 participants who were diagnosed with stroke, dementia, depression or head trauma were excluded. These exclusions left 422 participants eligible for analysis, as described in Figure 1.

Figure 1. Study population from Ansung cohort study



Assessment of cognitive impairment and depression

Cognitive impairment and depression scale were measured at both baseline and follow-up. Cognitive impairment was evaluated by K-MMSE and KDSQ. K-MMSE has been specifically developed and evaluated for the assessment of general cognitive function in older Korean population (55). K-MMSE score is a 30-point questionnaire, and any score greater than or equal to 23 points out of 30 indicates a normal cognition. Below this, scores can indicate moderate to severe (<17 points) and mild cognitive impairment (17 – 22 points). KDSQ is a sensitive screening test to detect early dementia patients, not influenced by age and educational level (56). KDSQ score is a 15-point questionnaire, and any score greater than 5 points is suggestive of cognitive impairment. Depressive symptoms were assessed by 15-item Korean geriatric depression scale (GDS-K) (57). Δ K-MMSE and Δ HOMA-IR were defined as follows:

Δ K-MMSE = follow-up K-MMSE – baseline K-MMSE

Δ HOMA-IR = follow-up HOMA-IR – baseline HOMA-IR

Measurements of anthropometric parameters

Face-to-face or telephone interviews were used to obtain data on lifestyle, sociodemographic factors, including age, gender, duration of education, past medical history, drinking and smoking status. Former smokers were defined as those who had smoked >5 packs of cigarettes during their lifetime, and quitted for

at least 6 months before baseline. Former drinkers were defined as those who had consumed 5 g ethanol/day and quitted for at least 6 months before baseline. Past medical history including diabetes, hypertension, stroke, dementia, head trauma, depression, and other mental illness was defined as a self-reported diagnosis from hospital.

The height and body weight were measured using standard methods while the participants were wearing light-weight clothes by trained staff using a scale and a wall-mounted extensometer. BMI was calculated as the weight divided by height squared (kg/m^2).

Laboratory assessments and homeostasis model assessment of insulin resistance (HOMA-IR) calculation

All of the participants fasted for 14 hours before undergoing blood sampling. Plasma was separated immediately by centrifuge (2000 rpm, 20 min, at 4℃), and measurements were conducted immediately. Plasma glucose level was measured using hexokinase method (ADVIA 1650 Auto Analyzer, Bayer, Leverkusen, Germany), and plasma insulin level was measured by IRMA test kit (bioSource Europe S.A., Niverlles, Belgium). Fasting TC, HDL-C, LDL-C, and TG levels were measured enzymatically using the Hitachi 747 chemistry analyzer (Hitachi, Tokyo, Japan). The HbA1c level was determined using high-performance liquid chromatography by Bio-Rad Variant II HbA1c analyzer (Bio-Rad, Montreal, Quebec, Canada). APOE ε4 genotyping was done using the method of Hixson and

Vernier (58) only for consenting participants. The genotype was categorized as the presence or absence of the ε4 allele. HOMA-IR was computed using following formula:

HOMA-IR = fasting plasma insulin (μIU/mL) x fasting plasma glucose (mg/dL) x 0.0555 / 22.5 (59)

Statistical analysis

Data were presented as means ± standard deviation (SD) in normal distribution, as median (IQR) in non-normal distribution, or as n (%) in categorical data. The paired *t* test and Student's *t* test for normal distribution, or Wilcoxon signed-rank test and Mann-Whitney *U* test for non-normal distribution were used for the comparison of baseline characteristics. A Pearson correlation coefficient was used to estimate the relationship between cognitive function and other parameters.

Associations of cognitive function and other factors were analyzed using multivariable linear regression models. In model 1, adjustment was done for age, gender, baseline K-MMSE score, education duration, and baseline GDS-K score. Model 2 adjusts for factors of model 1 and additionally adjusts for smoking status, history of diabetes and hypertension, and BMI. Model 3 adjusts for factors of model 2 and additionally adjusts for Apoε4 genotype. A p value of <0.05 was considered to be significant. Statistical analyses were performed using the SPSS for

Windows (Version 22.0; SPSS Inc.; Chicago, IL, USA).

