Experimental Gerontology 89 (2017) 15–19

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Uric acid may be protective against cognitive impairment in older adults, but only in those without cardiovascular risk factors

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ARTICLE INFO

Article history:
Received 3 October 2016
Received in revised form 30 November 2016
Accepted 2 January 2017
Available online 4 January 2017

Section Editor: Christian Humpel

Keywords:
Uric acid
Hyperuricemia
Cognitive function
Dementia
Cardiovascular risk factor

ABSTRACT

Uric acid (UA) may not only prevent development of cognitive dysfunction owing to its antioxidant efficacy, but also may worsen cognitive functions by gaining pro-oxidant character. The present study attempts to uncover this paradoxical association between UA and cognitive impairment in elderly. 1374 elderly patients were retrospectively evaluated and included in the study. Participants underwent determination of circulating UA levels and comprehensive geriatric assessment. A serum UA concentration ≥ 7.0 mg/dL in males and ≥5.7 mg/dL in females were considered hyperuricemia. The mean age of patients was 76.72 ± 8.76 years. The prevalence of hyperuricemia was 36.6%. Significant differences was determined between the patients with and without hyperuricemia in terms of age, gender, body mass index, score of Charlson Comorbidity Index (CCI), triglyceride level, and the prevalence of dementia, diabetes, hypertension and Congestive Heart Failure (CHF) ($p < 0.05$). When the effect of diabetes, hypertension and CHF between the groups has been statistically adjusted, the prevalence of dementia was significantly higher in those with lower UA in the absence of effect of DM, HT and CHF ($p < 0.05$). Higher UA is associated with better cognitive performance in the absence of cardiovascular risk factors, and these risk factors may potentially suppress this protective effect of higher UA in the older adults.

1. Introduction

Identifying risk factors for dementia, which are frequently seen among older adults, and taking early preventive measures or descelerating progression of cognitive disorders primarily Alzheimer Disease (AD), has been one of the significant goals of scientific world. After the studies, particularly those conducted in 1990s, demonstrating that AD is the disease with the highest treatment failure rate, determination of modifiable risk factors has gained much more importance (Solomon et al., 2014; Isik, 2010). The major risk factors include cardiovascular diseases such as diabetes, hypertension, obesity, and high cholesterol level; and accordingly, the hypothesis “What's good for the heart is good for the brain” has arisen (Solomon et al., 2014; Isik, 2010).

Hyperuricemia is one of the numerous cardiovascular risk factors; however, biological effects of uric acid are debatable (Feig et al., 2008). Uric acid is a natural antioxidant compound with beneficial characteristics, but preclinical studies have demonstrated that it is also a pro-inflammatory compound and elevated uric acid level has been found to be associated with the risk of myocardial infarction, stroke and cardiovascular mortality (Ruggiero et al., 2009). The potential mechanisms that explain this relation include stimulation of vascular smooth muscle cell proliferation induced by uric acid, proinflammatory characteristic of soluble uric acid, and uric acid mediated endothelial dysfunction by impairing nitric oxide production (Mazza et al., 2001; Johnson et al., 2003; Niskanen et al., 2004). Nevertheless, uric acid reduces oxidative stress in plasma owing to this property and may play a preventive role against the development of neurodegenerative processes that cause dementia by means of its antioxidant characteristic, which removes free oxygen radicals (Miller et al., 1993; Breteler, 2000).

Earlier studies demonstrated lower uric acid levels in patients with mild cognitive impairment (MCI) and AD as compared to the control group; (Rinaldi et al., 2003; Kim et al., 2006) on the contrary, some epidemiological studies reported that hyperuricemia was associated with the situations that lead to dementia (Ruggiero et al., 2009; Niskanen et al., 2004; Breteler, 2000). While experimental studies reveal that uric acid displays neuroprotective character against stroke, (Yu et al., 1998) other studies have concluded that high uric acid level is a predictive marker for stroke despite its default beneficial characteristic (Hozawa et al., 2006). As the consequence, effect of uric acid on cognitive functions has not been clarified because of its variable character.

Enlightening the potential beneficial or harmful effects of uric acid on cognitive functions in older adults may provide hints in developing

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http://dx.doi.org/10.1016/j.exger.2017.01.002
0531-5565/

efficient therapies for dementia. For this purpose, the present study aimed to assess the association between serum uric acid level and cognitive functions in older adults.

