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Long-Term Subclinical Hyperglycemia and Hypoglycemia as Independent Risk Factors for Mild Cognitive Impairment in Elderly People

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Dementia is one of the most common geriatric diseases, and mild cognitive impairment (MCI) is considered to be incipient dementia. MCI patients have elevated risk of progressing to dementia. Multiple metabolic abnormalities have an unconfirmed effect on MCI risk, and taking adequate measures against metabolic abnormalities might prevent the developing of MCI. Thus, the present study explored the association of MCI risk with common metabolic abnormalities, such as hyperglycemia, hypoglycemia, hyperlipidemia and hypouricemia, and to provide the basis for MCI prevention. A total of 1,262 elderly outpatients with normal cognitive function and without confirmed diabetes mellitus, hyperlipoidemia and gout were enrolled. During the five-year follow-up period, 142 subjects were diagnosed with MCI according to Mini Mental State Examination and Montreal Cognitive Assessment. Furthermore, annual blood glucose, glycated hemoglobin, lipids and uric acid values were obtained, and mean of each indicator was calculated. Only mean values were included in the study to reflect long-term effect of metabolic abnormalities on MCI risk. Thus, the increased risk of MCI was associated with the mean values of blood glucose < 4.7 mmol/L (RR: 1.57, 95% CI: 1.14-2.32), blood glucose ≥ 6.3 mmol/L (RR: 1.49, 95% CI: 1.03-2.39), glycated hemoglobin ≥ 5.9% (RR: 2.28, 95% CI: 1.59-3.91), triglycerides ≥ 2.0 mmol/L (RR: 2.79, 95% CI: 2.14-3.79), total cholesterol ≥ 5.5 mmol/L (RR: 2.37, 95% CI: 1.69-3.39) and uric acid ≤ 380 μmol/L (RR: 1.62, 95% CI: 1.08-2.51). In conclusion, long-term subclinical hyperglycemia, hypoglycemia, hyperlipidemia, and hypouricemia are independent risk factors for MCI in elderly people.

Keywords: hyperglycemia; hyperlipidemia; hypoglycemia; hypouricemia; mild cognitive impairment
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Introduction

Dementia is one of the most common geriatric diseases, and more than 7.7 million cases suffer from dementia annually around the world (Hayakawa et al. 2015). Due to lack of therapies, many patients have a poor quality of life and even lose dignity before death (Pai 2008; Olsen et al. 2016). Mild cognitive impairment (MCI) is considered to be a transitional state between normal aging and dementia (Luchsinger et al. 2007). At this stage, effective intervention might reduce the incidence of dementia and improve the prognosis of patients (Winblad et al. 2004). However, pathogenesis of MCI still remains unclear, and many risk factors for MCI have not been well elucidated (Meguro 2008).

In the past many years, an increasing number of studies have focused on the cognitive impairment in patients with diabetes mellitus (DM), and have revealed that DM might show negative effect on human cognitive function (Parikh et al. 2011; Cheng et al. 2012). One study has even suggested that elderly people with relative high blood glucose level in normal range also suffer from cognitive impairment (Mortby et al. 2013). Moreover, some studies have reported possible therapeutic effect of hypoglycemic measures on cognitive impairment (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group et al. 2007; Luchsinger et al. 2011), and repeated hypoglycemic episodes caused by inappropriate treatment may still cause the progression of dementia (Whitmer et al. 2009).

Some other studies have reported that hyperlipemia contributes to atherosclerotic plaque formation and increases risk of dementia (Kloppenborg et al. 2008; Chan et al. 2014). High serum non-high density lipoprotein (HDL) cholesterol may be an independent risk factor of cognitive impairment in patients with acute ischemic stroke

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(Lu et al. 2016). Like hypoglycemic drugs, lipid-lowering therapy has a potential benefit of improved cognition in patients (Bornstein et al. 2014).

In addition, serum uric acid (UA) levels might be decreased in patients with Alzheimer's disease and Parkinsonism dementia (McFarland et al. 2013; Al-khateeb et al. 2015). A published meta-analysis in 2016 has reported a significant relationship between lower serum level of UA and development of Alzheimer's disease and Parkinsonism dementia (Khan et al. 2016).

However, association of MCI with serum glucose, lipids and uric acid levels in elderly people have not been well investigated, and a firm conclusion cannot be drawn. Therefore, we conducted a prospective study enrolling more than 1,000 subjects, and tried to confirm the speculation whether MCI risk has a qualitative and quantitative association with chronic blood glucose, lipids, uric acid levels in elderly people.

Materials and Methods

Subjects

The study had been approved by the ethics committee of Tianjin Medical University General Hospital. A total of 1,300 outpatients were enrolled in the study from Department of Geriatrics, Tianjin Medical University General Hospital between January 1, 2009 and December 31, 2010. Inclusion criteria were listed as follows: (1) subjects were greater than or equal to 60 years old; (2) subjects had normal cognitive function on admission; (3) subjects did not have DM, hyperlipidemia and gout on admission, and subjects had not received any oral hypoglycemic agents, insulin therapies, hypolipidemic agents, allopurinol and uricosuric agents during the follow up period; (4) subjects agreed to receive medical examinations and face to face interviews annually; and (5) subjects signed written informed consent forms. Subjects with acute cardiocerebral vascular diseases, systemic autoimmune diseases, serious infection, malignancies and mental diseases were excluded from the study.