Results

Baseline characteristics

Clinical characteristics of the study participants at baseline and follow-up are described in Table 1. Mean follow-up duration was 5.9 ± 0.1 years. The mean age at baseline is 69.3 ± 2.9 years at baseline, and 222 (52.6%) of participants were men. Education duration was 7.1 ± 3.6 years. Participants with hypertension were 115 (27.3%) at baseline, and increased to 207 (49.1%) at follow-up. Participants with diabetes were 89 (21.1%) at baseline, and increased to 113 (26.8%) at follow-up. K-MMSE score was significantly changed from 26.5 ± 1.9 to 25.4 ± 2.9, decreased of -1.0 (IQR 4.0). KDSQ score was significantly increased from 2.0 (IQR 3.0) to 3.0 (IQR 5.0). GDS-K score was significantly increased from 2.0 (IQR 3.0) to 2.0 (IQR 5.0). Lipid profiles such as low density lipoprotein, high density lipoprotein, triglyceride levels were significantly reduced, and creatinine level was significantly increased during follow-up. HOMA-IR, fasting insulin and HbA1c levels were not significantly changed. APOE ε4 genotype was found in 72 (17.1%) participants (Table 1).

Table 1. Baseline characteristics of participants in baseline and follow-up

	Baseline (n=422)	Follow-up (n=422)	*p*-value
Age, years	69.3 ± 2.9	75.3 ± 2.9	< 0.001
Gender (male), n (%)	222 (52.6)		
Education duration, years	7.1 ± 3.6		
Hypertension, n (%)	115 (27.3)	207 (49.1)	
Diabetes, n (%)	89 (21.1)	113 (26.8)	
Ever smoker, n (%)	151 (35.8)	167 (39.6)	
Current alcohol intake, n (%)	198 (46.9)	194 (46.0)	
Body mass index, kg/m^2	23.9 ± 3.1	23.7 ± 3.3	0.015
K-MMSE baseline, score	26.5 ± 1.9	25.4 ± 2.9	< 0.001
Δ K-MMSE, score	-1.0 (4.0)		
HOMA-IR baseline	1.78 (1.23)	1.79 (1.25)	0.970
Δ HOMA-IR	-0.02 (1.12)		
KDSQ, score	2.0 (3.0)	3.0 (5.0)	< 0.001
GDS-K score	2.0 (3.0)	2.0 (5.0)	< 0.001
Fasting insulin, μIU/L	8.8 ± 5.4	8.8 ± 4.2	0.845

HbA1c, %	5.8 ± 0.8	5.8 ± 0.7	0.616
Low density lipoprotein, mg/dL*	121.6 ± 29.7	107.9 ± 29.5	< 0.001
High density lipoprotein, mg/dL*	43.1 ± 10.1	44.2 ± 11.8	0.001
Triglyceride, mg/dL*	132.1 ± 69.2	122.3 ± 60.9	0.002
Creatinine, mg/dL	0.9 ± 0.2	1.1 ± 0.3	< 0.001
APOE ε4 genotype, n (%)	72 (17.1)		

K-MMSE, Korean mini mental status examination; HOMA-IR, homeostasis model assessment of insulin resistance; KDSQ, Korean dementia screening questionnaire; GDS-K, Korean geriatric depression scale; APOE ε4, apolipoprotein ε4.

Paired *t*-test for normal distribution, and Wilcoxon signed-rank test for non-normal distribution were done between baseline and follow-up data. Continuous variables are given as means ± standard deviation for variables with normal distribution, otherwise as medians (interquartile range). Categorical variables are given as n (%).

* Lipid profile was evaluated only in participants not on dyslipidemia treatment.