2. Method

2.1. Patients

Medical records of 1622 patients that presented to the geriatrics clinic between January 2014 and February 2016 and underwent comprehensive geriatric assessment (CGA) were reviewed. A total of 1374 patients,who were available for study design, had no exclusion criteria, and had complete medical records, were retrospectively enrolled. The study was compliant with the Declaration of Helsinki and was approved by the local ethics committee.

2.2. Inclusion criteria

2.2.1. Patients with dementia

Dementia was diagnosed according to DSM-IV criteria. The diagnosis of cognitive impairment (CI), including Mild cognitive İmpairment (MCI), AD, dementia with Lewy body (DLB), behavioral variant Frontotemporal Dementia (bvFTD), Vascular Dementia (VaD), Normal pressure hydrocephalus (NBH),and Parkinson's Disease Dementia (PDD) was established according to diagnostic criteria (McKhann et al., 1984; Mc Keith et al., 2005; Rascovsky et al., 2011; Lopez et al., 1994; Relkin et al., 2005; Martinez-Martin et al., 2011). In addition, each of these patients was evaluated via Magnetic Resonance Imaging.

2.3. Exclusion criteria

Exclusion criteria:
Patients,

- who were in delirium state at evaluation
- who had psychotic diseases (schizoaffective disorder, etc.)
- who had treatment-refractory major depressive disorder
- with the history of diseases that may seriously impair their general health status such as acute cerebrovascular event, gastrointestinal bleeding, sepsis, acute renal failure, acute coronary syndrome, acute hepatic failure, or acute respiratory distressor history of staying in an intensive care unit in the last month;
- with alcohol and substance abuse
- with diseases that are likely to cause both hyperuricemia and cognitive disfunction such as myelo-lymphoproliferative disease, malignancy, end-stage renal failure, or hyperparathyroidism
- who took allopurinol treatment
- with mixed dementia or MCI

2.4. Comprehensive geriatric assessment (CGA): (Soysal P et al., 2014)

Socio-demographic characteristics of the participants including age, gender, education and living environment were recorded. All patients were examined to determine whether they have cataract, hearing loss, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, peripheral vascular disease, hyperlipidemia, cerebrovascular disease, depression, dementia, or polypharmacy in their medical history. Besides, comorbidity status of the patients was assessed using Charlson comorbidity index. Cognitive functions of the patients were evaluated by Cognitive State Test (COST) Mini–Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA) test (Babacan-Yildiz et al., 2013). In addition, scores of the Geriatric Depression Scale (GDS) and basic and instrumental Activities of Daily Living (BADL and IADL, respectively) indexes were also recorded for each patient.

2.5. Laboratory findings

Results of routine laboratory analyses were recorded to determine biochemical, metabolic and nutritional states of the patients. Serum uric acid concentration was studied together with other biochemical analyses on Beckman Coulter AU5800 Autoanalyzer in the Dokuz Eylul University Central Laboratory. Serum uric acid concentration was measured by colorimetric spectrophotometric method. A serum uric acid concentration $\geq$7.0 mg/dL in males and $\geq$5.7 mg/dL in females was considered hyperuricemia (De Giorgi et al., 2015).

2.6. Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation. Kolmogorov-Smirnov test was used to analyze continuous variables in terms of suitability for normal distribution. Continuous variables with normal distribution were analyzed by Independent Sample *t*-test, whereas continuous variables without normal distribution were analyzed by Mann-Whitney *U* test and Kruskal-Wallis test. Differences in proportions were analyzed using chi-square test. The relation between the parameters was analyzed by Pearson's correlation analysis. Probabilities <0.05 were considered significant. Statistical analyses were done using SPSS 15.0 (SPSS Inc.) package program. The stratified chi square test was used in adjustment for age, age, gender, body mass index, Charlson Comorbidity Index and comorbidities.

3. Results

The mean age of 1374 patients was 76.72 $\pm$ 8.76 years, and 64.1% of them were female. The prevalence of hyperuricemia was 36.6% (41.4% in females, and 28.3% in males). Of these patients, 255 (18.5%) had been diagnosed with dementia (133 CE, 16 VaD, 27 FTD, 33 LBD, 31 NBH, 15 PDD). Significant differences were determined between the patients with and without hyperuricemia in terms of age, gender, body mass index (BMI), score of Charlson Comorbidity Index (CCI), triglyceride level, and the prevalence of dementia, DM, HT and CHF ($p < 0.05$) (Table 1).