Data collection

Demographic information, education level, medical history, treatment history and other useful information of each subject was obtained by a face to face interview. Then, fasting and two-hour postprandial blood specimens were collected from each subject on admission. Fasting serum levels of blood glucose, triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL), HDL, glycated hemoglobin (HbA1c) and uric acid (UA) were determined in biochemical laboratory in Tianjin Medical University General Hospital within 2 hours. Two-hour postprandial serum level of blood glucose was also determined in the same laboratory. Meanwhile, each subject received a series of cognitive function and activities of daily living tests.

Serum levels of fasting blood glucose (FBG), postprandial blood glucose (PBG), TG, TC, LDL, HDL and UA were measured using a siemens ADVIA-2400 automatic biochemical analyzer (Erlangen, Germany). Serum level of HbA1c was determined using a siemens BNP II protein analyzer (Erlangen). Normal ranges were 3.9-6.1 mmol/L for FBG; < 7.8 mmol/L for PBG; 4.0-6.0% for HbA1c; 0.5-1.7 mmol/L for TG; 2.9-6.0 mmol/L for TC; < 3.12 mmol/L for LDL; 0.7-2.0 mmol/L for HDL; and 208-428 μmol/L (male) and 155-357 μmol/L (female) for UA.

Due to the variability of blood pressure value and multiple serological indicators (such as HbA1c and UA), mean value of each indicator during the follow up period was calculated. Only the mean values were included in the analysis.

Cognitive function evaluation

Cognitive function was assessed using Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scales (Molloy and Standish 1997; Olson et al. 2008). In MMSE, full mark was 30 points. Less than 20 points and 24 points were regarded as cognitive impairment separately in patients with ≤ 12 years education and > 12 years education. In MoCA, full mark was also 30 points. Less than 25 points and 26 points were regarded as cognitive impairment separately in patients with ≤ 12 years education and > 12 years education.

Activities of daily living evaluation

Activities of daily living were assessed using Instrumental Activities of Daily Living Scale (IADL) (Lawton and Brody 1969). There were nine questions in IADL, and each question had three optional answers (full dependence, partial dependence and independence). Full mark of IADL was 27 points.

Diagnosis of mild cognitive impairment

Diagnosis of MCI was determined by clinical consensus. Diagnostic criteria of MCI were listed as follows: (1) There was memory impairment or deficit in one or more other cognitive domains confirming by MMSE and MoCA; (2) general cognitive and functional abilities were still preserved, and daily life was not obviously affected; and (3) subjects did not meet the diagnostic criteria of dementia (Petersen 2004). On the contrary, the subjects who had not any cognitive impairments were regarded as "normal cognitive function".

Follow up

The length of follow-up period was five years (60 months). Annually, all subjects received a series of biochemical (FBG, PBG, HbA1c, UA and blood lipids), cognitive function (MMSE and MoCA) and activities of daily living tests (IADL). If a subject was diagnosed with MCI, the follow up of this subject was finished. The mean follow-up period of the MCI patients was 3.5 ± 1.1 years.

Data analysis

In the study, SPSS version 17.0 (Chicago, IL, USA) was used for statistical analysis. Continuous and categorical variables were showed separately by mean ± standard deviation and frequency. Differences of continuous and categorical variables were determined separately by independent sample t test and chi-square test. Difference of MCI incidences according to the metabolic factors was detected using survival analysis. Pearson correlation analysis was used to evaluate the connection between neuropsychological test scores and the metabolic factors. If a P value was less than 0.05, it was regarded as statistical significance. Receiver operating characteristic curve analysis was used to calculate the cut off values for the metabolic factors. Association of MCI with the metabolic factors were assessed by multivariate logistic regression analysis. Relative risk (RR) and 95% confidence interval (CI) were calculated in the analysis. If a 95%CI did not include value 1, it was regarded as sta-

tistical significance.

Results

On admission, 1,300 outpatients were included in the study. During the follow up period, sixteen, eleven and ten subjects separately died of acute cerebrovascular disease, acute myocardial infarction and malignancies. Another one moved to other city. So, 38 subjects were lost, and 1,262 subjects were enrolled finally. Annual neuropsychological tests found 142 MCI patients during the follow up period, and the remaining 1,120 subjects had normal cognitive function at the end of the follow up.

Scores of MMSE, MoCA and IADL in 1,262 subjects on admission were 28.8 ± 1.5, 28.3 ± 1.8 and 24.2 ± 2.3, suggesting that the subjects on admission had normal cognitive function and activities of daily living. Scores of MMSE, MoCA and IADL in 142 MCI patients at the time of diagnosis were 24.7 ± 2.1, 24.1 ± 2.0 and 21.5 ± 2.0, suggesting that cognitive function and activities of daily living in MCI patients were obviously impaired.