Comparison of baseline characteristics between participants with Δ K-MMSE ≤ -1 and > -1

Participants were divided into 2 groups according to a median value of Δ K-MMSE; those with Δ K-MMSE ≤ -1 (n = 229), and Δ K-MMSE > -1 (n = 193). Δ K-MMSE values of each group were -3.0 (IQR 3.0) in participants with Δ K-MMSE ≤ -1, and 1.0 (IQR 2.0) in those with Δ K-MMSE > -1. Participants with Δ K-MMSE ≤ -1 had significantly shorter education duration (p = 0.003), and higher baseline score of K-MMSE (p < 0.001) than those with Δ K-MMSE > -1. Age, gender, history of hypertension and diabetes, smoking and drinking status, BMI, baseline HOMA-IR, Δ HOMA-IR, baseline KDSQ and GDS-K score, fasting insulin level, HbA1c level, lipid profiles, creatinine level, and APOE ε4 genotype status did not show significant difference between 2 groups (Table 2).

Table 2. Baseline characteristics of participants according to Δ K-MMSE

	Δ K-MMSE ≤ -1 (n=229)	Δ K-MMSE > -1 (n=193)	*p*-value
Age, years	69.5 ± 2.9	69.1 ± 2.9	0.129
Gender (male), n (%)	116 (50.7)	106 (54.9)	0.434
Education duration, years	6.6 ± 3.7	7.6 ± 3.5	0.003
Hypertension, n (%)	61 (26.6)	54 (27.9)	0.819
Diabetes, n (%)	47 (20.7)	42 (21.9)	0.431
Ever smoker, n (%)	80 (34.9)	71 (36.8)	0.760
Current alcohol intake, n (%)	106 (46.3)	92 (47.7)	0.845
Body mass index, kg/m^2	24.0 ± 2.9	23.8 ± 3.2	0.706
K-MMSE baseline, score	26.8 ± 2.0	26.1 ± 1.7	< 0.001
Δ K-MMSE, score	-3.0 (3.0)	1.0 (2.0)	< 0.001
HOMA-IR baseline	1.73 (1.27)	1.82 (1.17)	0.316
Δ HOMA-IR	0.12 (1.15)	-0.14 (0.93)	0.002
KDSQ, score	2.0 (3.0)	2.0 (3.0)	0.375
GDS-K score	2.0 (4.0)	2.0 (3.0)	0.715
Fasting insulin, μIU/L	8.5 ± 3.4	9.2 ± 4.2	0.172

HbA1c, %	5.8 ± 0.8	5.8 ± 0.7	0.365
Low density lipoprotein, mg/dL*	120.5 ± 27.9	122.9 ± 31.6	0.388
High density lipoprotein, mg/dL*	42.8 ± 9.4	43.4 ± 11.1	0.519
Triglyceride, mg/dL*	130.3 ± 65.1	134.3 ± 73.9	0.558
Creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	0.988
APOE ε4 genotype, n (%)	35 (15.5)	37 (19.5)	0.300

K-MMSE, Korean mini mental status examination; HOMA-IR, homeostasis model assessment of insulin resistance; KDSQ, Korean dementia screening questionnaire; GDS-K, Korean geriatric depression scale; APOE ε4, apolipoprotein ε4.

Student's *t*-test for normal distribution, and the Mann-Whitney *U* test for non-normal distribution were done. Continuous variables are given as means ± standard deviation for variables with normal distribution, otherwise as medians (interquartile range). Categorical variables are given as n (%).

* Lipid profile was evaluated only in participants not on dyslipidemia treatment.

Correlation between Δ K-MMSE and other parameters

Pearson's correlation analyses were performed to assess correlation between Δ K-MMSE and other parameters. Participants with more decreased Δ K-MMSE had older age (r = -0.111, p = 0.022), higher baseline score of K-MMSE (r = -0.224, p <0.001), and more increased Δ HOMR-IR (r = -0.151, p = 0.002) (Figure 2). Participants with more decreased Δ K-MMSE had shorter duration of education (r = 0.156, p = 0.001). BMI, baseline HOMA-IR, KDSQ score, GDS-K score, fasting insulin level, HbA1c level, lipid profiles, and creatinine level did not show significant correlation with Δ K-MMSE (Table 3).