The difference between the groups in terms of dementia continued when adjusted for age ($p < 0.05$), but disappeared when adjusted for gender and BMI ($p > 0.05$). When the patients were dichotomized as CCI $\leq$ 1 and CCI $\geq$ 2 and were adjusted accordingly, the relation between dementia and hyperuricemia continued in those with low index score, whereas there was no relation between these parameters in those with high index score. When the effect of DM, HT and CHF between the groups has been adjusted statistically, it was determined that there is no difference between the groups in terms of dementia. Furthermore, the prevalence of dementia is significantly higher in those with lower uricemia in the absence of these comorbidities ($p < 0.05$) (Table 2).

Serum uric acid concentration in the patients with and without dementia was 5.43 $\pm$ 2.07 mg/dL and 5.78 $\pm$ 1.82 mg/dL, respectively and the results were significantly different ($p < 0.05$). However, there was no difference between the types of dementia and hyperuricemia or serum uric acid concentration ($p > 0.05$) (Table 3).

No correlation was determined between serum uric acid concentration and MMSE, COST, MOCA, BADL, IADL and YGDS in the patients either with or without dementia ($p > 0.05$).

4. Discussion

The present study has demonstrated that serum uric acid concentration is lower in older adults with dementia without cardiovascular risk factors but that this interrelation disappear in those with cardiovascular risk factors.

Worldwide prevalence of hyperuricemia changes between 2.6% and 36% depending on mean age, race, living environment and the cut-off

Table 1
Characteristics of the participants in the groups with and without hyperuricemia.

	HU (−) 871	HU (+) 503	*P value*
Age	76.21 ± 9.00	78.46 ± 7.95	*<0.001*
Female (%)	58.7	71.8	*<0.001*
Education (years)	7.11 ± 4.70	6.39 ± 4.51	*0.013*
BMI (kg/m^2)	27.50 ± 5.26	29.94 ± 5.33	*<0.001*
Number of using drugs	5.43 ± 3.46	5.35 ± 3.36	*0.684*
CCI	0.96 ± 1.04	1.2 ± 1.15	*0.006*
Comorbidities (%)			
Dementia	21.5	13.3	*0.029*
Depression	31.3	33.4	*0.438*
Cerebrovascular disease	8.8	10.9	*0.250*
Diabetes Mellitus	27.6	33.5	*0.026*
Hyperlipidemia	18.9	19.7	*0.760*
Hypertension	62.9	81.1	*< 0.001*
Coronary artery disease	18.5	18.3	*0.923*
Congestive heart failure	6.5	11.5	*0.002*
Peripheral vascular disease	3.0	4.0	*0.344*
COPD	8.8	9.5	*0.676*
Hypothyroidism	17.8	21.1	*0.148*
Geriatric assessment			
MMSE	24.21 ± 6.00	24.69 ± 5.22	*0.303*
COST	22.84 ± 5.90	22.39 ± 5.93	*0.481*
MOCA	22.84 ± 5.09	22.69 ± 4.69	*0.796*
YGDS	3.41 ± 3.50	3.36 ± 3.41	*0.821*
MNA	10.8 ± 2.2	11.0 ± 2.2	*0.117*
BADL	87.07 ± 20.39	87.07 ± 19.56	*0.998*
IADL	10.91 ± 5.53	10.89 ± 6.46	*0.939*
Laboratory data			
CRP (mg/L)	13.96 ± 33.19	16.35 ± 36.53	*0.461*
TSH (uIU/mL)	1.75 ± 2.45	2.07 ± 5.39	*0.184*
25(OH)D (ng/ml)	18.84 ± 17.46	17.40 ± 13.82	*0.162*
Vitamin B12 (pmol/L)	489.84 ± 383.68	506.12 ± 394.94	*0.490*
Folic acid (ng/mL)	9.41 ± 15.28	9.10 ± 5.85	*0.697*
Triglycerides (mg/dL)	131.06 ± 67.92	148.66 ± 67.36	*<0.001*
HDL-kol (mg/dL)	54.13 ± 14.48	52.58 ± 13.78	*0.087*
LDL-kol (mg/dL)	128.98 ± 37.90	127.29 ± 38.96	*0.486*
HbA1c (%)	7.33 ± 3.83	6.78 ± 1.14	*0.062*
Fasting blood glucose (mg/dL)	110.74 ± 45.15	112.05 ± 36.23	*0.621*