As shown in Table 1, the subjects were divided into MCI group and non-MCI group according to the outcome of cognitive function. There was no difference in sex, age, race, baseline body mass index and baseline abdominal circumference between the MCI group and the non-MCI group (P = 0.458, P = 0.266, P = 0.399, P = 0.941 and P = 0.528). There was also no difference in baseline incidences of retinal arteriosclerosis, hypertension, ischemic heart disease and ischemic cerebrovascular disease between these two groups (P = 0.744, P = 0.781, P = 0.755 and P = 0.687). During the follow up period, mean values of systolic and diastolic blood pressures were significantly higher in the MCI group than that in the non-MCI group (P = 0.032 and P = 0.001). Mean values of FBG, HbA1c, TG and TC were also higher in the MCI group compared with the non-MCI group (P = 0.002, P = 0.004, P = 0.008 and P < 0.001). However, mean value of UA was lower in the MCI group compared with the non-MCI group (P < 0.001). Because gender was equivalent between the MCI group and the non-MCI group, the study combined male and female data in

Table 1. Characteristics of elderly participants according to cognitive impairment status.

	MCI	Non-MCI	P value[b]
Total (n)[a]	142	1,120	—
Baseline			
Male (n, %)	99 (69.7)	814 (72.7)	0.458
Age (yrs, mean±SD)	71.4 ± 8.3	72.2 ± 7.8	0.266
Han (n, %)	133 (93.7)	1026 (91.6)	0.399
BMI (kg/m^2, mean±SD)	24.7 ± 3.0	24.8 ± 3.4	0.941
AC (cm, mean±SD)	90.2 ± 8.3	90.0 ± 8.9	0.528
RA (n, %)	91 (64.1)	702 (62.7)	0.744
Hypertension (n, %)	28 (19.7)	210 (18.8)	0.781
IHD (n, %)	43 (30.3)	325 (29.0)	0.755
ICD (n, %)	57 (40.1)	430 (38.4)	0.687
Mean during follow up period			
SBP (mmHg, mean±SD)	147.5 ± 15.9	143.8 ± 20.0	0.032
DBP (mmHg, mean±SD)	77.8 ± 10.6	74.4 ± 12.1	0.001
FBG (mmol/L, mean±SD)	5.6 ± 1.6	5.3 ± 1.0	0.002
PBG (mmol/L, mean±SD)	7.3 ± 2.7	7.1 ± 2.3	0.276
HbA1c (%, mean±SD)	5.8 ± 0.6	5.6 ± 0.6	0.004
TG (mmol/L, mean±SD)	1.8 ± 0.8	1.5 ± 1.1	0.008
TC (mmol/L, mean±SD)	5.1 ± 1.1	4.8 ± 0.9	＜0.001
LDL (mmol/L, mean±SD)	2.9 ± 0.9	2.9 ± 0.8	0.372
HDL (mmol/L, mean±SD)	1.2 ± 0.5	1.3 ± 0.4	0.067
UA (μmol/L, mean±SD)	329.4 ± 76.6	366.8 ± 120.8	＜0.001

[a]Among the 1,300 subjects on admission, 38 subjects had been lost during the follow up period. Finally, 1,262 subjects were included in the present study. They were 142 patients with mild cognitive impairment and 1,120 subjects with normal cognitive function.

[b]Difference of continuous variables was detected using independent sample t test; Difference of categorical variables was detected using Chi-square test; If a P value < 0.05, it was considered to be significant.

MCI, mild cognition impairment; SD, standard deviation; BMI, body mass index; AC, abdominal circumference; RA, retinal arteriosclerosis, IHD, ischemic heart disease; ICD, ischemic cerebrovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; PBG, two hours postprandial blood glucose; HbA1c, glycated hemoglobin; TG, triglyceride; TC, total cholesterol; LDL, low density lipoprotein; HDL, high density lipoprotein; UA, uric acid.

the following analysis.

As shown in Fig. 1A, B, all subjects were divided into hypoglycemia group and hyperglycemia group according to the mean value of FBG (5.5 mmol/L). In the hypoglycemia group, receiver operating characteristic curve analysis reported the cutoff point for FBG was 4.7 mmol/L (sensitivity = 88.2%, specificity = 66.3%, area under the curve = 0.837, P < 0.001). In the hyperglycemia group, the cutoff point for FBG was 6.3 mmol/L (sensitivity = 77.9%, specificity = 72.1%, area under the curve = 0.757, P < 0.001). In addition, the cutoff points for HbA1c, TG, TC and UA were 5.9%, 2.0 mmol/L, 5.5 mmol/L and 380 μmol/L (Fig. 1C-F).