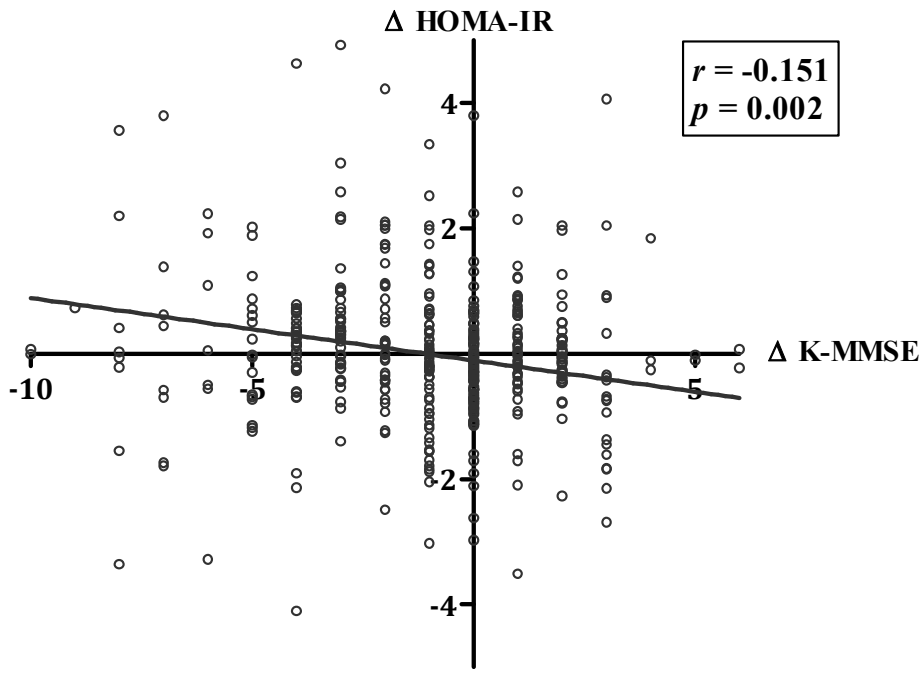
Table 3. Correlations between Δ K-MMSE and other parameters

	Correlation coefficients *(r)*	***p*-value**
Age, years	-0.111	0.022
Education, years	0.156	0.001
K-MMSE baseline, score	-0.224	<0.001
Body mass index, kg/m^2	-0.008	0.873
KDSQ, score	0.049	0.318
GDS-K, score	0.010	0.837
HOMA-IR baseline	0.056	0.254
Δ HOMA-IR	-0.151	0.002
Fasting insulin, μIU/L	0.074	0.130
HbA1c, %	-0.055	0.257
Low density lipoprotein, mg/dL*	0.043	0.378
High density lipoprotein, mg/dL*	-0.014	0.774
Triglyceride, mg/dL*	0.036	0.459
Creatinine, mg/dL	0.042	0.384

K-MMSE, Korean mini mental status examination; HOMA-IR, homeostasis model assessment of insulin resistance; KDSQ, Korean dementia screening questionnaire; GDS-K, Korean geriatric depression scale. Pearson's correlation analyses were done between Δ K-MMSE and parameters.

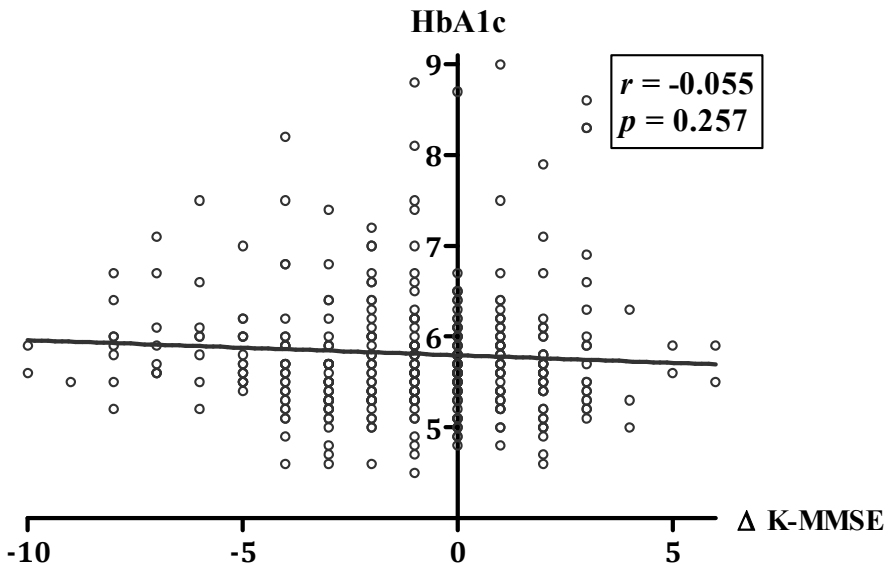
* Lipid profile was evaluated only in participants not on dyslipidemia treatment.