BADL: Basic Activity Of Daily Living (0 [worst]–100 [best]); CCI: Charlson Comorbidity Index, COPD: Chronic Obstructive Pulmonary Disease; CRP:C-Reactive Protein; HDL-C: High- density lipoproteins cholesterol, LDL-C: Low-density lipoproteins cholesterol; TSH: Thyroid - stimulating hormone; COST: Cognitive State Test (0 [worst]-30 [best]); IADL: Instrumental activity of daily living (0 [worst]-23 [best]); MMSE: Mini-Mental State Examination (0 [worst]-30 [best]); MNA: Mini Nutritional Assessment (0 [worst]-14 [best]); YGDS: Yesavage Geriatric Depression Score (15 [worst]-0 [best]); 25(OH)D: 25hydroxyvitamin D.

value accepted for hyperuricemia (Lin et al., 2015). In the present study, the prevalence of hyperuricemia in the patients was 36.6%, which is higher than the prevalence of hyperuricemia in the general population of Izmir province (12.1%) (Sari et al., 2009). We attributed this difference to the facts that study population consisted of older adults and the cut-off value used to diagnose hyperuricemia was lower (Sari et al., 2009). Additionally, different from many of the earlier studies, it was demonstrated that hyperuricemia is more prevalent in females in this study (Ruggiero et al., 2009). This may have resulted from females' accounting for the majority of study population and having higher mean BMI and higher prevalence of HT.

Previous studies have failed to clearly demonstrate the presence of a relation between uric acid concentration and cognitive functions. In these studies, it was reported that uric acid may either protect against harmful effects of free radicals and may prevent development of cognitive dysfunction owing to its antioxidant efficacy or may worsen cognitive functions by gaining pro-oxidant character under certain conditions (Mazza et al., 2001; Johnson et al., 2003; Niskanen et al., 2004; Rinaldi et al., 2003). The studies conducted to date have suffered from several methodological limitations such as small sample size, lack of information about confounders, and limited neuropsychological evaluation. Therefore, it has been made to eliminate such limitations and aimed

Table 2
Comparison of the groups with and without hyperuricemia in terms of dementia after adjusting for age, gender, body mass index, Charlson Comorbidity Index and comorbidities.

	HU (−) n:871%	HU (+) n:503%	*p* value
Age			
65–74	14.4	6.8	**0.02**
75–84	23.5	13.5	**0.04**
>85	32.8	29.0	0.50
Gender			
Female	13.5	12.3	0.61
Male	22.4	17.7	0.27
Body mass index			
<20	32.8	24.4	0.23
20–25	20.4	13.0	0.07
>25	16.5	14.7	0.65
Charlson comorbidity index			
≤1	20.7	14.5	**0.014**
≥2	27.8	25.2	0.69
Diabetes mellitus			
(+)	14.1	17.7	0.33
(−)	24.1	15.7	**0.03**
Hypertension			
(+)	18.4	16.0	0.35
(−)	28.6	19.3	**0.04**
Congestive heart failure			
(+)	17.2	18.5	0.87
(−)	21.7	16.0	**0.02**
Triglyceride level			
<200 mg/dL	16.2	12.3	**0.08**
≥200 mg/dL	15.2	15.7	0.98

to eliminate this parodoxic effect of uric acid on cognitive functions in this study.