As shown in Table 2, all subjects were divided into several groups according to the cutoff points for FBG, HbA1c, TG, TC and UA. Multivariate logistic regression analysis reported that mean values of FBG < 4.7 mmol/L and ≥ 6.3 mmol/L were both associated with the increased risk of MCI in the elderly people (RR: 1.57, 95% CI: 1.14-2.32 and RR: 1.49, 95% CI: 1.03-2.39). In addition, mean values of HbA1c ≥ 5.9%, TG ≥ 2.0 mmol/L, TC ≥ 5.5 mmol/L and UA ≤ 380 μmol/L were also related to the increased risk of MCI (RR: 2.28, 95% CI: 1.59-3.91; RR: 2.79, 95% CI: 2.14-3.79; RR: 2.37, 95% CI: 1.69-3.39; and RR: 1.62, 95% CI: 1.08-2.51).

As shown in Fig. 2, survival analysis reported that the subjects with mean values of FBG < 4.7 mmol/L, FBG ≥ 6.3 mmol/L, HbA1c ≥ 5.9%, TG ≥ 2.0 mmol/L, TC ≥ 5.5 mmol/L and UA ≤ 380 μmol/L showed higher incidences of MCI during the follow up period (P < 0.001, P = 0.033, P < 0.001, P < 0.001, P < 0.001 and P = 0.009).

As shown in Table 3, the subjects with mean values of FBG < 4.2 mmol/L and ≥ 8.3 mmol/L showed significantly higher risk of MCI separately compared with the subjects with mean values of FBG < 4.7 mmol/L and ≥ 6.3 mmol/L (RR: 2.93, 95% CI: 1.69-4.77 and RR: 2.15, 95% CI: 1.18-

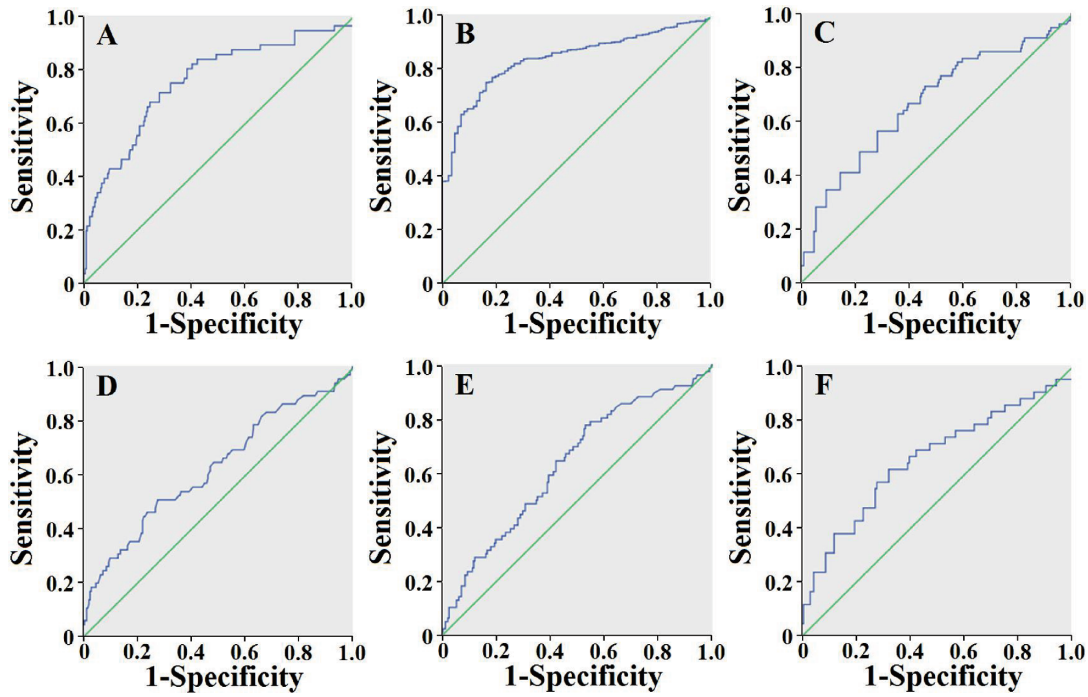

Fig. 1. Receiver operating characteristic curves for mild cognitive impairment risk prediction in elderly subjects.

A: A cutoff point for high serum level of fasting blood glucose (≥5.5 mmol/L) during follow up period was 6.3 mmol/L, yielding the sensitivity of 77.9% and the specificity of 72.1% in predicting mild cognitive impairment risk (Area under the curve = 0.757, P < 0.001).

B: A cutoff point for low serum level of fasting blood glucose (< 5.5 mmol/L) during follow up period was 4.7 mmol/L, yielding the sensitivity of 88.2% and the specificity of 66.3% in predicting mild cognitive impairment risk (Area under the curve = 0.837, P < 0.001).

C: A cutoff point for serum level of glycated hemoglobin during follow up period was 5.9%, yielding the sensitivity of 71.8% and the specificity of 62.6% in predicting mild cognitive impairment risk (Area under the curve = 0.654, P < 0.001).

D: A cutoff point for serum level of triglyceride during follow up period was 2.0 mmol/L, yielding the sensitivity of 63.9% and the specificity of 60.1% in predicting mild cognitive impairment risk (Area under the curve = 0.627, P = 0.002).