Figure 2. Correlation between Δ K-MMSE and Δ HOMA-IR



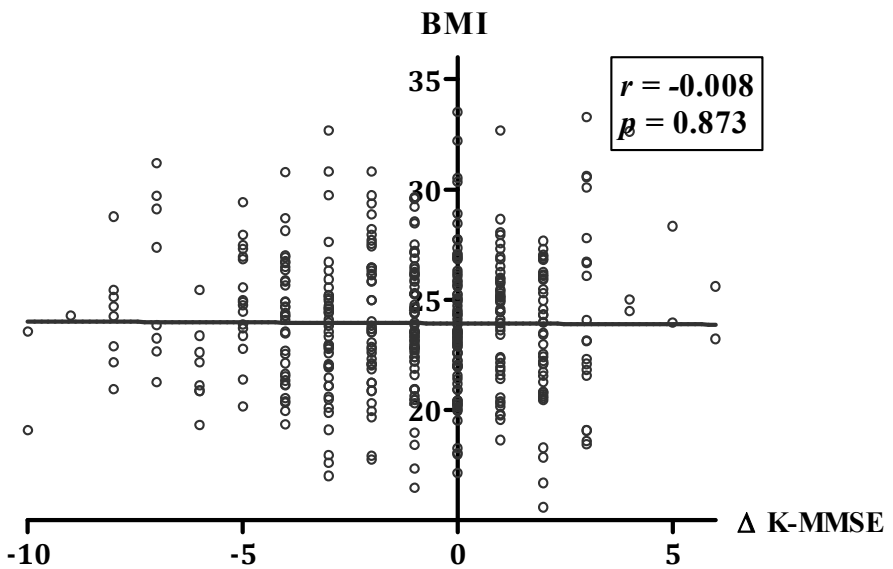
K-MMSE, Korean mini mental status examination; HOMA-IR, homeostasis model assessment of insulin resistance.

Figure 3. Correlation between Δ K-MMSE and baseline HbA1c in participants with diabetes



K-MMSE, Korean mini mental status examination.

Figure 4. Correlation between Δ K-MMSE and BMI in participants with diabetes



K-MMSE, Korean mini mental status examination; BMI, body mass index.

Correlation between K-MMSE and other parameters at baseline

Pearson's correlation analyses were performed to assess correlation between K-MMSE at baseline and other parameters. Participants with lower K-MMSE at their baseline had shorter education duration (r = 0.393, p <0.001), higher KDSQ score (r = -0.129, p =0.008), and higher GDS-K score (r = -0.128, p 0.008). Baseline age, BMI, baseline HOMA-IR, Δ HOMA-IR, fasting insulin level, HbA1c level, lipid profiles, and creatinine level did not show significant correlation with baseline K-MMSE (Table 4).

Table 4. Correlations between K-MMSE and other parameters at baseline

	Correlation coefficients *(r)*	*p*-value
Age, years	-0.016	0.746
Education, years	0.393	<0.001
Body mass index, kg/m^2	-0.058	0.240
KDSQ, score	-0.129	0.008
GDS-K, score	-0.128	0.008
HOMA-IR baseline	0.006	0.902
Δ HOMA-IR	-0.027	0.586
Fasting insulin, μIU/L	-0.019	0.703
HbA1c, %	0.034	0.481
Low density lipoprotein, mg/dL*	-0.002	0.961
High density lipoprotein, mg/dL*	-0.031	0.526
Triglyceride, mg/dL*	-0.020	0.974
Creatinine, mg/dL	0.021	0.840

K-MMSE, Korean mini mental status examination; HOMA-IR, homeostasis model assessment of insulin resistance; KDSQ, Korean dementia screening questionnaire; GDS-K, Korean geriatric depression scale. Pearson's correlation analyses were done between Δ K-MMSE and parameters.