Ruggiero et al. reported that high serum uric acid concentration may be associated with poor cognitive status in a cross-sectional study. However, they considered those with MMSE score < 26 were cognitively healthy, excluded those who had mild ADL or IADL disabilities due to cognitive impairment, and performed neuroimaging in none of the patients with dementia. Moreover, it has not been explained according to which criteria the cut-off values > 7.5 mg/dL in males and > 6.2 mg/dL in females have been determined (Ruggiero et al., 2009). Due to all these concerns especially related to patients selection, certain doubts have arisen concerning the results of that study. Another study with similar outcomes has used the data from Brisighella Heart Study and enrolled the patients who had no history of cardiovascular disease (CVD) and chronic drug use; (Cicero et al., 2015) however, it was not explained the rationale of evaluating cognitive functions of the participants according to the MMSE score's being under or over 27; and it was obvious that there was significant difference between the cases in terms of age, systolic blood pressure and fasting blood glucose. Furthermore, due to the including only the patients without CVD and chronic drug use the results of that study are difficult to adapt to daily practice. In the other study, Perna et al. analyzed 1144 geriatric patients also according to the presence of CVD, and they reported that elevated uric acid concentration is associated with cognitive impairment in the presence of CVD (Perna et al., 2016). However, in that study, all the patients only evaluated with Cognitive Telephone Screening Instrument which does not allow evaluation of basic cognitive dimensions such as visiospatial functions, agnosia, apraxia and naming (Kliegel et al., 2007). Despite of their limitations, all of the above-mentioned studies have concluded that hyperuricemia is a modifiable risk factor for cognitive impairment.

On the other hand, the Rotterdam study has already reported that high uric acid concentration is associated with white matter lesions and atrophy and cognitive impairment due to vascular injury, (Verhaaren et al., 2013) and a current meta-analysis was concluded

Table 3
Comparison of types of dementia according to hyperuricemia and to serum uric acid concentrations.

Dementia	HU (−) n:188 %	HU (+) n:67 %	p*	Serum uric acid (mg/dL)	p**
AH (n:133)	52.6	50.7	***0.730***	5.58 ± 2.06	***0.558***
FTD (n:27)	11,1	8,6		5.72 ± 2.41	
LBD (n:33)	13.8	10.4		5.13 ± 2.25	
VAD (n:16)	4.8	10.4		6.32 ± 3.05	
NBH (n:31)	11.7	13.4		5.70 ± 1.41	
PDD (n:15)	5.8	6.0		4.66 ± 1.88	

p*: Comparison according to the presence of hyperuricemia.
p**: Comparison according to the blood uric acid.

that the relationship between blood uric acid concentration and cognitive impairment may differ especially in patients with VaD compared to other dementia subtypes; (Khan et al., 2016) whereas, Molshatzki et al. reported that there was an association between low uric acid and cognitive impairment in the patients with cardiovascular disease in a 10-year follow-up period (Euser et al., 2009). When it is considered the higher uric acid is a risk factor for cardiovascular disease, it seems that all these results may be accepted for vascular cognitive impairment. Accordingly, highest serum uric acid concentration was determined in 16 patients with vascular dementia in the present study, even though it was not statistically significant and the number of patients was insufficient. For this reason, it might have been helpful to design the studies and to determine the subtypes of dementia using comprehensive geriatric assessment including neuroimaging and neuropsychological evaluation; and thus, longitudinal studies are required.

While in another outcome derived from the data of Rotterdam study, baseline uric acid concentration of the participants without dementia were interrelated to their cognitive functions after 10 years; adjusting only for CVD risk factors and it was reported that high uric acid concentration may be protective against dementia, (Euser et al., 2009) it was concluded that the relationship between blood uric acid concentration and cognitive impairment was not consistent across all kinds of dementia despite the heterogeneity and risk of various biases of the studies included in the meta-analysis mentioned before (Khan et al., 2016). In the present study, it is demonstrated that the cognitive impairment or dementia is associated with low uric acid in the absence of cardiovascular comorbidities such as DM, HT and CHF. So it seems that interrelations between higher uric acid and cognitive impairment is no more paradoxically than higher uric acid is associated with better cognitive performance in the absence of effect of cardiovascular risk factors. These risk factors may lead to supress this protective effect of higher uric acid in the older adults.

In the light of these studies, it can be said that uric acid plays a proinflammatory role in the presence of vascular risk factos by interacting with these factors and impairs oxidative balance in favor of pro-oxidants, causes cerebral hypoperfusion by enhancing development of atherosclerosis due to endothelial dysfunction, and thus have negative impact on cognitive functions (Cervellati et al., 2014). On the contrary, low serum uric acid concentration in AD patients without these risk factors is striking (Al-khateeb et al., 2015). Uric acid is an antioxidant that neutralizes 60% activity of free radicals in human circulation. Therefore, inflammation may be triggered and destructions may be seen in many tissues such as brain due to exposure to the toxicity of these radicals in the patients with low serum uric acid concentration (Ames et al., 1981). All these results support the hypothesis that oxidative stress and inflammation may play a role in cognitive impairment primarily in AD.