E: A cutoff point for serum level of total cholesterol during follow up period was 5.5 mmol/L, yielding the sensitivity of 62.3% and the specificity of 64.1% in predicting mild cognitive impairment risk (Area under the curve = 0.604, P < 0.001).

F: A cutoff point for serum level of uric acid during follow up period was 380 μmol/L, yielding the sensitivity of 61.1% and the specificity of 63.8% in predicting mild cognitive impairment risk (Area under the curve = 0.656, P = 0.002).

Table 2. Relationship between several metabolic factors and mild cognition impairment risk.

	MCI (n)	Total (n)	RR (95%CI)[b]
Total (n)[a]	142	1,262	—
Fasting blood glucose (mmol/L)			
4.7≤FBG<6.3	97	966	Reference
<4.7	26	167	1.57 (1.14, 2.32)
≥6.3	19	129	1.49 (1.03, 2.39)
Glycated hemoglobin (%)			
<5.9	91	1002	Reference
≥5.9	51	260	2.28 (1.59, 3.91)
Triglyceride (mmol/L)			
<2.0	78	973	Reference
≥2.0	64	289	2.79 (2.14, 3.79)
Total cholesterol (mmol/L)			
<5.5	83	961	Reference
≥5.5	59	301	2.37 (1.69, 3.39)
Uric acid (μmol/L)			
>380	24	310	Reference
≤380	118	952	1.62 (1.08, 2.51)

[a]Among the 1,300 subjects on admission, 38 subjects had been lost during the follow up period. Finally, 1,262 subjects were included in the present study. They were 142 patients with mild cognitive impairment and 1,120 subjects with normal cognitive function.

[b]Associations of mild cognition impairment with several metabolic factors were detected using multiple logistic regression analysis. If a 95% confidence interval did not include value 1, it was considered to be significant. The multiple logistic regression analysis was adjusted by gender, age, body mass index, race, abdominal circumference, onset of retinal arteriosclerosis, systolic blood pressure, diastolic blood pressure, serum levels of uric acid, triglyceride, total cholesterol, fasting blood glucose, two hours postprandial blood glucose, glycated hemoglobin.

MCI, mild cognition impairment; RR, pelative risk; CI, confidence interval; FBG, fasting blood glucose.

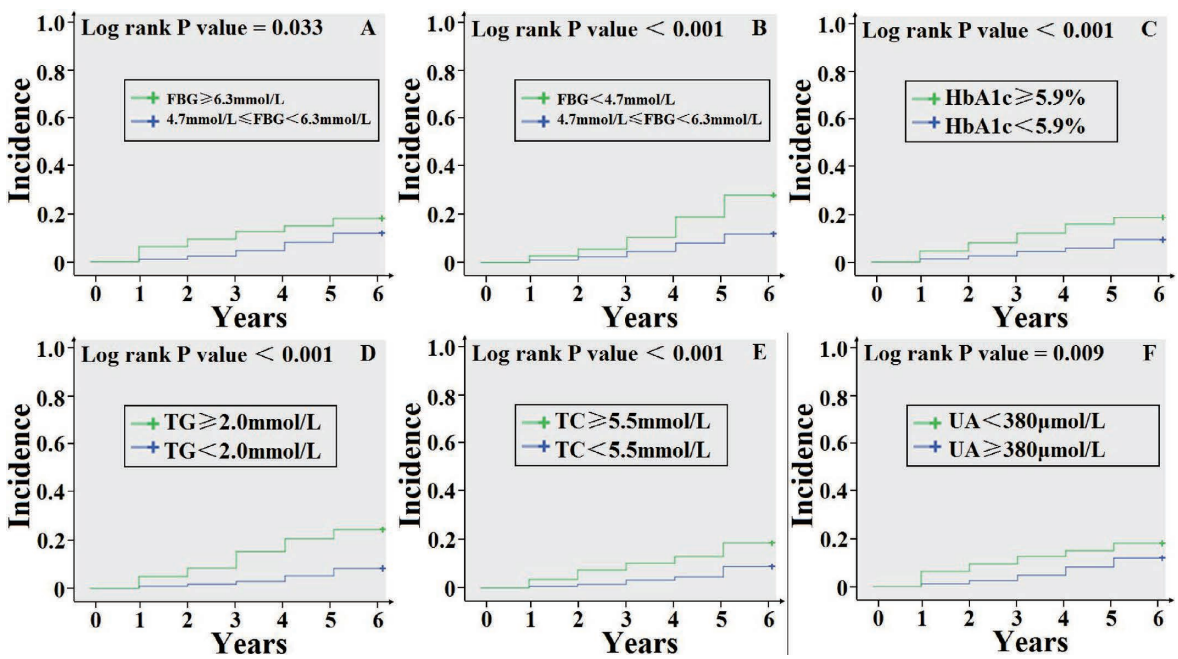

Fig. 2. Mild cognitive impairment risk survival analyses of elderly subjects according to several metabolic factors.

FBG, Fasting blood glucose; PBG, Postprandial blood glucose; HbA1c, Glycated hemoglobin; TG, Triglycerides; TC, Total cholesterol; UA, Uric acid.