* Lipid profile was evaluated only in participants not on dyslipidemia treatment.

Correlation between K-MMSE and other parameters at follow-up

Pearson's correlation analyses were performed to assess correlation between K-MMSE at follow-up and other parameters. Participants with lower K-MMSE at follow-up had older age (r = -0.119, p = 0.014) and shorter duration of education (r = 0.400, p < 0.001). However, BMI, KDSQ score, GDS-K score, HOMA-IR, Δ HOMA-IR, fasting insulin level, HbA1c level, lipid profiles, and creatinine level at follow-up did not show significant correlation with K-MMSE at follow-up (Table 5).

Table 5. Correlations between K-MMSE and other parameters at follow-up

	Correlation coefficients *(r)*	*p*-value
Age, years	-0.119	0.014
Education, years	0.400	<0.001
Body mass index, kg/m^2	-0.014	0.781
KDSQ, score	-0.074	0.132
GDS-K, score	-0.044	0.523
HOMA-IR at follow-up	-0.127	0.009
Δ HOMA-IR	-0.155	0.001
Fasting insulin, μIU/L	-0.156	0.001
HbA1c, %	-0.024	0.628
Low density lipoprotein, mg/dL*	0.011	0.829
High density lipoprotein, mg/dL*	-0.003	0.952
Triglyceride, mg/dL*	-0.027	0.584
Creatinine, mg/dL	0.094	0.054

K-MMSE, Korean mini mental status examination; HOMA-IR, homeostasis model assessment of insulin resistance; KDSQ, Korean dementia screening questionnaire; GDS-K, Korean geriatric depression scale. Pearson's correlation analyses were done between Δ K-MMSE and parameters.

* Lipid profile was evaluated only in participants not on dyslipidemia treatment.

Multivariate linear regression models for Δ K-MMSE with Δ HOMA-IR

After adjustment for age, gender, baseline K-MMSE score, education duration, and baseline GDS-K in model 1, participants with increased Δ HOMA-IR had significantly decreased Δ K-MMSE (B = -0.204, p = 0.003). Addition to model 1, adjustments were done for smoking status, history of diabetes and hypertension, and BMI in model 2, participants with increased Δ HOMA-IR had significantly decreased Δ K-MMSE (B = -0.199, p = 0.004). Addition to model 2, adjustments were done for APOE ε4 genotype status in model 3. Participants with increased Δ HOMA-IR remained to have significantly decreased Δ K-MMSE (B = -0.201, p = 0.004) (Table 6).

Table 6. Multivariate linear regression models of Δ K-MMSE with Δ HOMA-IR

	***B* of Δ HOMA-IR**	**95% CI**	***p***
Unadjusted	-0.151	-0.371 – -0.084	0.002
Model 1	-0.204	-0.339 – -0.068	0.003
Model 2	-0.199	-0.334 – -0.063	0.004
Model 3	-0.201	-0.337 – -0.065	0.004

K-MMSE, Korean mini mental status examination; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence interval.

Multivariable linear regression analysis was done. Model 1 adjusts for age, gender, baseline K-MMSE, education duration, baseline GDS-K. Model 2 adjusts for model 1 factors and additionally adjusts for smoking status, history of diabetes and hypertension, and body mass index. Model 3 adjusts for model 2 factors and additionally adjusts for APOE ε4 genotype status.

Discussion

In this community-based, prospective cohort study, it is found that cognitive decline was associated with increased insulin resistance over 6 years after adjusting for age, gender, baseline K-MMSE, education duration, baseline GDS-K, smoking status, history of diabetes and hypertension, BMI, and APOE ε4 genotype status. The study implicates that change of insulin resistance, not baseline HbA1c, BMI is associated with cognitive decline over 6 years in Korean geriatric population. The more insulin resistance increased, the more cognitive function decreased.