The powerful aspects of the present study include high sample size, all the participants' being over the age of 65 years, and all the participants' having undergone comprehensive geriatric assessment. In addition, comorbidities and laboratory parameters such as serum vitamin D, vitamin B12 and folic acid concentrations, as well as thyroid functions, which are known to influence cognitive functions and the deficiency of which is frequently encountered in older adults, were also investigated and information about subtypes of dementia has been given. Retrospective and cross-sectional design is the limitation of the present study. In addition, limited number of patients in other subtypes of dementia excluding AD, exclusion of the patients with mixed dementia and MCI, and not investigating the relation between uric acid and subdimensions of cognitive functions are the other limitations.

In conclusion, serum uric acid concentration is lower in older adults with dementia without cardiovascular risk factors. This result supports the hypothesis that oxidative injury may play a role in the pathogenesis of dementia and that uric acid may be protective against cognitive impairment owing to its anti-oxidant characteristic. However, favorable association between uric acid and cognitive functions may disappear in those with cardiovascular risk factors and its effect on oxidative balance may probably be impaired in favor of pro-oxidant.

Conflict of interest

None.

Financial disclosure

The authors have nothing to disclose.

Author contributions

Busra Tuven and Gulcin Unutmaz performed data collection; Pinar SOYSAL supported for statistical analysis, performed data analysis, manuscript writing and conceptualization; Derya KAYA contributed manuscript writing. A.T. Isık designed the study, and performed data analysis, manuscript writing.

References

Al-khateeb, E., Althaher, A., Al-khateeb, M., et al., 2015. Relation between uric acid and Alzheimer's disease in elderly Jordanians. J. Alzheimers Dis. 44 (3), 859–865.

Ames, B.N., Cathcart, R., Schwiers, E., et al., 1981. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc. Natl. Acad. Sci. U. S. A. 78, 6858–6862.

Babacan-Yildiz, G., Isik, A.T., Ur, E., et al., 2013. COST: cognitive state test, a brief screening battery for Alzheimer disease in illiterate and literate patients. Int. Psychogeriatr. 25 (3), 403–412 (Mar).

Breteler, M.M., 2000. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. Neurobiol. Aging 21 (2), 153–160.

Cervellati, C., Romani, A., Seripa, D., et al., 2014 Feb 15. Oxidative balance, homocysteine, and uric acid levels in older patients with late onset Alzheimer's disease or vascular dementia. J. Neurol. Sci. 337 (1–2), 156–161.

Cicero, A.F.G., Desideri, G., Riccardo, G.G., et al., 2015. Serum uric acid and impaired cognitive function in a cohort of healthy young elderly: data from the Brisighella Study. Intern. Emerg. Med. 10, 25–31.

De Giorgi, A., Fabbian, F., Pala, M., et al., 2015. Uric acid: friend or foe? Uric acid and cognitive function "Gout kills more wise men than simple". Eur. Rev. Med. Pharmacol. Sci. 19 (4), 640–646 (Feb).

Euser, S.M., Hofman, A., Westendorp, R.G., et al., 2009. Serum uric acid and cognitive function and dementia. Brain 132 (Pt 2), 377–382.

Feig, D.I., Kang, D.H., Johnson, R.J., 2008. Uric acid and cardiovascular risk. N. Engl. J. Med. 359 (17), 1811–1821.