Differences of mild cognitive impairment incidences according to several metabolic factors were detected using survival analysis. If a P value < 0.05, it was considered to be significant.

Table 3. Relationship between serum levels of several metabolic factors and mild cognition impairment risk.

	MCI (n)	Total (n)	RR (95%CI) [b]
Total (n) [a]	142	1,262	—
Fasting blood glucose (mmol/L)			
＜4.7	26	167	Reference
＜4.2	7	21	2.93 (1.69, 4.77)
Fasting blood glucose (mmol/L)			
⩾6.3	19	129	Reference
⩾8.3	13	43	2.15 (1.18, 3.86)
Glycated hemoglobin (%)			
⩾5.9	51	260	Reference
⩾7.9	27	68	2.08 (1.29, 3.07)
Triglyceride (mmol/L)			
⩾2.0	64	289	Reference
⩾4.0	41	89	2.12 (1.62, 2.97)
Total cholesterol (mmol/L)			
⩾5.5	59	301	Reference
⩾7.5	16	38	2.19 (1.42, 3.39)
Uric acid (μmol/L)			
⩽380	118	952	Reference
⩽330	71	433	1.34 (1.05, 1.85)

[a]Among the 1,300 subjects on admission, 38 subjects had been lost during the follow up period. Finally, 1,262 subjects were included in the present study. They were 142 patients with mild cognitive impairment and 1,120 subjects with normal cognitive function.

[b]Associations of mild cognition impairment with several metabolic factors were detected using multiple logistic regression analysis. If a 95% confidence interval did not include value 1, it was considered to be significant. The multiple logistic regression analysis was adjusted by gender, age, body mass index, race, abdominal circumference, onset of retinal arteriosclerosis, systolic blood pressure, diastolic blood pressure, serum levels of uric acid, triglyceride, total cholesterol, fasting blood glucose, two hours postprandial blood glucose, glycated hemoglobin.

MCI, mild cognition impairment; RR, pelative risk; CI, confidence interval.

Table 4. Correlations of neuropsychological scores with several metabolic factors.

	MMSE		MoCA	
	r[a]	P value[a]	r[a]	P value[a]
Fasting blood glucose	−0.036	0.2	−0.036	0.206
Glycated hemoglobin	−0.047	0.097	−0.040	0.152
Triglyceride	−0.084	0.003	−0.072	0.011
Total cholesterol	−0.048	0.085	−0.060	0.034
Uric acid	0.026	0.359	0.040	0.159

[a]Correlations of neuropsychological scores with several metabolic factors were assessed by pearson correlation analysis; If a P value < 0.05, it was considered to be significant.

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

3.86). In addition, mean values of HbA1c ≥ 7.9%, TG ≥ 4.0 mmol/L, TC ≥ 7.5 mmol/L and UA ≤ 330 μmol/L were also more closely related to the increased risk of MCI (RR: 2.08, 95%CI: 1.29-3.07; RR: 2.12, 95% CI: 1.62-2.97; RR: 2.19, 95% CI: 1.42-3.39; and RR: 1.34, 95% CI: 1.05-1.85).

As shown in Table 4, mean value of TG had a negative linear correlation with MMSE and MoCA scores (r = −0.084, P = 0.003 and r = −0.072, P = 0.011). However, such relationship was not found in FBG, HbA1c, TC and UA (P > 0.05).

Discussion

Though many studies have focused on the effect of multiple metabolic disorders on the onset and progression of cognitive impairment in elderly people (Cheng et al. 2012; McFarland et al. 2013; Lu et al. 2016), potential quantitative relationships between long-term blood glucose, lipids, uric acid levels and MCI risk have not been well elucidated.

The present study reported an about 50% increased risk of MCI separately in the subjects with FBG < 4.7

mmol/L and FBG ≥ 6.3 mmol/L. This confirmed a fact that long-term high blood glucose and low blood glucose both had an ability to promote the onset and progression of MCI in elderly people, although FBG might be in the normal range. A more effective blood glucose control strategy for MCI should be developed.

The study also revealed a 100% increased risk of MCI in the subjects with HbA1c ≥ 5.9%. But, we failed to prove the relationship between lower serum level of HbA1c and increased risk of MCI. One possible explanation was that HbA1c formation at molecular level was irreversible. It might gradually accumulate in the cell throughout the life cycle (Peterson et al. 1998; Miedema 2005). Therefore, HbA1c had an ability to show three-month average serum glucose concentration, but might not be sensitive to reflect the long-term low blood glucose level.

Long-term high serum levels of TC and TG separately resulted in about 180% and 140% increased risk of MCI, but serum level of LDL was equivalent between the MCI patients and the non-MCI subjects in the study. Thus, serum levels of TC, TG and non-HDL cholesterol might play a more important role in inducing atherosclerosis and MCI development, and clinical significance of LDL alone was limited (Cui et al. 2007; Bornstein et al. 2014; Klempfner et al. 2016).