This study is consistent with most of prior investigations (9-14), and it extends those findings in several ways. First, in this study, change of insulin resistance over time was associated with cognitive decline, not baseline insulin resistance. Most of previous studies showed only baseline insulin resistance data. Some studies showed that baseline insulin resistance was associated with cognitive dysfunction (9, 11-13), while other studies showed no association between baseline insulin resistance and cognitive dysfunction (10, 60). The studies with positive results were mostly studied in participants without cognitive dysfunction (9) or relatively younger participants (12). On the other hand, the studies with null results were mostly studied in participants with mild cognitive dysfunction or relatively elderly participants (10, 60). This study was done in elderly participants without cognitive impairments, and was consistent with previous studies from elderly that showed no

association between baseline insulin resistance and cognitive decline. However, change of insulin resistance over time was significantly associated with cognitive decline in elderly participants, which implies that control of insulin resistance could improve cognitive dysfunction in elderly community-dwelling population.

In terms of HbA1c, this result was coherent with some of previous studies that baseline HbA1c was not associated with progression of cognitive dysfunction (35, 36). However, there are other studies with different results that higher baseline HbA1c was associated with advanced cognitive dysfunction or dementia (33, 34). It is possible that the 6-year follow-up of this study might not long enough to see the effect of hyperglycemia on cognitive dysfunction. Studies with positive association had mean follow-up durations of 9 years in both studies (33, 34), while studies with null association were followed up for 6 years (35), and 1.6 years (36). Another possibility is that effect of hyperglycemia might be masked by ceiling effect in cognitive dysfunction because of old age, because population over age of 80 could have high rates of cognitive decline in both diabetic and non-diabetic participants (35). However, mean age of this study was 69.3, which was not higher than the mean ages of 74.2 (34), and 81.4 (33) in studies with positive results. So far, it could be hypothesized that improvement of insulin resistance might have stronger effect than hyperglycemia on cognitive dysfunction according to this work in Korean population.

In terms of body composition, this result was consistent with previous studies that BMI in elderly was not associated with change of cognitive dysfunction (47, 48). Although studies done in elderly population does not show consistent association (45-48), midlife obesity seems to have significant association with incident dementia (43). Considering different characteristics of previous studies, this result could be interpreted as a few possibilities. There is possibility that obesity might not be a significant risk factor in elderly. This is supported by inconsistent results from many studies about obesity (45-48), but relatively consistent results about vascular risk factors such as hypertension (61, 62). It is assumed that unlike vascular risk factors, obesity might have mixed effect with underweight participants. It is recently reported that subclinical early AD pathology could result as low BMI by deposition in the brain that regulates body composition (49). Also, considering that the study in midlife obesity was followed up for 21 years, current BMI may not have reflected lifetime or midlife BMI and variations in BMI with aging (43). High BMI in midlife, rather than current BMI, may be more likely to have influence on cognitive function in elderly.

There are several strengths of the current study. First, as far as I know, this is the first study which evaluated association between change of insulin resistance and change of cognitive function. It could be valuable data to elucidate the importance of control of insulin resistance in elderly to prevent cognitive dysfunction. Second, the study was analyzed from the Ansung Cohort study, which employs a large, community-based, prospective design and includes a relatively long-term follow-

up cohort with solid information concerning potential confounding factors. Third, I adjusted important covariates such as GDS-K, education duration, history of diabetes and hypertension, and apolipioprotein E4 genotype status. Also I excluded participants with previous history that could influence cognitive function such as stroke, dementia, depression or head trauma. Fourth, this is the first study in Korean that assessed association between insulin resistance and cognitive dysfunction. The study participants were only consists of Korean population, that this results could hardly be influenced by genetic variants among ethnicities.