Hozawa, A., Folsom, A.R., Ibrahim, H., Nieto, F.J., et al., 2006. Serum uric acid and risk of ischemic stroke: the ARIC study. Atherosclerosis 187 (2), 401–407.
Isik, A.T., 2010. Late onset Alzheimer's disease in older people. Clin. Interv. Aging 5, 307–311.
Johnson, R.J., Kang, D.H., Feig, D., et al., 2003. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 41 (6), 1183–1190.
Khan, A.A., Quinn, T.J., Hewitt, J., et al., 2016. Serum uric acid level and association with cognitive impairment and dementia: systematic review and meta-analysis. Age (Dordr.) 38 (1), 16 (Feb).
Kim, T.S., Pae, C.U., Yoon, S.J., et al., 2006. Decreased plasma antioxidants in patients with Alzheimer's disease. Int. J. Geriatr. Psychiatry 21 (4), 344–348.
Kliegel, M., Martin, M., Jäger, T., 2007. Development and validation of the cognitive telephone screening instrument (COGTEL) for the assessment of cognitive function across adulthood. J. Psychol. 141 (2), 147–170 (Mar).
Lin, H., Li, Q., Liu, X., et al., 2015. Liver fat content is associated with elevated serum uric acid in the Chinese middle-aged and elderly populations: shanghai Changfeng study. PLoS One 10 (10), e0140379.
Lopez, O.L1., Larumbe, M.R., Becker, J.T., et al., 1994. Reliability of NINDS-AIREN clinical criteria for the diagnosis of vascular dementia. Neurology 44 (7), 1240–1245 (Jul).
Martinez-Martin, P., Falup-Pecurariu, C., Rodriguez-Blazquez, C., et al., 2011. Dementia associated with Parkinson's disease: applying the Movement Disorder Society Task Force criteria. Parkinsonism Relat. Disord. 17, 621–624.
Mazza, A., Pessina, A.C., Pavei, A., et al., 2001. Predictors of stroke mortality in elderly people from the general population. The CArdiovascular STudy in the ELderly. Eur. J. Epidemiol. 17 (12), 1097–1104.
Mc Keith, I.G., Dickson, D.W., Lowe, J., et al., 2005. Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology 65 (12), 1863–1872 (Dec 27).
McKhann, G., Drachman, D., Folstein, M., et al., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34, 939e944.
Miller, N.J., Rice-Evans, C., Davies, M.J., et al., 1993. A novel method for measuring antioxidant capacity and its application to monitoring the antioxidant status in premature neonates. Clin. Sci. (Lond.) 84 (4), 407–412.
Niskanen, L.K., Laaksonen, D.E., Nyyssönen, K., et al., 2004. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch. Intern. Med. 164 (14), 1546–1551.
Perna, L., Mons, U., Schöttker, B., et al., 2016. Association of cognitive function and serum uric acid: are cardiovascular diseases a mediator among women? Exp. Gerontol. 81, 37–41 (Aug).
Rascovsky, K., Hodges, J.R., Knopman, D., et al., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain 134 (pt9), 2456–2477 (Sep).
Relkin, N., Marmarou, A., Klinge, P., et al., 2005. Diagnosing idiopathic normal-pressure hydrocephalus. Neurosurgery 57, 4–16.
Rinaldi, P., Polidori, M.C., Metastasio, A., et al., 2003. Plasma antioxidants are similarly depleted in mild cognitive impairment and in Alzheimer's disease. Neurobiol. Aging 24 (7), 915–919.
Ruggiero, C., Cherubini, A., Lauretani, F., et al., 2009. Uric acid and dementia in community-dwelling older persons. Dement. Geriatr. Cogn. Disord. 27 (4), 382–389.
Sari, I., Akar, S., Pakoz, B., et al., 2009. Hyperuricemia and its related factors in an urban population, Izmir, Turkey. Rheumatol. Int. 29 (8), 869–874.
Solomon, A., Mangialasche, F., Richard, E., et al., 2014. Advances in the prevention of Alzheimer's disease and dementia. J. Intern. Med. 275 (3), 229–250.
Soysal, P., Isik, A.T., Buyukaydin, B., et al., 2014. A comparison of end-stage renal disease and Alzheimer's disease in the elderly through a comprehensive geriatric assessment. Int. Urol. Nephrol. 46 (8), 1627–1632 (Aug).
Verhaaren, B.F., Vernooij, M.W., Dehghan, A., et al., 2013. The relation of uric acid to brain atrophy and cognition: the Rotterdam Scan Study. Neuroepidemiology 41 (1), 29–34.
Yu, Z.F., Bruce-Keller, A.J., Y, et al., 1998. Uric acid protects neurons against excitotoxic and metabolic insults in cell culture, and against focal ischemic brain injury in vivo. J. Neurosci. Res. 53 (5), 613–625.