The present study had also revealed a 60% increased risk of MCI in the patients with UA ≤ 380 μmol/L. Antioxidative effect should be implicated in such mechanism, and more research must be conducted to confirm the speculation. In addition, the study had found "dose-effect" relationship between the metabolic indicators and risk of MCI (Table 3).

The study did not find significant linear correlations between neuropsychological scores and most metabolic factors. It partly proved the diversity of MCI pathogenesis. First, vascular dysfunction (e.g., atherosclerosis) was a major pathogenic factor for dementia and MCI (Elias et al. 1997). Second, chronic high blood glucose in human body exerted serious impact on cognitive function, which was related to advanced glycated end products and reactive oxygen species (Wright et al. 2006). Third, repeated low blood glucose was a vital situation, and could lead to cerebral energy failure and neuronal necrosis (Auer 2004). Fourth, phosphorylated tau protein and depositional amyloid-β peptide were two pathological indicators for dementia, which were associated with insulin signaling pathway (Farris et al. 2003).

There were many potential risk factors for cognitive impairment, such as sex, age, body mass index and blood pressure (Stein et al. 2012; Cova et al. 2016; Tully et al. 2016). However, the present study did not find any differences in sex, age and body mass index between the MCI patients and the non-MCI subjects. Multivariate logistic regression analysis also adjusted by sex, age, body mass index and blood pressure, and provided some exciting results. Therefore, we did not think these factors could affect the conclusion.

In conclusion, the present study has demonstrated that long-term subclinical hyperglycemia, hypoglycemia, hyperlipidemia and hypouricemia are independent risk factors for MCI in elderly people.

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Conflict of Interest

The authors declare no conflict of interest.

References

Al-khateeb, E., Althaher, A., Al-khateeb, M., Al-Musawi, H., Azzouqah, O., Al-Shweiki, S. & Shafagoj, Y. (2015) Relation between uric acid and Alzheimer's disease in elderly Jordanians. *J. Alzheimers Dis.*, **44**, 859-865.

Auer, R.N. (2004) Hypoglycemic brain damage. *Metab. Brain Dis.*, **19**, 169-175.

Bornstein, N.M., Brainin, M., Guekht, A., Skoog, I. & Korczyn, A.D. (2014) Diabetes and the brain: issues and unmet needs. *Neurol. Sci.*, **35**, 995-1001.

Chan, D.C., Barrett, P.H. & Watts, G.F. (2014) The metabolic and pharmacologic bases for treating atherogenic dyslipidaemia. *Best Pract. Res. Clin. Endocrinol. Metab.*, **28**, 369-385.

Cheng, G., Huang, C., Deng, H. & Wang, H. (2012) Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern. Med. J.*, **42**, 484-491.

Cova, I., Clerici, F., Maggiore, L., Pomati, S., Cucumo, V., Ghiretti, R., Galimberti, D., Scarpini, E., Mariani, C. & Caracciolo, B. (2016) Body mass index predicts progression of mild cognitive impairment to dementia. *Dement. Geriatr. Cogn. Disord.*, **41**, 172-180.

Cui, R., Iso, H., Toyoshima, H., Date, C., Yamamoto, A., Kikuchi, S., Kondo, T., Watanabe, Y., Koizumi, A., Inaba, Y. & Tamakoshi, A. (2007) Serum total cholesterol levels and risk of mortality from stroke and coronary heart disease in Japanese: the JACC study. *Atherosclerosis*, **194**, 415-420.

Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; Jacobson, A.M., Musen, G., Ryan, C.M., Silvers, N., Cleary, P., Waberski, B., Burwood, A., Weinger, K., Bayless, M., Dahms, W. & Harth, J. (2007) Long-term effect of diabetes and its treatment on cognitive function. *N. Engl. J. Med.*, **356**, 1842-1852.

Elias, P.K., Elias, M.F., D'Agostino, R.B., Cupples, L.A., Wilson, P.W., Silbershatz, H. & Wolf, P.A. (1997) NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. *Diabetes Care*, **20**, 1388-1395.

Farris, W., Mansourian, S., Chang, Y., Lindsley, L., Eckman, E.A., Frosch, M.P., Eckman, C.B., Tanzi, R.E., Selkoe, D.J. & Guenette, S. (2003) Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc. Natl. Acad. Sci. USA*, **100**, 4162-4167.

Hayakawa, T., McGarrigle, C.A., Coen, R.F., Soraghan, C.J., Foran, T., Lawlor, B.A. & Kenny, R.A. (2015) Orthostatic blood pressure behavior in people with mild cognitive impairment predicts conversion to dementia. *J. Am. Geriatr. Soc.*, **63**, 1868-1873.

Khan, A.A., Quinn, T.J., Hewitt, J., Fan, Y. & Dawson, J. (2016)

Serum uric acid level and association with cognitive impairment and dementia: systematic review and meta-analysis. *Age* (*Dordr.*), **38**, 16.

Klempfner, R., Erez, A., Sagit, B.Z., Goldenberg, I., Fisman, E., Kopel, E., Shlomo, N., Israel, A. & Tenenbaum, A. (2016) Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the bezafibrate infarction prevention study and registry. *Circ. Cardiovasc. Qual. Outcomes*, **9**, 100-108.