There are also potential limitations in this study. First, although I included known confounding factors, there are still concern regarding residual confounding factors such as time-dependent factors, family history, and nutrients. Second, since the past medical history was based on questionnaires, recall bias may have occurred because questionnaires were dependent on the memory of participants. To overcome this limitation, interviews were done by qualified interviewers. Third, this results might not be applied to different ethnicities because I only included Korean population.

In conclusion, increased insulin resistance was associated with decreased cognitive function over 6 years in Korean population, independent of APOE ε4 genotype status. However, baseline HbA1c and BMI were not associated with change of cognitive function. Based on this result, further studies will be needed to evaluate the effect of modulation of insulin resistance on cognitive dysfunction in elderly.

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노인에서 인지기능에 영향을 미치는 대사적 특성에 관한 안성 코호트 기반 연구

국문초록

서론: 노인 인구의 지속적인 증가로 인하여 인지기능저하는 삶의 질에 있어 환자뿐만 아니라 부양 가족에게도 큰 사회적 문제로 대두되고 있다. 그러므로 본 연구에서는 우리 나라의 노인 인구에서 대사적인 요인들 – 고혈당, 인슐린 저항성, 그리고 비만 – 이 인지 기능 저하의 위험 인자로써 연관성이 있는지 알아보고자 한다.

방법: 본 연구는 현재 안성에서 진행 중인 지역사회 코호트인 안성 코호트 연구를 기반으로 하였다. 그 중 65세 이상 인구 총 1,387를 대상으로 하여 평균 6년 간 추적관찰 하였다. 그 중 K-MMSE 검사를 2 번 이상 시행한 인구인 422명을 대상으로 분석을 진행하였다. 6년 동안의 K-MMSE 검사의 변화량과 고혈당, 인슐린 저항성, 비만의 지표가 유의하게 연관성이 있는지 Pearson 연관 분석 및 다변량 선형 회귀 분석을 이용하여 분석하였다.

결과: 총 422명의 연구대상자의 평균 나이는 69.3 ± 2.9세였으며, 그 중 222명(52.6%)은 남성이었다. 평균 교육기간은 7.1 ± 3.6년이었다.

평균 6년간의 관찰 기간 중 K-MMSE 점수는 유의하게 1.0 (사분범위 4.0)점 감소하였으며, HOMA-IR은 통계학적으로 유의하게 변화하지 않았다.

연구대상자들 중 관찰 기간 동안 K-MMSE 점수가 많이 감소하였을수록 교육 기간은 짧은 경향을 보였고(p = 0.001), 나이가 많았으며(p = 0.022), 기저 K-MMSE 점수가 높았고(p < 0.001), 인슐린 저항성이 관찰 기간 중 많이 증가하였다(p = 0.002).

연구대상자들 중 기저 K-MMSE 점수가 낮은 사람일수록 교육 기간은 짧은 경향을 보였고(p < 0.001), KDSQ 점수는 높았으며(p = 0.008), K-DSQ 점수도 높은 경향을 보였다(p = 0.008). 또한, 최종 K-MMSE가 낮은 사람일수록 나이가 많았고(p = 0.014), 교육 기간은 짧은 경향을 보였다(p < 0.001).

K-MMSE 점수의 변화량과 HOMA-IR의 변화량의 관계는 나이, 성별, 기저 K-MMSE 점수, 교육 기간, 기저 GDS-K 점수, 흡연 여부, 당뇨와 고혈압 유병여부, 체질량지수, apolipoprotein E4 유전형으로 보정하였을 때에도 유의하게 유지되었다(B = −0.201, p = 0.002). K-MMSE 점수의 변화량과 HbA1c, 체질량 지수의 관계는 위의 변수들로 보정한 이후 유의성이 유지되지 않았다(HbA1c B = −0.055, p = 0.257, 체질량지수 B = −0.008, p = 0.873).

결론: 본 한국 노인 인구의 6년 관찰 연구에서, 인슐린 저항성의 증가는 인지기능의 감소와 유의하게 연관되어 있으며, 가능한 여러 인자들을 보

정하였음에도 유의성이 유지되었다.

주요어: 인지기능 장애; 인슐린 저항성; 비만; HbA1c; K-MMSE; HOMA-IR.

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