Kloppenborg, R.P., van den Berg, E., Kappelle, L.J. & Biessels, G.J. (2008) Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *Eur. J. Pharmacol.*, **585**, 97-108.

Lawton, M.P. & Brody, E.M. (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*, **9**, 179-186.

Lu, D., Li, P., Zhou, Y., Xu, X., Zhang, H., Liu, L. & Tian, Z. (2016) Association between serum non-highdensity lipoprotein cholesterol and cognitive impairment in patients with acute ischemic stroke. *BMC Neurol.*, **16**, 154.

Luchsinger, J.A., Palmas, W., Teresi, J.A., Silver, S., Kong, J., Eimicke, J.P., Weinstock, R.S. & Shea, S. (2011) Improved diabetes control in the elderly delays global cognitive decline. *J. Nutr. Health Aging*, **15**, 445-449.

Luchsinger, J.A., Reitz, C., Patel, B., Tang, M.X., Manly, J.J. & Mayeux, R. (2007) Relation of diabetes to mild cognitive impairment. *Arch. Neurol.*, **64**, 570-575.

McFarland, N.R., Burdett, T., Desjardins, C.A., Frosch, M.P. & Schwarzschild, M.A. (2013) Postmortem brain levels of urate and precursors in Parkinson's disease and related disorders. *Neurodegener. Dis.*, **12**, 189-198.

Meguro, K. (2008) Clinical features of mild cognitive impairment and dementia in a community: an update of the Osaki-Tajiri Project. *Tohoku J. Exp. Med.*, **215**, 125-131.

Miedema, K. (2005) Standardization of HbA1c and optimal range of monitoring. *Scand. J. Clin. Lab. Invest. Suppl.*, **240**, 61-72.

Molloy, D.W. & Standish, T.I. (1997) A guide to the standardized Mini-Mental State Examination. *Int. Psychogeriatr.*, **9** Suppl 1, 87-94; discussion 143-150.

Mortby, M.E., Janke, A.L., Anstey, K.J., Sachdev, P.S. & Cherbuin, N. (2013) High "normal" blood glucose is associated with decreased brain volume and cognitive performance in the 60s: the PATH through life study. *PLoS One*, **8**, e73697.

Olsen, C., Pedersen, I., Bergland, A., Enders-Slegers, M.J., Jøranson, N., Calogiuri, G. & Ihlebæk, C. (2016) Differences in quality of life in home-dwelling persons and nursing home residents with dementia − a cross-sectional study. *BMC Geriatr.*, **16**, 137.

Olson, R.A., Chhanabhai, T. & McKenzie, M. (2008) Feasibility study of the Montreal Cognitive Assessment (MoCA) in patients with brain metastases. *Support. Care Cancer*, **16**, 1273-1278.

Pai, M.C. (2008) Delusions and visual hallucinations in dementia patients: focus on personal history of the patients. *Tohoku J. Exp. Med.*, **216**, 1-5.

Parikh, N.M., Morgan, R.O., Kunik, M.E., Chen, H., Aparasu, R.R., Yadav, R.K., Schulz, P.E. & Johnson, M.L. (2011) Risk factors for dementia in patients over 65 with diabetes. *Int. J. Geriatr. Psychiatry*, **26**, 749-757.

Peterson, K.P., Pavlovich, J.G., Goldstein, D., Little, R., England, J. & Peterson, C.M. (1998) What is hemoglobin A1c? An analysis of glycated hemoglobins by electrospray ionization mass spectrometry. *Clin. Chem.*, **44**, 1951-1958.

Petersen, R.C. (2004) Mild cognitive impairment as a diagnostic entity. *J. Intern. Med*., **256**, 183-194.

Stein, J., Luppa, M., Luck, T., Maier, W., Wagner, M., Daerr, M., van den Bussche, H., Zimmermann, T., Köhler, M., Bickel, H., Mösch, E., Weyerer, S., Kaufeler, T., Pentzek, M., Wiese, B., et al. (2012) The assessment of changes in cognitive functioning: age-, education-, and gender-specific reliable change indices for older adults tested on the CERAD-NP battery: results of the German Study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). *Am. J. Geriatr. Psychiatry*, **20**, 84-97.

Tully, P.J., Dartigues, J.F., Debette, S., Helmer, C., Artero, S. & Tzourio, C. (2016) Dementia risk with antihypertensive use and blood pressure variability: a cohort study. *Neurology*, **87**, 601-608.

Whitmer, R.A., Karter, A.J., Yaffe, K., Quesenberry, C.P. Jr. & Selby, J.V. (2009) Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA*, **301**, 1565-1572.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., Nordberg, A., Bäckman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., de Leon, M., DeCarli, C., et al. (2004) Mild cognitive impairment −beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J. Intern. Med.*, **256**, 240-246.

Wright, E. Jr., Scism-Bacon, J.L. & Glass, L.C. (2006) Oxidative stress in type 2 diabetes: the role of fasting and postprandial glycaemia. *Int. J. Clin. Pract.*, **60**, 308-314.